

Policy Options for Formulary Development in Middle-income Countries



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Karla Hernandez-Villafuerte, Martina Garau,
Adrian Towse, Louis Garrison, Simrun Grewal

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Karla Hernandez-Villafuerte¹, Martina Garau¹, Adrian Towse¹,
Louis Garrison², Simrun Grewal²

¹Office of Health Economics, ²University of Washington

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Submitted by:

OHE Consulting Ltd
(a registered company number 09853113)
Southside, 7th Floor
105 Victoria Street
London SW1E 6QT
United Kingdom

For further information please contact

Martina Garau
Senior Economist
Tel: +44 (0)20 7747 8867
mgarau@ohe.org
Or
Adrian Towse
Director
Tel: +44 (0) 20 7747 1407
atowse@ohe.org

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1. INTRODUCTION

A number of middle-income countries (MICs) are evolving their health systems toward universal health coverage (UHC). Such countries typically have limited drug formularies and some form of an essential drugs list. As these health systems continue to evolve to better meet patient needs, formulary decision-making processes may also need to evolve.

Recently, international organizations such as the World Health Organization (2014 World Health Assembly) have suggested the use of health technology assessment (HTA) as a key tool to inform formulary expansion surrounding UHC.

While there are many approaches to HTA, it has become synonymous with the resource-intensive use of cost-effectiveness analysis to assess and appraise the value of new drugs, as undertaken by NICE in the UK.

This report explores different HTA and decision making approaches to help understand which options might be the most appropriate in an MIC context.

1.1. Objectives and structure of the report

PhRMA retained OHE Consulting to explore options and recommend methods that could help MICs efficiently and effectively identify medicines for formulary inclusion. A particular emphasis was placed on incorporating a country's health system organization and national priorities into this framework.

Key research questions included:

- As they evolve toward UHC, how should MICs approach drug formulary decision making?
- How might macro-level decision making factors (focusing on the health system organisation and its priority setting) and micro-level factors (intervention-specific effects) be used or combined in the formulary decision-making process?
- Which policy options best balance budget impact, value, and clinical importance when determining which new medicines should be included on the national formulary?

The report is structured as follows:

- Section 1 includes report purpose and scope;
- Section 2 summarizes methods used;
- Section 3 explores micro-level factors, macro-level factors, aggregation methods, affordability measures, and process-related issues;
- Section 4 summarizes results; and
- Section 5 discusses results and policy implications for decision makers in MICs.

2. METHODS

To achieve study objectives, OHE Consulting performed a targeted literature review¹, conducted interviews with experts, and ran a structured workshop with a sub-set of the interviewees which included surveying them before and after the workshop.

The literature review explored:

- Key decision-making approaches associated with the organisation and the “architecture” of the health care systems (macro-level decision making), and
- Identified micro-level factors associated with formulary-decision making including (a) benefit-related considerations (e.g. effectiveness, wider societal impacts), (b) processes to make decisions and (c) tools/approaches, if available, to manage access to innovative, higher cost treatments.

The literature search around micro-level factors was focused around three middle-income countries and two high-income countries:

- Three middle-income countries: Brazil, Thailand, and Taiwan. These countries were selected as they have experience with formal decision making processes surrounding formulary development and the literature was therefore assumed to be more robust than in other countries;
- Two high-income countries: Germany and UK (focusing on England, given the separate HTA processes existing in England, Wales, Scotland and Northern Ireland). These two countries represent two major alternative approaches currently used to measure medicines value: (a) cost-effectiveness analysis, mainly using the quality-adjusted life year (QALY) gained, in order to measure and value health effects; and (b) therapeutic added value, often focusing on the assessment of clinical benefits which feeds into price setting/negotiations (Towse and Barnsley, 2013). For the first category we selected the UK, given the worldwide reputation of NICE, and for the second category we selected Germany because of its differences from NICE.

More details on the literature review methods and results are available in Appendix 1.

Based on the literature review and OHE Consulting’s existing expertise, a preliminary list of macro-level factors, micro-level factors, and process-related issues that are potentially relevant to formulary decision making was derived. Semi-structured one-hour long telephone interviews were then conducted with 13 experts who provided a view on these factors, particularly in the context of MICs and relevant country examples, as applicable. Appendix 2 provides the interview guide that was distributed to the experts in advance of the telephone interview. A portion of each interview was tailored to the individual interviewee’s expertise.

Interviews were conducted with experts who were either International health experts (economists or health economists) who have advised or worked for an international organisation, and/or have knowledge of approaches that could potentially be applied in the context of MICs; or local decision makers (country-specific experts) who have a direct experience of formulary development or reimbursement decisions in one or more MICs. In addition to the semi-structured interviews, we invited interviewees to

¹ Given the large body of literature on micro and macro formulary decision making and the parameters of the deliverable, the literature review was structured as a ‘rapid evidence assessment’ as opposed to an exhaustive review of the literature. The rapid evidence assessment was designed to capture key points surrounding the topic in a systematic fashion.

participate in a one-day workshop that took place on 13th of June 2015 in Oslo (Norway). Apart from the international and national experts that were able to participate, two industry representatives provided their perspectives and experiences during the workshop. Table 1 indicates the areas of expertise and relevant experiences of people involved at the different stages of our elicitation view process, including interviews.

Table 1

Study participants

Area of expertise/experience	Interviews	Survey	Workshop
HTA/coverage decisions in high income countries and advisor to MICs	6	3	3
Health systems in high income countries and advisor to MICs	1	-	-
Health systems and international organisations researchers	3	1	-
HTA bodies/payers in MICs	3	3	2
Life science industry	-	1	2
Total	13	8	7

Source: Authors' analysis

A survey was distributed in advance of the workshop in order to enable participants to form a view on the key points we wanted to explore during the workshop, including selected macro-level and micro-level factors, as well as other potentially relevant factors in the formulary decision-making process. Appendix 3 outlines the tasks that participants were asked to complete.

The workshop was structured around these issues and aimed at discussing possible policy approaches to formulary development in MICs, focusing in particular on their feasibility and methodological challenges. In order to identify where consensus was achieved, the same survey was re-administered at the end of the workshop. Results for both rounds of the survey are presented in Appendix 3.

All interviews and discussion at the workshop were recorded and transcripts obtained. The latter were coded by using Atlas.ti®, a qualitative data analysis software package, to identify key themes and create logic links among them. Ultimately, a framework of 83 codes was developed and 501 response quotations were populated. The next section explores the topics reflected in this final framework and includes insights.

3. ANALYSIS

The aim of this section is to analyse the evidence collected during the literature review, interviews, and workshop.

Ahead of presenting the analysis, it is worth emphasising that there exists a wide variability in characteristics between MICs, such as the level of development of the health systems, organization of institutions, people's values and expectations, and income level among others. As reflected by some of the experts interviewed, any effort to improve the allocation of the scarce resources in a particular MIC should consider these differences.

As such, our analysis does not aim at providing a definitive list of steps that should be followed by every country, but rather aims at outlining a framework of recommended elements that should be considered and adapted to each specific drug formulary decision making process.

Based on the information collected and our previous experience at OHE Consulting, we have categorized the elements to consider into five groups: macro-level factors, micro-level factors, aggregation methods, affordability measures, and organisation of the decision making process.

Also ahead of presenting the analysis, we set out the following concepts and definitions:

- **Middle income countries (MICs)**: The World Bank's definition includes countries with a gross national income per capita of more than \$1,045 but less than \$12,746 (Bank, 2015).
- **HTA** as per the Health Technology Assessment International definition: "HTA is a field of scientific research to inform policy and clinical decision-making around the introduction and diffusion of health technologies" (Health Technology Assessment International (HTAi), 2014).
- A **drug formulary** is a list of prescription drugs, both generic and brand name, that are reimbursed (totally or partially) by an insurer.
- The **functions of the health system** as: organisational structures and financing, such as approaches to link performance to rewards and service delivery arrangements; health workforce, including staff training to acquire necessary skills and planning for human resources needed; governance and regulation; and quality assessment and assurance, including introduction of clinical guidelines to encourage good practice (World Health Organization (WHO), 2007).
- **Macro-level decision-making** is defined as making decisions that concern the organisation and the architecture of a health care system. This may include, for example, elements related to service delivery arrangements and disease priority setting (Towse, et al., 2011)
- **Micro-level decision-making** is defined as focussing on resource allocation decisions for specific health technologies, such as adding a new medicine to a national drug formulary, or proposing to use particular medicines as part of standard treatment guidelines (Towse, et al., 2011).

3.1. Macro-level factors

In this analysis, Macro level factors encompass approaches for designing and organizing the health system such as configuration of service delivery, payment, incentive schemes, and disease priorities.

Such factors have a particularly important role in MICs because the majority of health systems are implementing or considering reforms, which together with changes in their epidemiological profiles such as aging populations and the rising prevalence of chronic and other non-communicable diseases, have redefined the priorities of the health sector.

Generally speaking, in high income countries (HICs), we take these considerations for granted as the basic health needs of the population, such as access to primary care, have been addressed. In this situation, the decision to include new elements in a drug formulary can be taken at the margin (a new treatment is basically added (or not) to the

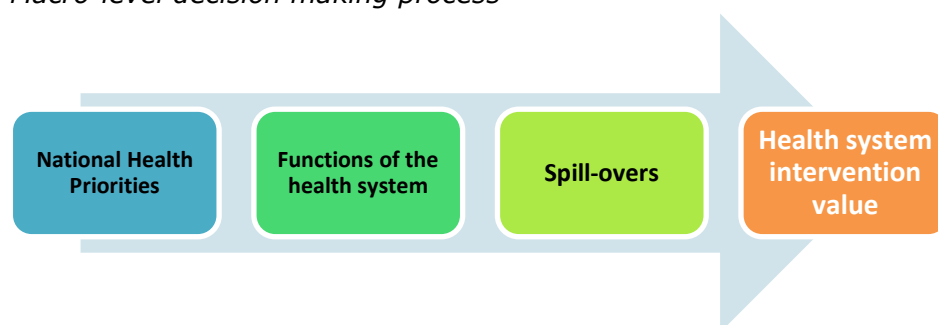
current situation). In MICs, however, where basic healthcare needs are oftentimes not met, considering a medicine in isolation could lead to inefficient decisions.

Interviewees indicate that, although important, such considerations are normally missed in the drug formulary decision-making process.

"... especially for middle-income countries it is very important that you address the priority healthcare needs of the population so there should be a link with the macro-level healthcare system. Often, as far as I have experienced, there is no link between the health priorities or the disease burden and how priorities are set at a more micro level." International expert

For our analysis we use three clusters of elements, as shown in Figure 1. First, we examine national health priorities that should be considered when selecting treatments as possible candidates for inclusion in the formulary. Some countries, such as Thailand, use this as a form of priority setting to identify which interventions that should be assessed via a formal HTA. Second, we profile components of the health system necessary to assess the capacity for providing access to the new treatment. Third, we discuss how there can be positive spill-overs of a new treatment which go beyond clinical benefits for patients and can be captured by other parts of the health system.

*Figure 1
Macro-level decision making process*



Source: Adapted from that used in the ICER Value Framework (Institution for Clinical and Economic Review, 2015)

3.1.1. National priorities

The first cluster of macro-level elements include those which consider whether or not a new treatment matches the priorities of the health system. For instance, those treatments that improve outcomes for the diseases which have the greatest current and future impact on the health of the population might be considered candidates for inclusion in the formulary. Countries might define health priorities based on political choice or systematic priority setting (e.g. disease burden). However, only the latter can facilitate an efficient allocation of resources at the micro level. Two interviewees pointed out that political and personal interests can distort decision-making (*"certain diseases are being prioritised because it happens that the President's family might have someone who has that health condition"*).

In addition to disease priorities, certain MICs are, or are planning to undertake, major reforms to strengthen their health systems in pursuit of Universal Health Coverage (UHC) and must address the question of benefit package, i.e. what types of services, products and technologies should a UHC system cover? Decisions around which drugs place on formulary would ideally allocate budget to treatments which provide the most value in terms of meeting the health needs of the population. Such decisions are

generally constrained by the goals of UHC which aim to provide adequate financial risk protection, i.e., the idea of providing everyone with some level of coverage. Therefore, in their journey to UHC, MICs might require clear statements that reflect national priorities and, from them, seek to balance benefits package with budget considerations. (Hernandez-Villafuerte, et al., 2015). Expert interviews concurred that such priority statements should be used to guide the formulary decision-making process:

"It (UHC) is about improving financial protection, reducing the gap between the need for and use of services and improving quality. It is doing that within some sort of budget constraint, so it requires some priority setting in terms of what are you going to do first." International expert

When products are either not included on a formulary or are only partially reimbursed, patients are forced to either pay out-of-pocket (OOP) or do without. Such OOP payments can be catastrophic. As such, decisions surrounding an intervention's formulary placement and coverage might consider a country's co-payment structure and potential financial impact on patients. In Thailand, for example, the public insurance scheme includes in the benefit package the renal replacement therapy (dialysis), which is an expensive, not cost effective intervention. Dialysis is included because if the treatment were not covered, patients nevertheless need its life-savings benefits and would otherwise *"bankrupt themselves"* from out-of-pocket expenditures.

Workshop participants agreed that protection from catastrophic financial risk is a very important factor in the context of formulary decisions (*"healthcare systems provide peace of mind because you are covered"*). This was reinforced by the fact that provision of financial security is also motivating the pursuit of UHC.

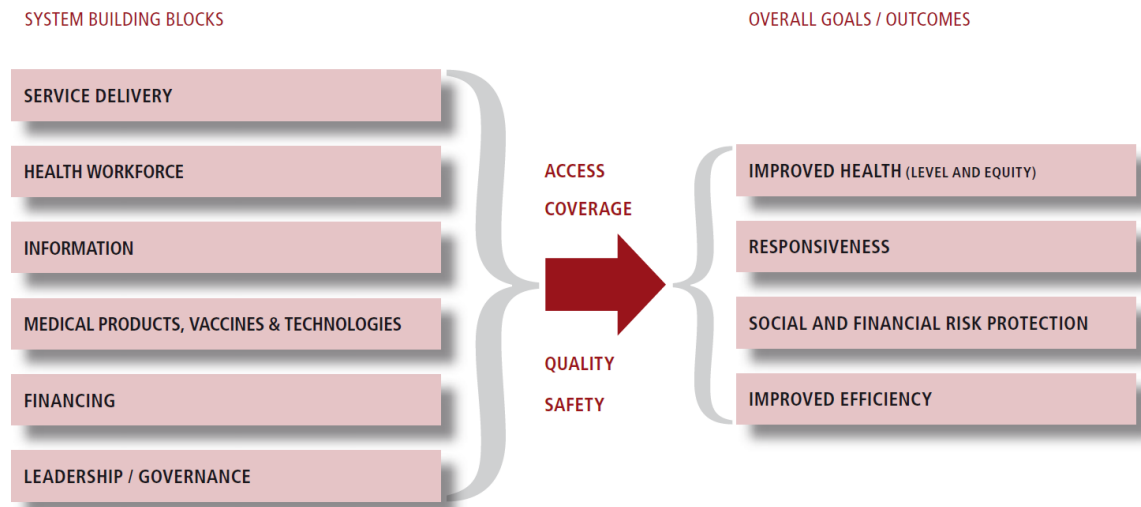
In fact, one analytical method to protect against catastrophic patient financial burden mentioned by experts was "extended cost-effectiveness analysis" (Verguet, et al., 2015). The method was developed by a group of health economists to include financial risk protection within a traditional cost-effectiveness framework. It has been recommended by experts interviewed and in the literature that degree of catastrophic health burden might be used as a decision making criteria within the context of cost-effectiveness analysis. (Norheim, et al., 2014).

3.1.2. Current functions of the health system: preparedness of the health system to provide the new intervention (WHO building blocks)

The second cluster of macro-level factors relates to the current functions of the health system. Once the treatments that match the health system priorities have been defined, a second question is whether the current health system has the capacity to provide access to the new treatment for an entire patient population in a safe, high quality way that minimizes waste of resources. Policy makers must consider weaknesses and strengths of the current health system with a particular focus on how the treatment would be provided within the existing infrastructure, including the expertise and availability of the workforce. A framework commonly used in the literature to describe the functions of the health system is the WHO six building blocks: (1) governance, (2) essential medical products, vaccines and technologies, (3) financing, (4) service delivery, (5) health workforce, and (6) health information systems (WHO, 2007).

Figure 2 shows the framework proposed by the WHO which links six building blocks to the overall goals and outcomes of the health system (World Health Organization (WHO), 2007). As discussed below, these six blocks might form the basis for the analysis of a health system's capacity to achieve the maximum benefit from a new treatment.

Figure 2
The WHO Health System Framework



Source: World Health Organization, 2007

The most commonly discussed block in both the literature review and in expert interviews was **service delivery**. Service delivery includes all services needed to diagnose, treat, and promote health surrounding a disease (Atun, et al., 2004) (Cavagnero, et al., 2008) (Frank, 2010) (Tromp and Baltussen, 2012) (Velasco Garrido, et al., 2010). If a health system does not have the elements necessary to adopt and deliver a new treatment, its potential benefits cannot be achieved.

"...adaptation feasibility issue, it is very interesting because if you want to reimburse a targeted treatment and there are no diagnostic tests available and there is no infrastructure to manage it, then it is quite a silly decision to expect any yield of the outcome from the treatment." -International expert

Closely related to service delivery is the **health workforce** block (Lee, et al., 2007) (Nsubuga, et al., 2010) (Palen, et al., 2012). More specifically, decision makers must ask if their health system has a sufficient number of workers (e.g. nurses, doctors, etc.) appropriately distributed at health facilities, who are competent, responsive and productive. The expertise of these workers and their capacity to treat all patients in clinical need is additionally critical to assess. The information available for many possible health treatments, e.g. clinical effectiveness, is based on the assumption that the health professionals have the capability to correctly prescribe and apply the treatment to the patient.

"In India... they have a huge out-of-pocket burden on medicines, so some people, including us, are pushing for free medicine schemes. On the one hand, that seems okay, but on the other it makes me really nervous about exactly what kind of medicines are going out there, who is prescribing it and what kind of damage that can do, so maybe it is not so okay in fact." International expert

In the case of the MICs, these factors are particularly important because many health reform initiatives to increase primary health and strengthen secondary care directly depend upon improving service delivery and the available health workforce. A set of quantitative indicators reflecting the current fitness of a health system's health workforce and service delivery might be considered in the context of formulary decisions.

"... you can add a separate list of criteria which the decision needs to fulfil for the drug to be able to perform or to be used. I think that this kind of separate sub-list or whatever, they need to exist. The thing here is that it is the first mover disadvantage, because if you are a targeted therapy which comes first, you need to design the system, and then the second one is already able to use that system and the third one is even easier and so on." International expert

According to the WHO, suggested indicators might include the number of outpatient department visits per 10 000 population per year; number and distribution of health facilities offering specific services per 10 000 population; number of health workers per 10 000 population; annual number of graduates of health professions educational institutions per 100 000 population by level and field of education; and others (World Health Organization (WHO), 2010). However, when selecting a set of indicators it is necessary to select only those that are relevant to the group of treatments being evaluated for formulary placement. For example, denosumab, a treatment for osteoporotic fragility fractures, is applied through a subcutaneous injection that must be injected by a health professional in a health care centre. In addition, patients require blood tests before and during the treatment (Davies, et al., 2011) (NICE, October 2010). In this case, indicators selected should measure the number of professionals in the different regions of the country who can inject the drug, as well as the number of laboratories and their capacity to conduct the regular blood tests.

With regard to **essential medical products, vaccines and technologies** (Frank, 2010) (Tromp and Baltussen, 2012), the role of country-specific essential medicines lists (EMLs) and the WHO model list of essential medicines are considered together. While some experts believe the WHO list should serve as the minimum package provided within a country and automatically be included in country-specific EMLs, others believe that the WHO list should serve as a guide-post and medicines on it should only be added if they are appropriate within the context of the specific health system, epidemiological need and align with national priorities.

"Taking flu vaccine as an example, we follow the WHO's recommendation every year, we buy the vaccine, but (our country) is located in an area influenced by the Americans, Europeans, and Asians, so every year the flu vaccine is wrong, but the officers take the recommendation from WHO.. (the WHO model list) is the old framework that should be put aside or just (used) for reference." -National Experts

"The essential drug list of the WHO covers almost many diseases and conditions, and we use that as chapters for our formulary." -National Expert

"We are talking about middle-income countries, so (..) the WHO essential drug list ..(is) what people should have access to and then we get to what else can the country afford." International Expert.

At the workshop, participants agreed with the view that there is a limited role for the WHO list ("it is just a general guidance") and that it might be more valuable in low income countries rather than middle income countries. However, they felt MICs in the upper income levels might consider the WHO list as the 'minimum package;' although, in specific circumstances, some interventions might need separate evaluation before being included on the national (or local) formulary. In addition, depending on resources available, other interventions might also be considered for inclusion.

Another WHO building block is “**financing**” which includes two elements (Atun, et al., 2004) (Cavagnero, et al., 2008) (Tromp and Baltussen, 2012) including both the capacity of the health system to protect individuals from catastrophic effects caused by out-of-pocket payments of health services, as well as options to raise funds for health.

The financing structure also has a significant influence on the creation of **incentives** in the system. Some of these incentives could affect the uptake of the new drug. For instance, some Chinese hospitals get reimbursed based on their prescription volume, which gives them the opportunity to negotiate better prices with the pharmaceutical companies and keep the margin between reimbursed price and negotiated price as revenue.

Other finance-related aspects include the total resources allocated to health and the extent of the health budget’s capacity to increase. For instance, a drug considered to have good ‘value’ may nevertheless be omitted from a formulary because its immediate budget impact is too great.

“... changing the healthcare budget or formulary ... if you talk about transportation, and we only had bicycles at one time, now we have cars and planes, should the budget for transportation be bigger than it was before? If you could not carry three things, now you can carry 30 things, would you have the same budget?” International expert

However one expert suggested that if a new medicine is deemed to be a good value it can be included into a sort of “wish list” and then funded only when additional resources are available.

Another factor mentioned in the interviews is the role of the **disease-specific funds and programmes**. Some MICs have specific funds for particular diseases, which may be partially or totally financed by external donors. Particularly in low income countries, health capacity can be expanded through resources offered as part of a specific fund or program. For instance, in some African countries the adoption of HIV programs developed the medicine counselling skills of pharmacists and pharmacy technicians, thereby benefiting non-HIV patients as well (Embrey, et al., 2009). However, care must be taken to avoid the duplication of efforts between special program resources and efforts already in place.

“When you have a vertical programme quite often there is duplication of resources in human resources and facilities. I do not know about drug procurement when you have a vertical programme, whether they still procure through a centralised procurement process or is it separate? I guess it depends on the countries and we know it is very inefficient to organise it that way.” International expert

It is worth emphasising that all of the aforementioned macro-level factors are undergoing periodic change, particularly in MICs where health reforms are actively underway. However, there are relatively static or predictable factors within which can be considered in the short- and medium-term, such as the numbers of surgeons and nurses. Other factors have the possibility to change in the medium term, such as the number of primary care facilities which are projected to grow in an effort to expand access to rural patients and take pressure off of over-crowded hospitals.

With regard to **governance**, some interviewees discussed legislative mechanisms that can hinder efficient allocation of resources. For instance, in some Latin American

countries, there are legal shortcuts that allow patients to pre-empt the formulary process and receive new medicines that are not in the national benefit package or have not been evaluated by the HTA body.

"Latin American people use the legal process to get therapy. It is not included on the list, say, the drug we need, so you go to a lawyer and the lawyer can sometimes get you that therapy through a legal mechanism. Then of course it does not matter whether it is on the list or not." International expert.

The last function refers to **health information systems** (Atun, et al., 2004) (Tromp and Baltussen, 2012). Interviewees conceded that while it was not a factor directly impacting the formulary decision-making, it was relevant later in the process surrounding of procurement and delivery.

3.1.3. Positive spill-overs generated by the introduction of a new intervention

A final group of macro-level elements for consideration are the positive spill-overs that can result from introducing a new treatment. These can be divided into two sub-categories: (1) improvement of correlated disease patterns and (2) treatment impact on the health system. First, when a specific disease is treated, there can be positive spill-overs for correlated diseases patterns. An example of particular interest for the MICs is the relationship between non-communicable diseases (NCD), such as diabetes, and communicable diseases (CD), such as tuberculosis, which have overlapping risk populations and long-term care needs (Remais, et al., 2012). There is also evidence showing that patients suffering from diabetes have a higher risk of contracting malaria (Danquah, et al., 2010). The spill-over effects of correlated disease, especially between NCDs and CDs together, is rarely taken into account during formulary decision-making processes. However, factoring this consideration in could help to better the potential value of a new treatment.

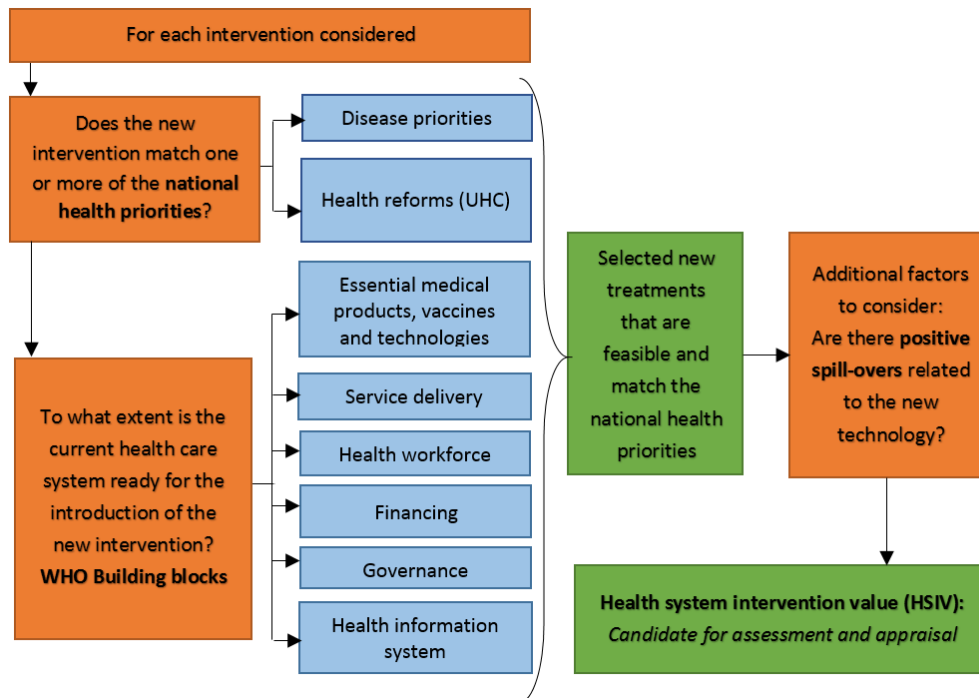
A second source of positive spill-overs is the treatment's impact on the health system. For example, the decentralization of the HIV treatments generated legislative changes in some countries in order to enable health care staff other than pharmacists to dispense medicines (Embrey, et al., 2009). This allowed the health system to deal with the lack of pharmacists and so benefited the treatment of other diseases.

3.1.4. Summary of macro-level factors

Figure 3 shows the relationships between the macro-level factors. The first question is whether the treatment matches the national health priorities in terms of structural reforms and disease priorities. Second, it is important to understand whether the treatments can be implemented given the current health system infrastructure, possibly using the WHO building blocks as an assessment framework. During this step it is important to consider that most health systems in MICs undergoing constant change and possible improvements that may impact the treatment should be considered. Finally, the last question is whether the treatments might have positive spill-overs that match the priorities of the health system.

If these considerations are made, this macro-level factor analysis could help identify those treatments that better match the national priorities, whose implementation is feasible and that could produce positive spill-overs along the health system. The result of these three elements is called health system intervention value (HSIV).

Figure 3
Macro-level decision making considerations for the introduction of a new health technology



Source: Authors' analysis

3.2. Micro-level factors

Micro-level factors refer to a treatment's attributes of value. In this section we explore possible approaches to measuring micro-level factors and experts reaction to them.

The health benefits of a treatment were, not surprisingly, seen as the most valuable attributes.

"...under the Taiwan situation, if it is as good as the current or even better than the current disease regimen, then NHIA is supposed to welcome the product. Then the next [consideration] is the financial... Sometimes they talk about equity and other things like severity or things like that, but it is not relatively very important or very rarely mentioned." National expert

Table 2 lists a robust set of such attributes of value identified in OHE Consulting's previous work, in the literature review, and in the interviews with the experts. These factors are grouped into intervention-specific, disease-related, equity, and financial factors. Intervention-specific factors comprise the direct effects of a new intervention, including clinical benefits. The disease-related factors focus on the characteristics of the disease targeted before the new intervention is introduced. Equity factors relate to the non-health characteristics of the targeted patient population. Finally, financial aspects refer to costs incurred or savings accrued by the health care system or wider economy when the new treatment is introduced (while some decision makers perceive these factors, financial factors go beyond acquisition cost).

The purpose of this section is to provide a high-level list of value attributes that can be relevant in the context of formulary decision-making in MICs, and possible concerns surrounding them. It must be underscored, however, that these factors can sometimes compete with each other (for example, maximising health benefits versus giving priority

to the most severely ill), so trade-offs between them should be carefully and explicitly considered when making decisions.

Table 2
Attributes of Value

<i>Categories</i>	<i>Attributes of Value</i>	<i>Possible Measures</i>
<i>Intervention-specific</i>	<i>Health effects/clinical effectiveness (including life extension)</i>	<ul style="list-style-type: none"> • <i>Clinical outcomes according to the type of disease, e.g. oncology: progression-free survival.</i> • <i>DALY, QALY</i>
	<i>Patient reported outcome²</i>	<ul style="list-style-type: none"> • <i>EQ-5D</i>
	<i>Treatment side effects profile</i>	
	<i>Impact on existing processes of care or care pathways</i>	
	<i>Patient convenience/ Patient opinions</i>	<ul style="list-style-type: none"> • <i>Compliance with prescribed regimens</i>
<i>Disease-related</i>	<i>Severity of health condition</i>	<ul style="list-style-type: none"> • <i>disease progression</i> • <i>likelihood of death</i> • <i>likelihood of high inpatient expenses</i> • <i>likelihood of lengthy hospital stay</i> • <i>burden of disease</i> • <i>absolute health loss</i>
	<i>Realisation of potential</i>	<ul style="list-style-type: none"> • <i>Giving similar "fair chance" to benefit from health care to all patients</i>
	<i>Size of the population targeted by the treatment</i>	<ul style="list-style-type: none"> • <i>Patient number</i>
<i>Characteristics of the target population</i>	<i>Socioeconomic status, age, ethnicity, area of residence, gender</i>	<ul style="list-style-type: none"> • <i>Gini Index</i>
	<i>Impact on non-health factors (e.g. social stigma)</i>	
<i>Financial factors</i>	<i>Cost offset (per patient) to the health care system</i>	<ul style="list-style-type: none"> • <i>Costs (per patient) of implementing the new intervention net of savings to the health system (including intervention/s displaced)</i>
	<i>Indirect costs, including impact on non-health public sectors, productivity gains, care for others (impact on individuals/ households)</i>	
	<i>Budget Impact</i>	

Source: Authors' analysis

² Included in some metrics of health effects such as the QALY

3.2.1. Intervention-specific attributes

As mentioned, the health effects of a product is of paramount importance. Given limited resources for the assessment process, this may be one of the only micro-factors that is considered.

"... what we are saying is the effort, to the extent that it is appropriate and technically feasible, is going into that health effect bit, potentially the value bit, where is the cost-effectiveness... there is a list of what matters, but in terms of what is the equity impact or what is the disease severity, that is not usually quantified for the decision-makers". International expert

The ability to appropriately measure health benefits is critical and will be discussed further. However, according to the interviewees, it is critical to consider a country's ability to collect, analyse and place clinical value into their country's context.

"I think what a lot of these countries do not have is good epidemiological data relating to their own country, so it is sometimes difficult to estimate the total health gain from using a particular medication even if you have the clinical trials that you can generalise to your own country, but you have still got to apply that relative risk reduction to some evidence, some baseline risk in your own country". International expert

While it was beyond the scope of this study to address transferability of clinical evidence and HTA decisions (i.e., data sharing between countries), we know from the HTAi Asia Policy Forum that assessment and appraisals based on transferred clinical data is considered to be more appropriate than the transfer of HTA decisions themselves, and when handled appropriately, is considered to be useful for decision making.

However, views are mixed about the use of patient-reported outcomes or measures of patients' quality of life (QOL), particularly in relation to the resources available in the MICs to collect and use them.

"Sorry to say but, no. The reason for that is that it sounds good but I have not really seen any working examples of decision-making in middle-income countries based on valid and reliable QOL data without a lot of investment prior to that. If I need to develop a formulary, I want to develop a formulary and I am not really ready to collect the data." International expert

"A lot of these countries have their own tariff for some of the generic health benefits/quality of life measures like EQ-5D; and I think in Latin America, three or four countries have their own tariff like EQ-5D, so I do not know why you could not measure some of these quality of life aspects in the way that we do in Europe." International expert

There are few MICs investing in the estimation of patient-reported outcome measures. For example, there has been some EQ-5D valuation work in Brazil, and an EQ-5D-5L valuation study in Uruguay has just been reported, but a full value set is not available. Nevertheless, while the use of patient-reported outcomes in decision making in MICs is very limited, it is likely to increase in the future as many countries are now starting to conduct valuation studies following the EuroQol Group's standardised international protocol. However, the capacity of using patient-reported outcomes will depend on the specific situation and financial resources of each country. Using other countries' tariff might not be appropriate given the substantial demographic between high income and

lower income countries (the latter having a younger population who might have different preferences compared to older populations).

The results of patient-reported outcomes also point out the use of metrics that combine mortality and morbidity, such as disability-adjusted-life-years (DALYs), to assess health benefits. Some experts suggest that DALYs are easier to estimate and more intuitive for the policy makers to understand than quality-adjusted life-years (QALYs). However, we find a mix of views, since another group of experts consider that the QALY is a better reflection of the particular conditions of the country.

"...think they would be better to use QALYs rather than DALYs for example. The DALYs are useful for organisations like WHO that are trying to get some kind of international summary of impact but within a given country if you have the tariff for one of the well-known measures I do not see why you should not use that to get QALYs." International expert

Additionally, one of the international experts pointed out that, given the lack of resources in the MICs, the marginal health benefit of a treatment should also be compared to the marginal benefits of treatments affecting other diseases, and weighted by the size of the population that will be positively affected by the treatment.

"I can take a step forward, and I think that diabetes can properly be managed. If I take, let us say, Alzheimer's, I am less optimistic because the population can be relevant, but the achievable effect with current medication is quite poor... so severe disease/ large improvement [in a] large population is good, but a severe disease/small improvement [in a] smaller population would be [an outcome] that is less attractive." International Expert

The effect of a new treatment on existing care pathways was also one of the factors that emerged during the analysis. It is important to know whether a new drug gives an opportunity to improve upon a reimbursement protocol or pathway compared to existing options. We note that this aspect might also be captured through macro-level analysis associated with service delivery capacity required to support the intervention.

Another attribute mentioned, although not considered key to those interviewed was patient convenience, which refers to those drugs that are easier to apply and could therefore increase the compliance with prescribed regimens. For instance, a drug which creates a reduction in the frequency of applications or allows for the substitution of injectable for oral prescriptions, generates patient convenience.

"I think issues like patient convenience are a little bit more controversial. If you expanded health effects to include quality of life I think in most of these countries we would not be going beyond that into things like convenience and ease of use. I think we should consider convenience insofar as it might affect quality of life and adherence to therapy but I do not think many of these countries would value convenience for its own sake." International Expert

3.2.2. Disease-related attributes

Some MICs are in the process of pursuing UHC. As a result, the size of the population that will use new drugs is likely to increase. Treatments that maximise benefits while minimizing budget impact to treat the target population are attractive, as reflected in the following comment:

"The size of the population targeted, I suppose if you think of that as some idea of the health gain you might obtain that seems to be a reasonable factor to include although obviously if you go further down the size of the patient population could also influence budget impacts, so it will be worthwhile considering the size of the population insofar as it would help us appreciate the potential amount of health gain we are likely to be able to gain from introducing a therapy." International expert

Severity of condition is an additional attribute of potential value in the decision-making process. Measures such as disease progression, likelihood of death, likelihood of high inpatient expenses, likelihood of lengthy hospital stay and burden of disease could be used to estimate the current situation of the disease.

3.2.3. Characteristics of the target population

In MICs there can be high variability within a country in terms of health status and access to the health services due to differences in socioeconomic level, geography (urban/rural), and more. Since one of the objectives of the UHC is to ensure that all people have access to the needed health care services (WHO, 2010), equity could be an important factors to consider in formulary decision making processes.

"In terms of the equity criteria I guess socioeconomic status would be probably the least important one as far as I am concerned... obviously ethnicity tends to be a major issue in many of these countries mainly because the boundaries were drawn up by colonial powers that did not really understand some of the ethnic mix that would likely to be in a given country." International expert

Moreover, each country takes its own approach to operationalizing equity. For instance, Philippines considers equity in its decision making process by taking the age of the affected population into account, but not factors such as ethnicity:

"As far as age is concerned, there is a tendency to help the people who are younger and the government released what is known as a Z package... there is no favouritism in terms of ethnicity--that is not something in the criteria for developing this equity formula; so ethnicity is not an important issue." National expert

However, at the workshop one expert pointed out that equity should be assessed as a macro-level factor and not as a micro-level consideration.

"I would be afraid to include equity here because it seems to me that we have already included factors which are very close to equity at the macro-level and I would not like to incorporate it here, from a very real life perspective that incorporating equity as a micro-level factor I think may render the technical decision-makers vulnerable to political particular interests and lobbying, whereas if we have disease priorities or demographic priorities, I think it is set at a higher level where the decision-making framework is done in a more structured and less particular way." -International expert

The final equity-related factor for consideration that emerged from the literature review was the interaction between existing social stigmas and the new treatment. Interviewees commented that this was a stronger factor in low income countries, such as those with high incidence rates of HIV, but not in general to MICs.

3.2.4. Financial factors

As reflected in Table 2, the final category of micro-level considerations is financial factors including value for money, budget impact, and indirect economic impact. Value of a new treatment in relation to the existing standard of care and budget impact will be discussed in depth. Ahead of discussing them, however, it should be noted that indirect costs, including impact on the non-health public sector and impact on individuals/households, was not deemed to be an essential consideration by our experts.

Perhaps indirect costs were not considered critical in the context of MICs, or, as one interviewee pointed out, it is not realistic to believe that countries with limited health economics capability would be able to consider indirect costs in medicines' assessments. Another interviewee suggested that they can be considered on a case by case basis when their impact on costs or benefits is substantial.

3.2.5. Value for money and budget impact

A key challenge policy makers face during the formulary decision making process is how to generate maximum value from formulary listings, in the context of financial constraint. It is therefore not surprising that experts identified budget impact as one of the most important financial factors for consideration (see table 3).

"...when you say "value", they (payers) actually do not think of cost-effectiveness at all, they think budget impact. That is what they manage; that is what they have to worry about". International expert

"... in most of the countries this has been replaced tacitly or by a budget-driven approach, so the budget impact logic superseded the cost-effectiveness logic. Socially, let us say that beneficial part of economic evaluation is practically gone. I think it was a counter-reaction to try to incorporate other elements into decision making to offset the budget impact domination...". International expert

Although critical to the decision-making process, many MICs do not have sufficient capacity to accurately estimate the volumes and prices associated with the new treatment.

"...(our) committee, they focus only on the financial impact. They ask hard questions, a lot of difficult questions regarding how this P (price) comes out and Q (quantity) comes out and how do you know how many patients would use that kind of new drug. It is so hard, even we have claims data set because the new drug, not necessarily properly coded in your comparator drugs, the users, so we have a lot of headaches". National expert

"Actually for Q there are I think at least 20/25 different techniques you can find for Q, from prescription targets, through software, through campaigns, soft and hard, but they are all fragmented". National expert

"It is hard for NHIA and us, HTA, to actually have a good estimate of how this is really cost for the next physical year. I mean, whenever I see budget impact, I have a headache!". National expert

Some experts also pointed out how difficult it can be to estimate, and ultimately achieve, the projected estimates. Factors such as the level of substitution between the new drug and the standard treatment must be precisely factored into estimates.

" I think it needs to extend more to saying what is it in the system that also needs to change so that it can actually take advantage of this type of efficiency gain. This is kind of a cost-shifting issue, so it is at what level is the budget set or what unit in the system is the budget set and where are the gains going to start to be played over who has got financial responsibility".

3.2.6. Summary of micro-level factors

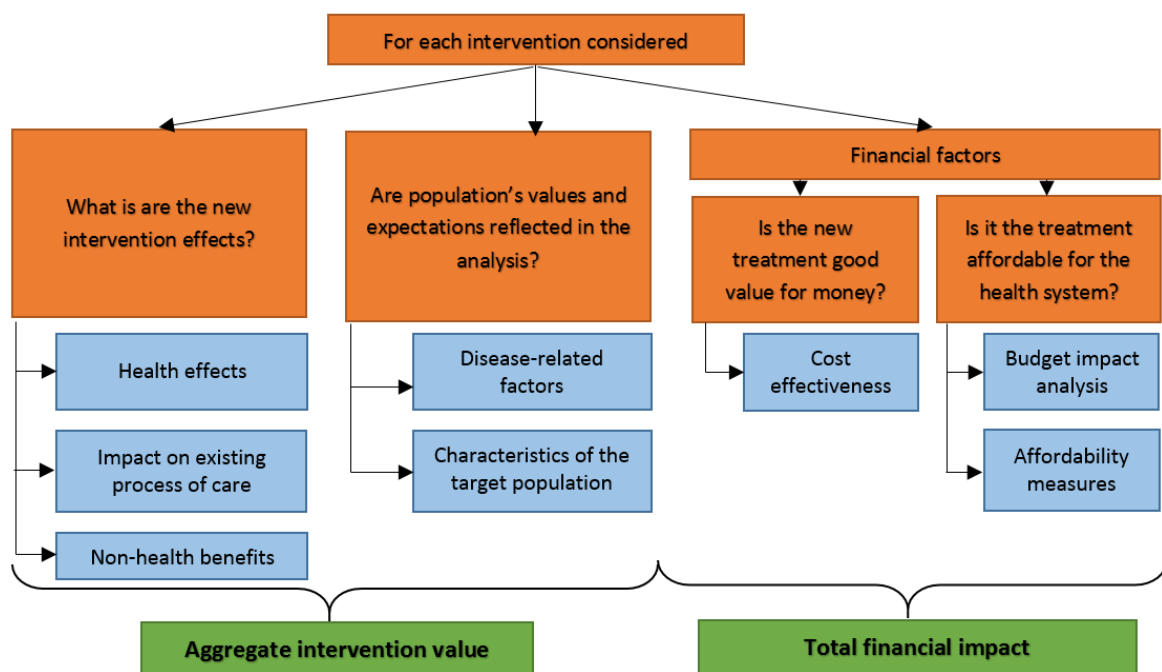
Figure 4 summarizes the interaction between the value of the intervention and financial constraints. The first part of the micro-level decision making is to identify the benefits of the new intervention by exploring the health related effects, including patient reported outcomes. Second, the population values and expectations should be considered with particular focus on the population affected and characteristics related to the disease. The importance that society assigned to these factors could tip the balance towards a particular intervention. The assessment of these two parts lead to the development of the aggregate value of the intervention.

Once the benefits of the intervention are assessed, it is important to evaluate whether these benefits represent good value for money. In this regard, one possibility is to perform a cost-effectiveness analysis or other economic evaluation.

Finally, the total budget impact of the intervention should be estimated in order to understand whether payers can afford to provide the new intervention. The objective of this part of the analysis is to allow the maximum number of interventions with significant benefits to be funded by the health care system.

Figure 4

Micro-level decision making and finance considerations for the introduction of a new health technology



Source: Authors' analysis

3.3. How to determine the overall value of medicines in formulary decision making? (Aggregation approaches)

In the previous sections we outlined possible attributes of value (e.g. directly related to health effects of the intervention, related to the condition targeted, and to the impact to the whole health system) that might be considered in formulary decision-making. Each of these attributes should be measured and relevant evidence must be provided in order to show how individual interventions perform against them. As such, the next step in the value assessment process is the identification of an *aggregation* approach which can:

- ensure that national or local decision making committees have a structure to take into account all relevant attributes of value; and
- identify competing attributes (or criteria), and define the trade offs between them.

Although this section is linked to the aggregation of micro-level factors, depending on the structure of the drug formulary decision making process, macro-level factors could also be included alongside them.

The importance of choosing an aggregation approach were echoed by our experts who pointed out that, regardless of the aggregation approach followed, the process and decision-making criteria must be clearly stated, transparent, and replicable. The interviewees agreed that, generally, there is a lack of this type of disclosure in most MICs. They also highlighted that because of the lack of structure it is difficult to deal with conflicts or divergent views between the committees' members.

"In Bulgaria they will say that we take all these factors into consideration: prevalence, social disease burden, social (...) that is the facet, nothing is being done behind it because exactly the structure is missing". International expert

"Where I think we are then is saying a deliberative process is needed... That is actually a big step forward for a lot of countries, both now and particularly if they were expanding their coverage. The second bit is the importance of an explicit framework, so everyone is clear what, in principle, is in that list and has been taken into account, and that may or may not require some legal changes to enable that to happen". International expert

"..if you ask people from Thailand, they will say we have deliberative process. I think it is not really performing that is my personal opinion.... I think these kind of things change over time; it depends on composition of people and how people say something differently in the groups". National expert

In addition to clearly stating a transparent set of decision-making criteria, the experts agreed that the next question is the extent to which the selected criteria should be explicitly measured (for example, by using quantitative indicators) and specifying the values and processes driving decision making. It emerged that experts believe that certain criteria such as the "contextual issues" (for example, political objectives) cannot be quantified and it would therefore be desirable to combine both quantitative and qualitative elements in the selected approach. The aggregation approaches discussed below represent different levels of formalising the decision making process and applying explicit measurements.

Finally, experts also agree that there is not a one-size-fit-all aggregation approach that should be applied to every country. Factors such as capacity of the country, remit of the

institutions involved, audience that will use the decision, and expectations of a society, can all inform determining the most appropriate aggregation approach and decision-making criteria for a specific country.

The following options for aggregation are based on our literature review (see Appendix 1) and our previous works (including Sussex et al, 2013). Moreover, their viability in the context of MICs at was discussed with our expert workshop and, ultimately, experts voted on the most useful and least useful aggregation options (see Appendix 4 for results).

3.3.1. Therapeutic added value (based on clinical outcomes)

The first aggregation approach is based on the German IQWiG model. The approach is focused on health effects measured by clinical outcomes to develop a “therapeutic added value” index of the intervention as compared to standard of care which can inform price decisions. In the German model, the HTA body IQWiG classifies the therapeutic added value of new drugs compared to the standard of care according to six categories that range from “Remarkable additional benefit” to “Less benefit than the comparator.” Only drugs showing an additional benefit can be priced above the comparator or the reference group price (Gerber, et al., 2011). More details on the German system can be found in Appendix 1.

This approach did not obtain any support from the experts and did not stimulate much discussion, likely because it relies only on the consideration of health benefits from clinical trials while experts felt other attributes of value and sources of evidence were additionally important.

3.3.2. Therapeutic added value and other factors via a deliberative process

This aggregation approach is based on a system similar to those used by France and Taiwan (see Appendix 1 for details on Taiwan) which combines the “therapeutic added value” index as mentioned above, in addition to a range of other factors such as equity. Moreover, these factors are considered by the committee via a deliberative process. This aggregation system is similar to the one applied in Taiwan and France.

Both before and at the workshop the experts agreed this aggregation approach was the most useful in the context of MICs decision making and they agreed that a desirable system should consider a wide range of criteria including health and non-health attributes of value. The group compared this approach with the MCDA option, discussed below. The MCDA carries this approach a step further to weight individual criteria to be evaluated in the context of a formal framework, however this concept is seen as potentially difficult in an MIC context.

“...MCDA quantification of individual elements (...) should be part of the menu, as it were, but is actually for the more sophisticated tastes, as in it is actually quite hard to do and is an extra stage after the investment in the decision making process, having a deliberative process, having an explicit framework, then the quantification part is something that could come beyond that, but when those other things were in place”. International expert

Regardless, this aggregation approach, “Therapeutic added value” and other factors via a deliberative process,” was preferred by our experts because it met the key objectives of a desirable approach as outlined at the start of this section:

- (1) it brings structure to the drug decision making process;

- (2) it can be adapted to the particular context and capacities of the country; and
- (3) it combines quantitative and qualitative aspects.

3.3.3. Collaborative approach

The collaborative approach is a variation of the previous approach where the “clinical effectiveness” assessment is conducted as part of a multi-country evaluation process, while the drug formulary decisions based on specific criteria and values of a country or jurisdiction are made at a national or local level. The key advantage of this approach is to avoid duplication of efforts in the assessment of clinical evidence that might be the same for a group of countries, and is therefore more efficient than having separate assessment processes in every country.

This approach did not gain any support or interest of the experts.

3.3.4. Incremental cost per health outcome and a deliberative process

The next approach is similar to the one used by NICE in England and Wales whereby the incremental costs and benefits per patient are combined in an aggregate measure so that committee members consider an incremental cost per health outcome of the intervention as compared to standard of care (such as cost per QALY gained). Other non-health factors can be considered alongside cost-effectiveness on an ad-hoc basis via a deliberative process. For example, NICE has developed explicit methods to assess cost and health gains but is less explicit in the way other considerations (such as severity of the condition) are incorporated into decision-making. More details on the English system can be found in Appendix 1.

As mentioned before, this “incremental approach” cannot be applied in a situation where important health needs are not yet addressed and a functioning health care system is not yet in place.

“we think the incremental approach is perfectly fine where you have a health financing system that is up and running, so like the UK or like most of Europe, and then quite a few of the middle-income countries like South Korea, Chile to some extent, Mexico, where you have a financing system that has sorted out what are the services going to cover... The difficulty is where you do not have a system that functions at all, or where you are starting up a new system, and then the incremental approach where you look at one intervention after another from all the other interventions is just not appropriate”. International expert

Some of the experts worried about the MICs applying an aggregation approach that it is not compatible with the context of the country or for which there is not enough capacity.

“ I think this is really one of the key things here, whether we can be NICE or we want to be NICE. I think the sad thing is we do not know the answer, because if we look critically at the community, then I think that the NICE approach has been positioned as a kind of flagship, as a superior type of decision making. So there is a drive to comply with NICE, there is a group pressure. I do not know if we ask around all in these markets whether they want to be NICE or they can be NICE, whether it would be an uninfluenced type of answer”. International expert

In general, the utilization of cost-effectiveness analysis in decision making in MICs and LICs is a topic of major discussion. The main concern is the level of resources and capacities needed for developing accurate estimates of costs and clinical outcomes that

could apply to specific context. For example, some MICs have important deficiencies in their health information system that result in lack of reliable databases.

"If we take cost-effectiveness, to translate it simply value for money or worth buying, it sounds so good, but all the apparatus which is behind, all the limited availability of data, all the distortion resource costs. (...) cost-effectiveness, it is so good intuitively, but it is so hard to turn into working practice that I would not certainly insist on it". International expert

Another concern raised by some experts is about the robustness of cost-effectiveness analysis when this requires a number of assumptions. In particular, it was highlighted that because the results are summarised in one metric (e.g. cost per QALY) this might hide the impact of key assumptions. This might be particularly misleading when decision makers consider the cost-effectiveness ratio in isolation while it should be considered in conjunction with other attributes of value.

" it is not fixed, set in stone. Even if the outcome of the cost-effectiveness is uncertain or maybe not effective or cost-effective, then you could argue it is a value from our society that we want to have negotiated because we want to give the access to the patients...Even on your micro it is a negative outcome, but from the system level it can be a positive outcome and therefore I like your remark that you should take the whole process into account". International expert

Moreover, it was felt that even in those cases where the onus to develop cost-effectiveness evidence is on the manufacturer, there might be lack of capacity to assess the quality of the submission. Nonetheless, there are examples of successful engagement between manufacturers and decision makers to share information and knowledge. For instance in Taiwan, there has been a cooperation between the assessment agency and companies to share data and projections on the financial impact of treatments.

Despite the aforementioned limitations, a number of the consulted experts considered cost-effective analysis as a helpful tool to discriminate between treatments. In a context of limited resources, such as in the MICs, it is necessary to identify those treatments in the same therapy area that are more cost-effective in order an effort to avoid the coexistence of more cost effective treatments together with less cost effective treatments aimed at treating the same condition.

"The formulary has been there for some time and there are often first line generic drugs available in the market, and if there is a new drug that wants to come in, it must prove that it has additional benefit for its price to offset the first drug that is already in the formulary. If a new drug wants to come in and they assess to be much better it will then come in but the other drug that is less cost effective will have to be removed from the formulary. If there is a new product, like an innovator drug, then there is a different assessment for the drug and it will be compared against known patient outcomes, based on clinical studies". National expert

This explains in part the increase in the use of the cost-effectiveness analysis in the MICs context. For instance, the Thai agency HITAP is primarily working around health benefit and cost-effectiveness aspect. For more details on the Thai system see Appendix 1.

There is great controversy on how to include the results of cost-effectiveness analysis into formulary decision making. In general, economists believe that the decision should

reflect the opportunity costs of financing the new treatment. Therefore, some experts argue in favour of the definition of a threshold value that reflect the opportunity cost for the society, while others consider that a threshold is a subjective measure that does not reflect the real opportunity cost of the intervention.

"If you take the cost per QALY, there are huge debates about where we put the thresholds and how do we interpret the thresholds and what is the value, for whom is the value and how did we come to this threshold". International expert

"...the current way that opportunity cost is being addressed is by a threshold...there is controversy about the WHO's benchmark and some of the attempts to develop thresholds locally in these countries. In most of the ones I deal with the starting position is to use the WHO guidelines of between one and three times GDP per capita, but I find that there is a lot of decisions that would be within that range so it is difficult to know whether you should say yes or no". International expert

Some experts pointed out that it is important to reflect how activities within the health care system are displaced in practice in order to fund the new intervention, in other words which parts of the health system will be directly affected by the adoption of the new intervention. An explicit and systematic approach to consider this would prevent the displacement of health services, such as health prevention, that although high cost-effectives might be cut to finance new treatments.

"...the decision-making process on what to cut is much less than rational. Unless you get into the choice type analysis of going forward and going backward, so not just looking at what you recommend but what you actually cut". International expert

"Those people will make the decision that is the least politically damaging for them or there is going to be the least public outcry so that when they have to cut, they are more likely to cut prevention or population prevention or things that do not have a big possibility of leading to political problems locally, rather than actually what is best for population health". International expert

"...the front page headline in the newspaper is much more powerful than advocating for prevention. You know, I still think that one of the powers of this analysis, if you do what you give up as well what you buy, is showing what you give up by buying something... I think what often gives up is the prevention. That is a problem in most countries now with the ageing populations because they are going to have amazing costs of treating cardiovascular diseases 15 years down the road unless they start taking prevention seriously". International expert

3.3.5. Multiple criteria decision analysis (MCDA)

An MCDA approach involves selecting attributes of value, weighting them according to their relative importance, scoring each medicine against the selected attributes and determine a final score. The weights can be based on the decision maker's or multiple stakeholders' preferences. For example, in Colombia a pilot applying an MCDA approach to support the decision making process of the national HTA body (IETS) has been conducted and reported as useful (presentation by Hector Castro at the 2015 HTAi meeting).

Key advantages of MCDA pointed out by the experts were: it includes a broad number of attributes of value, it provides a clear structure, and because it makes the weights

explicit it allows for a more transparent decision process. Nevertheless, the sophistication of the process needed to derive weights and combine them with the scores is seen as a disadvantage that could hinder the application of the MCDA in MICs. This was probably why the MCDA option lost support amongst the experts after the workshop as compared to before the workshop (Appendix 4 presents the results of the survey).

"I do not think the ultimate aim should always to have an MCDA, so it really depends on (...) what works for the country". International expert

"I would not use MCDA... because it has a connotation, it has an association which implies something complicated". International expert

"..there are some connotations of (...) (the term) MCDA (...) that are quite challenging even though it can be simplified. That is why I thought it might be good to have MCDA (or whatever ...) to be optional or in the second part of a deliberate process, because the key of MCDA is to have a more structured deliberative process ". National expert

3.3.6. International benchmarks and transferability of information

One major constraint on the ability of MICs to develop a structured drug formulary decision making process is limited capacity to correctly estimate the attributes of value. As such, experts suggest that the type of evidence to consider should be driven by a country's capacity to collect and analyse primary data and appropriately adapt the context of secondary results produced by other countries, be this clinical evidence, costs, or data in pre-structured models, to its own context.

There is a particular interest in the topic of transferability of clinical outcomes. While some experts consider clinical outcomes less dependent on the particular context than costs, others do not and are concerned that modifying clinical data could compromise the robustness of any model results.

" ... let us put aside the development and the generation of the evidence and the assessment element, focus on appraisal, decision making and following the money in your own healthcare system. Because everyone is investing in those first two steps, when really you can probably get away with utilising other quality sources and doing it, recognising the transferability element". International expert

One of the factors that experts believe could hinder the transferability of the external data and results is the difference between the comparator used in the external analysis and the current standard of care in the country.

"In those countries we studied that was the major frustration, that the stuff they were getting from companies was an adaptation of an international model but did not really help them in their setting because the current standard of care was different from the one that was compared to in the model". International expert

Nevertheless, there is a group of pragmatic experts that believe that, even if the country is not able to deal with the problem of transferability, it is better to use the available information from other countries than not have any evidence to inform a decision about the inclusion of a new drug on the formulary.

"I think that whenever there is local primary evidence, we are happy about it, but the non-existence of primary evidence does not mean that we cannot decide about the drug... If I want to solve a healthcare issue, if I want to develop a

formulary, if I want to provide access to patients, to new drugs, I am not going to spend too much time on this; I am going to take international benchmarks".

International expert

Moreover, the decision to use external information is not only about data, but also about final recommendations. Although there were not views related the advantage of one option over the other, the interviewees suggested that MICs are actually using both secondary data from, and final decisions of, other HTA agencies as part of their decision process.

"It is a question whether you want evidence collected in other countries or you take reimbursement decisions or health technology assessment in other countries as proxies for that evidence. I think that you can be extremely simplistic and you can take the second approach. If someone has decided that this is worth buying, then it is a proxy for me that it may be worth buying for me as well and I may have a second look, and we have a double check of the local set up, patient numbers, ethical ideology..., but not necessarily via model, not necessarily via primary health data". International expert

"Thailand... they use I think pretty much the same as Taiwan in terms of literature. In terms of access to national data, in some situations they have access and they can use it but some they could not and they use some sort of primary data collection based on expert opinion". National expert

"Taiwan... people know that we refer to the NICE and CADTH reports a lot, but actually our assessment reports now describe the present therapy, the current status of treatment, treatment patterns in Taiwan situation". National expert

"Philippines...because we do not have a local database, we then rely on published clinical trials from, says, the region or from other countries as a basis for our decision. It is not a perfect system but that is the way things go for the moment". National expert

Finally, when relying on secondary data from other countries, some experts raised concern about lack of transparency surrounding criteria used. It is therefore recommended that, where secondary information is used, decision-making criteria from benchmark countries must be explicitly stated.

"Each decision-maker acts entirely implicitly. The point here is that it should be done explicitly. It is not an acceptable way of decision-making that you look at Italy, I look at France and then we say something. We should publish which are the peer market countries, why they are peer markets, and what indicators, what benchmarks we are going to take into consideration". International expert

3.4. Affordability – viable policy options to take into account budget impact in formulary decision making

As mentioned above, policy makers are constrained by budget impact in their decision making. Nevertheless, it is possible to address financial constraints by including affordability measures designed to relieve financial burden in the decision making process. During the expert interviews we explored possible methods designed to decrease or manage budget impact, thereby increasing the probability of adopting beneficial new treatments during the value assessment stage. Table 3 summarises the explored approaches.

Table 3
Affordability measures

Affordability measures	Examples
<i>Measures that Affect the Volume Uptake</i>	
(1) Sub-group of the patient population/ "Appropriate use" rules	<ul style="list-style-type: none"> • Different reimbursed levels by disease or by social group • Reimbursement only for the sub-population for which the treatment is more effective (e.g. NICE in England)
(2) Alignment with clinical guidelines if available	<ul style="list-style-type: none"> • Russia introduced in 2000 an outpatient drug package that was linked to clinical guidelines around four conditions that they saw were driving unnecessary hospital admissions
<i>Measures that Affect the Price Paid</i>	
(1) Rebate schemes involving volume caps	<ul style="list-style-type: none"> • Australia and France use price-volume (revenue cap) agreements
(2) Managed entry agreements (MEAs)	<ul style="list-style-type: none"> • Outcome-based agreements • Coverage with evidence development when there is uncertainty about: (1) health effects/clinical outcome, (2) budget impact, and (3) population to be affected

Source: Authors' analysis

Some measures that affect the volume uptake, such as clinical guidelines, are designed to control budget impact by influencing physician prescribing patterns.

Volume uptake can also be affected by limiting reimbursement to those groups for which the treatment is more effective. This can work if the country has the capacity to correctly identify subpopulations for which the treatment is more effective. Another volume control mechanism is to assign different levels of reimbursement to sub-populations based on non-health attributes such as equity or disease groups, however concerns were flagged that such controls could suffer from the possible influence of political interest.

One expert emphasised the important role of clinical guidelines in ensuring implementation of formulary decisions. However, workshop participants agreed that, in the context of MICs, clinical guidelines are generally not available, so, in the short term, cannot be used as a tool to limit volumes.

" (What) I have seen in a number of countries is that there is a clinical guidelines framework and then there are final single reimbursement protocols which are stricter than the guideline but they are in line with the guideline. Then they serve as a tool to prioritise, to fix populations, to defer treatment to a certain extent, but based or in harmony or in alignment with the clinical guideline. I think this is why a clinical guideline is crucial, because if it is not there then the reimbursement decisions/ rules/ restrictions are not going to be clinically acceptable or fair". International expert

Other measures aimed at affecting prices include price-volume agreements, whereby the price paid is tied to the volume utilized, and managed entry agreements, including outcome-based agreements. While managed entry agreements were the most commonly

mentioned, experts expressed their concerns about the capacity required to successfully implement such contracts.

Other measures to tackle affordability that were suggested by experts include:

1. Assessing the overall value of the interventions (based for example on the attributes of value outlined in the previous sections) and then comparing it against the total budget impact of the intervention. Payers/ decision makers might be willing to pay a "budget impact premium" for those interventions with high incremental value versus the standard of care;
2. Programme budgeting;
3. Managing the budget for particular disease areas for example, managing a ring-fenced budget for tackling HIV. Currently, Colombia is testing the feasibility of this approach;
4. Budget impact scenario analyses: for example, different volumes or sub-populations.

3.5. Organisation of the decision making process

We have listed and discussed the macro-level factors, micro-level factors and possible aggregation approaches collected during the interviews and the literature review. However, as we mentioned at the beginning of the section, the particular context of the country is the key element that shapes the framework in which these three factors are interacting. In this respect, the organization of the decision making process is crucial. The division of responsibilities between different institutions and the number of steps in which the decision making process is split are the main drivers. For instance, the aggregation approach could vary when the treatment assessment and the final decision of including (or not) a drug in the formulary are the remit of two different institutions, in comparison with the case when there is only one responsible for both processes. Similarly, the price setting process can significantly impact considerations surrounding budget impact, affordability measures, and the interaction between health impact and costs effects.

The interviews provided different perspectives regarding the elements of the decision-making structure for consideration that will be discussed in this section. It is worth noting that some of the comments refer to the ideal organization system while others refer to the current situation. Both are important considerations in the context in which the implementing reform.

In general, the comments suggest that the decision making process is usually organized in different stages. For instance, in Taiwan the final decision is taken by the National Health Insurance Administration (NHIA), but when the NHIA committee does not achieve agreement, it is the Ministry of Health who decides whether the new treatment is included or not. Moreover, in Taiwan value attributes are evaluated first in determining whether a new treatment is worthy of listing, and pricing and the reimbursement decisions follow.

"Taiwan...I should say that because their decision is to agree or disagree the recommendation by NHIA, so if there is a very difficult decision no one wants to pick up so everyone sticks to their opinion, a final solution is sending this problem to our MOHW, to our minister for his final decision. We have two or three cases actually sent to our ministry. If there is consensus it is easy, so everyone is

happy. If there is no consensus and there is a very diverse opinion, then it will go to MOHW. Of course, MOHW will not make a decision on item basis, so they would ask NHIA to find some solution to solve the situation. It takes a lot of time to negotiate". National expert

Nevertheless, a few experts suggest that there is no major benefit in separating value assessment from the final listing decision. However, expert opinions vary regarding the interaction between value assessment and pricing/reimbursement decision. This may be partially explained by differences in the way finance organizations are structured within a health system. In some countries health provider, payer and budget-holders are concentrated in the same institution/health body. Other countries show a decentralization and budget allocation decisions may be made by separate institutions/health bodies than formulary decisions.

"In the international context they talk of appraisal as what they do and assessment is an input into the appraisal, so I think one organisation can do both. As far as pricing, that is often handled by the people who manage the budget and the entire healthcare system, so that is usually different people and, again, the HTA assessment and appraisal can feed into a pricing reimbursement position. It does not have to be same set of people". International expert

"We are beginning to see a blurring of that in the western world, with the use of HTA as price negotiation. It seems to me a bit artificial to separate the assessment from the pricing and reimbursement decision. I think the assessment should be done as independently as possible, that is certainly true, but why should we not allow the people making the pricing decision to use the cost-effectiveness study to help them decide what is a reasonable price to pay?". International expert

The next question is who should select the value attributes to be evaluated? This is perhaps the most difficult question to answer in a multi-stage decision making process, as the results of each stage affect the decisions in the others and if the value attributes differ between stages it could lead to incoherent decision-making. However, this does not mean that every attribute of value should be equally analysed at each stage of the process. For instance, it could be desirable to focus more on the macro-level factors during the prioritisation of the treatments than during the individual assessment. It could also be recommended to prioritise the budget impact and possible affordability measures during the pricing and reimbursing decision. A possibility could be, first, to clearly define the objectives and attributes of value for each stage, and second, to find an agreement between the different institutions in terms of concepts and importance of the attributes. The essential consideration is to ensure that final inclusion and reimbursement decisions avoid satisfying particular interests or reflecting value judgments of a particular group or institution, and instead meet the population's values and expectations.

"if you go to a government agency and they say, "This is my remit to look at safety and efficacy and this is how it is defined, that is my job", and you cannot get them to do anything else. In a sense, if you were saying here is a range of options for these processes in middle-income countries, maybe we have to think about should there be a well-defined remit or should there be independence? What should be in the remit? What should be left to a higher level body that they might provide input to?" International expert

"How do we come towards decision making within a specific context, either on a macro-level or within a hospital or on a micro-level... often we forget that indeed in some countries the decision about introducing a technology is not made by the HTA agency, but in our case by the Ministry of Health who could have also different value judgements, I would say, about whether or not to introduce a technology, even though we as a country adhere quite well to the principles that we mentioned before about how to do HTA in the proper way". International expert

Another question is whether decision making groups within a health system are organized such that the most appropriate group is positioned to influence policy that will eventually impact the health status of the population.

"So if you take a country like Mexico the ministry does have its basic list of drugs and it does have some kind of oversight for the whole healthcare system. If you talk to people in the ministry they feel they have some impact but you have a large social security system that basically has got its hands on 65% of the budget. So the question is who should have the HTA infrastructure should it be the Ministry of Health or should it be the social security system which is really making most of the important decisions". International expert

3.5.1. Expert committee

Part of the organisation of the decision making process is the composition of the committee that takes decisions.

"I think cost plays a major role. It depends on the committee's composition as well. That is why when the composition has changed, new people come. Of course, you mentioned that Thailand has (done) some research on MCDA before that was in the previous committee, but at this current committee, I was there for presenting my research, and I do not see any deliberative process. It is not cost-effective or it is cost-effective". National expert

"First of all, currently we have two committees, so I focus on expert committee because of their deliberative process... The later committee, they focus more on financial impact and mostly money. I wish they (expert committee) had a framework to discuss with, but currently they had this sequencing that they discussed effectiveness and then list it or not and then the price... Not every case they would think of a feasibility issue, because a lot of experts sitting in the committee, some of them are working with this committee for 20 years now, so there is an implicit rule in the room". National expert

Decision-making committees tend to undergo continuous change and operate under a set of implicit rules that could be a reflection of past practices. Moreover, as in all organisations, the background of committee members can influence deliberations possibly more than the actual objectives for which the committee was created. These biases can be particularly problematic in systems that lack structure, and result in the committee utilizing attributes of value that don't necessarily match what society values most.

"Some of them have been committee members for almost ten years and some of them are new. Some of them do work in medical centres or other specialised positions, oncologists and a couple of health economists. Almost 30 people form

this group... Over this 20 years they have developed very complicated pricing rules and other decision rules of the decision-making process". National expert

3.5.2. Stakeholders involved in developing a national drug formulary

When considering stakeholders in the decision-making process, findings from our study suggest that MICs should take two elements into consideration. First, although it is desirable to consider all sectors that will be affected by the decision, the more stakeholders, the more complex the deliberation can become and the more difficult it could be to achieve a consensus. This could both delay the inclusion of new treatments and increase the level of resources needed during the evaluation process. Therefore, while it is important to make balanced decisions, efficiency in decision making should be a consideration when selection the number of stakeholders to involve.

"(...) stakeholders have so many fragmented interests that the stakeholders themselves are an obstacle because they compete for limited resources, and this is true for patient organisations. When I have this kind of decision-making role, I could very well play patient organisations against each other just so that they killed themselves instead of me having to take a bad or a sad decision". International expert

One option might be to include all interested stakeholders during the evidence collection and assessment process, but then limiting the actual decision-making power to a smaller group.

"One strategy, I think, is to involve these people with shared development of decisions, but they are not part of everyday decisions. Strategy two is to involve a wider range of stakeholders into everyday decisions, but with consultation rights and not necessarily decision rights. Option number three is to have a differentiated voting system where you can assume that certain stakeholders are not budget holders, and if the decision results in a high budget outflow, extra budget outflow, then you need a strong majority, not 50 per cent plus for example, but 70 per cent plus for votes, in order for a positive decision". International expert

According to the analysis, a second factor to consider is the degree of trust between decision makers and certain stakeholders such the manufacturers. The level of trust could potentially impact application of sophisticated methodologies to measure and aggregate the attributes of values as well as the degree to which parties are able to feasibly collaborate to facilitate access to new treatments.

"The level of mutual distrust between manufacturers and decision-makers in these countries is much higher than in countries like the UK... I think it leads people to more simple solutions on approval than some of the more sophisticated that we (western countries) have because some of the more sophisticated ones rely on some kind of mutual trust and respect between the parties because they are complicated deals". International expert

"In a lot of middle income and lower income countries, there is more corruption involved in governmental processes". International expert

The following is a list of the stakeholders mentioned by the interviewees that should be considered during the decision making process:

1. National policy makers: the Ministry of Health was the policy maker most mentioned during the interviews. Additionally, the experts agree on the importance of including all relevant governmental agencies in the process.
2. Healthcare providers and payers: in cases where the government is not the main provider or the main payer, these institutions should also be involved in the process, e.g. social health insurance companies.
3. Industry associations: industry was also considered a key stakeholder. The participation could be in the form of a trade association, or the manufacturer of the technology. Some of the experts also observed the possible influence of the pharmaceutical industry on the clinicians and the patient associations.
4. Clinicians and health experts: for example, clinical associations, representatives from the medical profession and clinicians involved in the treatment of the disease.
5. Academic: during the assessment of the new technology.
6. Civil society organisations.
7. Patient associations: this was the stakeholder group mentioned most during the interviews.

4. OVERVIEW OF THE DECISION MAKING STAGES

Based on the expert opinions, the literature review, and our previous experience, it is possible to break down the decision-making process into four elements: (1) nomination and prioritisation; (2) assessment of selected interventions; (3) appraisal of selected interventions; and (4) financial assessment. (Table 4). Depending on the structure of the decision-making process, these stages could be the responsibility of a single committee or be divided among different committees or health institutions. The decisions could be taken, in the case of a tax-funded or single insurance fund, by a central government or decentralised across local administrations on behalf of the single payer, or, in a pluralistic system, assigned to multiple payers or insurance funds. If one of the objectives of a country is to consolidate or coordinate the “basic” package of insurance funds to provide some uniformity of provision of health care, then central assessment and appraisal of interventions might support that. However, regardless the structure of the decision-making process, the four elements should be set up.

First, macro-level factors will be important particularly during the nomination and prioritisation stage (Table 4 row 2), as macro-level factor analysis will allow decision makers to target the most feasible interventions that align with national priorities.

The second element of the decision-making process is the assessment of selected interventions (Table 4 row 3). In this case, the focus should be on the analysis of the micro-level factors, particularly the estimation of an aggregate measure of value of the intervention. Depending on the country’s resources, this can consist of a cost-effectiveness analysis or other economic evaluation but should also include consideration of the relevance of the other attributes of value discussed in section 3.2.

Once the drug value has been estimated, the committee responsible for the final decision should appraise both information from the macro-level analysis at the prioritisation stage

and the micro-level analysis from the assessment to decide whether the drug should be included in the formulary or not.

The final stage of the decision-making process shown in Table 4 is the financial assessment and appraisal when possible measures to make an intervention affordable are considered. The objective should be to maximize the number of treatments included in the formulary that resulted in high value in the macro and the micro assessment given the resources available.

We present the UK system as an illustrative example of the stages indicated in Table 4. The first stage is represented by NICE topic selection which is the process for identifying the interventions that will go through a NICE Technology Appraisal process. NICE is a non-Departmental Public Body, which means that it responds to the DH but it is independent from the government. Prioritisation criteria include "consideration of the population size, disease severity, resource impact and the value that NICE could add in carrying out a technology appraisal" (NICE website³). We note that health problems affecting certain subgroups that, for example, result in social stigma are also mentioned as factors to be potentially be considered. There seems to be a focus on micro-level factors. Although there is a mention of "significant impact on other health-related Government policies" as a possible criteria for prioritisation, it is not clear how this is incorporated and whether it has been invoked to date.

The assessment stage is conducted on behalf of NICE by independent organisations (academic centres) who collect, develop a cost-effectiveness model and/or review evidence provided by the manufacturer/s. Appraisal Committees are responsible for developing a view about whether the technology under examination represents good value for money. These decisions are based on a threshold, explicitly stated in the NICE method guide, representing the value of benefits forgone as a result of adopting the technology. The outcome of the appraisal is a recommendation on the most appropriate use of the technology within the English NHS. The NHS constitution formally specifies that patients have the right to receive treatments recommended by NICE in its health technology appraisal guides. This is in line with the mandatory nature of these NICE recommendations (Cerri, et al., 2014) (NICE, 2014).

The aggregation approach is based on a deliberative process of the appraisal committees. We note that the appraisal stage tend to focus almost exclusively on micro-level factors, particularly on the estimation of the incremental cost-effectiveness ratio (ICER). The other element of benefits that is considered (and explicitly mentioned in the NICE guide to methods) is the proximity to death of the patient and effect on survival that a new treatment has (End of Life policy). Other factors that have been indicated as playing a role include disease severity, disadvantage population and children (Rawlins, et al., 2010). However, those appear to be taken into account only on a case-by-case basis.

The Department of Health and the Secretary of State for Health are responsible for the management of the health system as a whole. Nevertheless, after the Health and Social Care Act 2012, some important functions and decision were transferred to the NHS England such as the overall budgetary control. (Thorlby and Arora, 2015) (Boyle, 2011). Therefore although NICE technology appraisal guidance are mandatory, budget impact analysis is addressed separately at the national or local Commissioner level where

³ <https://www.nice.org.uk/about/what-we-do/our-programmes/topic-selection>

budget holders identify priorities and make funding decisions. This has led to concerns over a potential disconnect between NHS broader priorities (i.e. patient experience of care), objectives pursued by the HTA body (i.e. maximising QALY/health gains), and budget holders' service priorities where affordability concerns become predominant.

Some affordability measures are, however, defined at the central/national level at the appraisal stage (although led by a separate committee). For example, Patient Access Schemes (PAS) can be agreed between the manufacturer and the Department of Health (DH) when a treatment does not prove to be cost effective (i.e. the ICER is higher than the pre-defined cost-effectiveness threshold). The most common type of PAS is a financially-based scheme (Puig-Peiro, et al., 2011)

Table 4
Decision making stages

	Decision making stages	Breadth of factors to consider	Value assessed	Decision on:	
	Nomination and prioritisation	Macro-level factors	Health system intervention value (HSIV)	Interventions to be assessed and appraised	
How stages are allocated and managed (process) varies from country to country	Assessment of the intervention	Micro-level factors	Aggregate intervention value and value for money	Recommendation for inclusion (or exclusion)	Decision making approaches (aggregation) varies from country to country
	Appraisal of the intervention	Micro-level factors	HSIV	Decision of inclusion (or exclusion)	
		Macro-level factors	Aggregate intervention value and value for money		
	Financial assessment	Budget Impact analysis	Financial sustainability	Affordability measure/s	

Source: Authors' analysis

5. DISCUSSION - IMPLICATIONS FOR DECISION-MAKERS IN MICS

There are four dimensions that should be considered to reform current formulary decision-making in MICS:

1. **Breadth of factors** to take into account to determine the value generated by new medicines: it is key to select "macro" factors that linked to health system objectives, such as UHC, as well as "micro" factors;
2. **Depth of assessment**, which refers to the approaches used to measure health benefits and other attributes of value, and the type of evidence used;
3. **Decision-making approaches**, which includes deliberative versus more structured methods to combine the factors assessed, and determine an aggregate measure of value to compare against the associated costs to implement the new intervention;

4. **Process**, which is related to how the tasks described above can be allocated across health actors (for example, independent health bodies) and to what extent they should be separated (for example central vs local assessments and decision making).

We discuss below possible ways to operationalise these dimensions, which will need to be adapted and combined depending on the characteristics of the country and on the type of benefit package.

On the **breadth of factors**, we have listed and analysed an extensive range of factors that policy makers can take into account (section 3.1 and 3.2). Given that many MICs are in the process of introducing substantial reforms to their health care system, it is crucial to ensure that formulary decisions are in line with those reforms and the objectives underpinning them. Experts consulted agreed that it is important to establish a formulary decision-making system that embraces a broad range of factors and does not consider health-related effects of interventions in isolation.

One way to ensure that macro-level factors (discussed in section 3.1) are taken into account in formulary decision-making is to set up a “prioritisation” or “targeting” process which could select the interventions that are deemed worth assessing and appraising in more depth to develop a formulary decision. At this stage, it would be appropriate to consider macro-level factors to understand:

- whether the new intervention can help tackle a condition which is seen as a national priority (either currently or whose burden is projected to increase);
- the extent to which the new interventions can be effectively introduced into the current health care system (given the current infrastructures and skills of the workforce); and
- whether the intervention can have positive or serendipitous effects (such as creating economies of scope within the health care sector) which could facilitate the achievement of health system goals (such as training for health care staff to deal with a specific disease that can be applied in other areas as well).

In Thailand, prioritisation of health topics is conducted by a panel comprised of representatives from four stakeholder groups (health professionals, academics, patient and civic groups). The panel selects at least ten topics yearly for assessment according to six prioritization criteria (Mohara, et al., 2012):

- size of the affected population;
- severity of the problem;
- effectiveness of the interventions;
- variation in clinical practice;
- economic impact on household expenditure; and
- ethical and social implications, including problem of marginalized and rare diseases.

After the selected topics are approved, economic evaluation and budget impact analysis are conducted by two health policy research institutes – the IHPP and HITAP – in collaboration with external experts. Other HTA bodies, such as NICE, have similar selection processes. This can ensure that detailed assessments and appraisals are only conducted for interventions that in principle are likely to have a significant impact on the

health systems. Compared to the existing processes, we recommend a stronger focus on the functions of the health system, including service delivery and treatment pathways, that can be influenced by a new intervention.

The selection of the criteria to consider in such a “prioritisation” process could reflect the preferences of the general public or, more specifically, of the populations in need (patients) or of payers’ representatives. Theoretical justifications have been provided for all options but the choice of the most appropriate approach remains normative. What we emphasise here is the need to ensure that the criteria included at this stage of formulary decision-making are consistent with the broader objectives of the health system (which could be not only to maximise the level of health but also to ensure an equitable distribution of health and other objectives related to the socio-political context). One way to start is to develop a comprehensive list based on existing literature and past experiences in the country, and then further elaborate on the basis of stakeholder consultation (Baltussen, et al., 2010).

On the **depth of assessment**, we outlined existing approaches, mainly referring to methods to measure health benefits (such as the QALY), and emphasised the challenges of applying certain methods in the context of MICs with limited resources and limited health economics expertise. As such, experts suggested that the type of evidence to consider should be driven by a country’s capacity to collect and analyse primary data and appropriately adapt the context of secondary results produced by other countries, such as clinical evidence, costs and models to its own context.

Initiatives operating within wide geographic regions could facilitate the development of common methodologies to conduct assessment of clinical evidence. In Europe, EUnetHTA has developed a “Core Model” outlining key elements (or a reference case) for assessors to generate robust cost effectiveness evaluations. Those common guidelines are particularly useful in countries with limited local expertise in health economics.

For other attributes of value (micro-factors discussed in section 3.2), the complexity of the approach used to measure them will depend critically on the level of resources available to conduct assessments. Norheim et al. (2014) provides a checklist of criteria that might constitute other health system goals, such as reduction of inequities and financial protection against illness costs, and refers to a number of ways to define and incorporate them in cost-effectiveness analysis (NICE, 2014) (Verguet, et al., 2015). We note that even if technical approaches exist, in many cases decision-makers in MICs might opt for more pragmatic approaches allowing them to measure relevant attributes, using categorical approaches, and score interventions accordingly (Youngkong, et al., 2012).

The **decision-making approach**, which relates to the method used to combine all the relevant factors, and is sometimes referred to as the appraisal, is an important element where major improvements to the current systems can be achieved. Our experts agreed that many decision-making systems are not very consistent and systematic in the way they appraise evidence and take simultaneously into account multiple—and often competing—objectives. The two key options that we explored in the report are: a deliberative process which would give committee members large scope to exercise their judgement (and make exceptions) to develop formulary decisions; and a more structured options which would still leave room for judgement but within a clear appraisal framework, including explicit criteria with explicit weights to express how they might be traded off against each other (e.g. how much in health benefits is the decision-

maker willing to give up in order to, for instance, address the severity of the condition), and clear justification is provided when exceptions are made. The latter option might involve some forms of MCDA such as those piloted in Thailand and Colombia.

Our experts expressed a preference for the deliberative process option—perhaps to ensure that “softer” criteria, such as political and contextual issues that cannot easily be quantified, can be still taken into account. However, they strongly supported the development of clear “structure” specifying and describing the criteria to consider. This might be considered as a partial form of MCDA that could involve a clear and explicit definition of the decision problem and of the criteria deemed relevant but without a formal criteria weighting. Evidence on individual interventions and their measured performance on each criterion can be represented in what is called a “performance matrix” and help structure the committees’ deliberations (Thokala et al., 2016), (Youngkong, et al., 2012).

Whichever approach for decision-making (aggregation) is chosen, it will be important to compare net costs of implementing the new intervention with the (aggregated measure of) benefits expected to be generated in order to provide access only to interventions representing good value for money. In other words, for those interventions showing high value, there is a need to consider whether providing access is sustainable in terms of total budget impact (in the first and in following years). This is what is considered in the “affordability” step and we discussed different options to tackle it (section 3.5).

Finally, in terms of process, the steps discussed which are presented in Table 4 (selection of the “priority” interventions, assessment of value attributes, decision-making for appraisal, and financial analysis or affordability measures) can be conducted by different actors in the health systems including stakeholders, technical experts, benefit package committees, and budget holders, respectively. The role of central versus local decision-makers will depend on the structure of the health system. For example, in countries with multiple insurers or with a strong budget devolution to individual jurisdictions, there is a case for a clear separation between the assessment of value, which could be done at the central level, and the decision-making part and the affordability/financial measures which could be dealt with at the local level to reflect local budget constraints.

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6. APPENDIX 1 – LITERATURE REVIEW METHODS AND RESULTS

The rapid evidence assessment (REA) conducted for this project was divided into two topics: (1) macro-level decision making which is related to the organization of the health system, and (2) micro-level decision making which is related to approaches followed by countries concerning decisions on individual health technologies.

6.1. Methods

This section presents the protocol followed during the literature review to put the issue of formulary development in the context of health system design.

In view of the vast number of publications related to macro and micro decision making process and the time constraints, we conducted a REA instead of a systematic literature review. Both the REA and the systematic literature review are systematic processes of gathering and reviewing evidence. However, the difference between the two lies in that the REA is constrained by the time availability and is usually aimed at capturing the key points collected in the evidence, while a literature review should exhaust all the possible sources of information with less consideration of the time spent. Given that REA is not a commonly use concept, along the document we are calling "literature review" to the process followed according with this protocol.

The literature review's main objective is to capture the relevant information regarding two different levels of the health system organization:

- (1) **Macro-level decision making:** The macro-level decision making comprise two searches
 - a. Organization of a health system (approaches of macro-level decision making recommended in the literature): articles and reports analysing the minimum elements that should be considered in the organization of a health system ("architecture of the health system") (e.g. the six building blocks of the health systems proposed by the WHO).
 - b. Macro-level decision making in practice: Approaches followed in practice for designing and organizing the health system in a selection of countries and whether those approaches considered the main elements capture in point (1). For example, approaches followed related to the configuration of service delivery, payment and incentive schemes, health workforce and priority setting at health system level.
- (2) **Micro-level decision-making:** Approaches followed by selected countries related to decisions on individual health technologies. This part should include identifying (a) which elements of the value of medicines are taken into account when making decisions (e.g. effectiveness, wider societal impacts), (b) processes to make decisions and (c) tools/approaches, if available, to manage access to innovative, high cost treatments.

The outcome of the search and review had informed the development of the interview guide for the key informant interviews which consisted of a list of conceptual blocks (both from the micro-level and macro-level decision-making) and relative description.

The macro level decision making search was conducted, first, without consideration of a particular country or region, and second, considering the selected countries. The micro-

level decision making literature review was narrowed only to the particular context of the selected countries:

- a. Three upper-middle-income countries: Taiwan, Brazil and Thailand.
- b. Two high-income countries: Germany and UK (focusing on England given the separated HTA processes existing in England, Wales, Scotland and Northern Ireland). The analysis of those two countries will provide important examples of the potential approaches that could be applied or adapted in countries with fewer resources.

The literature review was conducted based on the bibliographic database **PubMed** (more than 24 million records). The period included was from January 1995 to December 2014. Finally, the search was focused only on articles published in English.

6.1.1. Search criteria

The first step of the REA is the identification of the documents of interest based on the three search criteria: i. MeSH terms (Medical Subject Headings) (U.S. National Library of Medicine, 2014) which is a classification tools to index journal articles and books in the life science, ii. Specific criteria to search in the title/abstract related to the three health system organizations mentioned above, and iii. Specific criteria to search in the title. The PubMed tool allows the search according with MeSH criteria in which the article is classified.

The following lists of criteria have been applied with the corresponding number of results for each bibliographic database.

(1) Macro-level decision-making

- (a) **Organization of a health system** (without considering the country): 908 hits with the following criteria
 - **MeSH Criteria:** community health planning OR financing, government OR health care rationing OR health care reform OR health expenditures OR health plan implementation OR health planning guidelines OR health priorities OR health promotion OR health resources OR health services needs and demand OR health systems plans OR insurance coverage OR insurance, health, reimbursement OR mandatory programs OR national health programs OR regional health planning OR regional medical programs OR social security OR state health plans OR universal coverage AND
 - **Specific criteria in the title/abstract:** health reform OR healthcare system OR health care system OR health system **AND** successful OR strengthening OR building OR organizing
- (b) **Macro-level decision-making in practice** (considering the selected countries): 82 hits with the following criteria
 - **MeSH Criteria:** community health planning OR comprehensive health care OR cost allocation OR critical pathways OR fee for service plans OR financing, government OR financing, organized OR health care rationing OR health care reform OR health care sector OR health expenditures OR health facility planning OR health plan implementation OR health planning guidelines OR health planning

technical assistance OR health priorities OR health promotion OR health resources OR health services accessibility OR health services needs and demand OR health systems plans OR hospital planning OR decision making, organizational OR insurance coverage OR Insurance, Health OR insurance, health, reimbursement OR managed care programs OR mandatory programs OR medical assistance OR medication systems OR national health programs OR needs assessment OR organizational innovation OR organizational objectives OR patient care planning OR primary health care OR regional health planning OR regional medical programs OR reimbursement mechanisms OR social security OR state health plans OR universal coverage , AND

- **Specific criteria in the title/abstract:** priority setting health services OR healthcare system OR health care system OR health system OR health reform AND successful OR strengthening OR building OR organizing OR designing
- **Specific criteria in the title:** Brazil OR Thailand OR Germany OR UK OR England OR Mexico OR Philippines OR Taiwan OR middle income

(2) **Micro-level decision-making:** 401 hits with the following criteria

- **MeSH Criteria:** health planning guidelines OR health priorities OR health services needs and demand OR needs assessment OR committee membership OR medication systems OR drug utilization OR professional staff committees OR critical pathways OR costs and cost analysis OR economics, medical OR economics, nursing OR economics, pharmaceutical OR fees and charges OR prospective payment system OR reimbursement, disproportionate share OR reimbursement, incentive OR health care costs OR outcome assessment OR program evaluation OR survival analysis OR epidemiologic research design AND
- **Specific criteria in the title/abstract:** formulary OR health technology assessment OR health technologies OR HTA OR positive list OR negative list OR listing decision OR benefit package OR coverage OR drug tariff OR health technologies OR priority setting OR entry agreement AND
- **Specific criteria in the title:** Brazil OR Thailand OR Germany OR UK OR England OR Mexico OR Philippines OR Taiwan OR middle income

6.1.2. Exclusion criteria and selected sample

Using the criteria specified in the **macro-level decision making** and **micro-level decision-making** searches and after the exclusion of the repeated results a total of 908 a total of 1340 were selected.

The objective of the macro-level decision making related to the "*Organization of a health system*" is to capture information regarding the health system in general. Therefore, the following articles were excluded from the literature review.

- Articles related to specific interventions
- Articles related to specific countries

- Articles referring only to developed countries
- Clinical trials
- Theoretical papers
- Articles with a primary epidemiology focus
- Letters/commentaries

In the case of the macro-level decision-making in practice and the micro-level decision-making and the aim is to extract information related to the selected countries. Consequently, the exclusion criteria are as follow:

- Articles related to specific interventions
- Articles than mentions the selected countries, but with a focus on other countries
- Clinical trials
- Theoretical or pure econometric papers
- Articles with a primary epidemiology focus
- Letters/commentaries

The exclusion criteria was applied to the title of the 1340 articles. For the search focused on the selected countries a sub-sample of 39 articles were identified. Regarding the organization of a health system, a sub-sample of 133 articles were selected.

A most deep review of the abstracts was conducted. An additional group of articles in which the topic and/or the methodology applied were not related to the objectives of the analysis was excluded. For the micro-level decision making a total of 12 articles were included in the literature review and for the macro-level decision making the selected sample corresponds to 21 articles.

In addition to the selection of articles, official documents and key documents collected from previous studies were included. *Table 5* shows the number of articles extracted from the literature review according with the country.

Table 5
Selected Articles by Country and Levels of the Organization of the Health System

	Articles from the literature review	Additional articles	Total
<i>Micro-level factors decision making literature review</i>			
The UK	3	7	10
Germany	1	14	15
Brazil	4	6	10
Taiwan	0	11	11
Thailand	1	13	14
Multiple countries	1	1	1
<i>Macro-level factors decision making literature review</i>			
	21	4	25
Total	31	56	87

Source: Own elaboration

6.2. Results of the literature review on macro-level decision making

This section presents the results of the literature review related to the macro-level decision making. Based on selected articles, the main objective is to examine the minimum elements that should be considered in the describing the organization of a health system ("architecture of the health system") and during the priority-setting process.

The main objective of the overall project is to develop and analyse solution-oriented approaches for formulary development in middle income-countries (MICs) whose health systems are evolving towards universal health care (UHC). Therefore, we aim to identify the elements that could be useful during the decision process related to the introduction of new treatment or intervention as part of the basic health package in MICs. This summary is not intended to capture all elements of a decision process, but those elements related to the general organization of the health system or the macro level decision making.

The results of the REA suggest three different groups of elements that should be considered during the assessment of a new treatment or interventions: 1) intermediate goals of the health system, 2) current characteristics of the health system and 3) positive spill-overs as a result of the introduction of a new health technology.

The health system goals are usually defined in general terms. In this sense, the WHO suggests in its World Health Report 2000 three general goals that every health system should pursue: 1) health in terms of outcome and equity, 2) social and financial risk protection, and 3) responsiveness to what people want and expect (WHO, 2000; Kutzin, 2013). The ultimate aim of a health system is the maximum accomplishment of these goals. However, these general goals can have different nuances depending on the relative importance that each country assigns to them. For instance, gender equality is more important for some countries while others give a higher value to socioeconomic equality. Therefore, there are in each particular health system a group of "intermediate goals" which could be defined as a country conceptualization of the general goals of the health system. For the decision making process it is essential that the intermediate goals are clearly specified such that they could be properly included into the analysis to made the best use of the scarce resources. In this way, the criteria to consider during the decision making process would reflect the values and needs of the population. Following this, Tromp and Baltsussen (2012) propose a multi-criteria decision making process in which the intermediate goals of the system are the main criteria to be considered. For instance, it is important to analyse whether the intervention is in accordance with the expectations of the population not only in health matters, but also in other aspects such as cultural particularities. They suggest that the treatment should match the health distributional goals of the country. For example, for a particular country it could be desirable to improve ethnicity equality over gender equality, in which case it would be desirable to assign a higher value to those treatments that improve ethnicity equality.

Based on the reviewed literature, it has been possible to identify six intermediate goals that it would be advisable to consider during the priority-setting process:

- Health level impact: For instance, it would be desirable to formally specify the importance that factors such as disease incidence and prevalence, disease burden and rare diseases have for the country.

- Equity: The dimension to judge during the consideration of equity varies between countries. For instance, the decrease of inequality is a main goal for the South Africa's government which is advocated in order to improve access to health services for the families in the lower level of income. In the case of Brazil, not only the income inequalities but also the regional inequalities are of great concern for the policies makers.
- Number of population to be affected: In the case that to pursue the universal health coverage (UHC) is a central objective for the health system; the policy makers could be more interested in treatments that benefit the largest proportion of the population.
- People values and expectations: The success of a priority-setting process depends on the public confidence and acceptance of the decisions. With this in mind, a decision-making process should be a reflection of public values. In this sense, it is desirable for the policy makers to increase public awareness of the priority-setting process and awareness of the articulation of public values for priority-setting (Kapuriri and Martin, 2010; Kutzin, 2013). The potential benefit of a new treatment or intervention would be easier to maximize when the assessment considers all the relevant social and ethical consequences and the population is aware of these considerations (Velasco Garrido et al., 2010).

Impact on non-health factors: Jenniskens et al. (2012) conducted a survey in five African countries to a variety of participants (health workers, national government members, community leaders and members of the community). The results suggest that for the majority of the interviewees not only the seriousness of the disease matters, but also the related negative and social effects when priorities are set. The stigma of a disease can change the level of importance of a new treatment. For instance, the social rejection of HIV patients explains in part the disproportionate investment in this disease in countries in which it is not even in the top 10 causes of death.

Impact on broader health system priorities (e.g. sanitation and access to health services): It is important to expand our view with respect to the functions that a health system must perform (Frank, 2010). Aspects such as access to clean water and energy supply should also be included during the priority-setting process.

The context of each health system is different; therefore, each country should consider its own particularities and develop its intermediate goals accordingly before considering any inclusion into the basic health package. In addition, Tromp and Baltussen (2012) suggest that policy makers should assign a hierarchical order of importance to the health system goals such that the process of decision between different health technologies will be clear and transparent. It would be recommended that the order reflect the preferences of the population. In this sense, the analysis of Jenniskens et al. (2012) indicates that there has been a progress in involving different stakeholders in the priority-setting process.

The second group of macro level elements to consider during the decision making process is the related to the current health system situation or ability of current system to deliver efficiently the new technology. In this regard, one of the conclusions drawn from the program children HeartLink (non-governmental organization that support the development of health treatment in LMICs) indicates that the foundation of the success in any program development effort is to understand the environmental and health care system factors along with the medical factors involved (Dearani JA, et al., 2010). This

because the potential benefit of a new health technology or health program depends on the capacity of the health system of providing access to the treatment to the entire population in need in a way that can be classified as safe, efficient, high quality and related to the minimum waste of resources (Atun et al., 2004). The results of the REA emphasises the widely spread of the health system building blocks framework proposed by the WHO as a way of analysing the different elements involve in the efficient functioning of health system (Tromp and Baltussen, 2012; WHO, 2007):

- Service delivery (Atun et al., 2004; Countdown Working Group on Health Policy and Health Systems, 2008; Frank, 2010; O'Kane et al., 2008; Velasco Garrido et al., 2010): The priority-setting process should determine whether the technology can be provided, which are the setting in which the intervention is to be delivered, the resources necessary to ensure access to products and services, and the means of achieving the optimal results from them. For instance, Atun et al. (2010) mention the main role of the delivery system in the effectiveness of the ambulatory tuberculosis treatment. In around 110 countries, antituberculosis drugs were supplied through integrated supply systems for essential drugs. In addition, the insurers should ensure the quality of the service delivery. In this sense, the coherence and knowledge of the context are central to the success of a program for improving quality (Mate KS et al., 2013).
- Health workforce (Ahmed et al., 2010; Jenniskens, et al., 2012; Nsubuga, et al., 2010; Lee et al., 2007; Palen et al., 2012): It is important to consider the actual capacities in terms of human capital and the investment required to improve this capacity to successful delivered the new health intervention.
- Health information systems (Atun et al., 2004; O'Kane et al., 2008): The health system should account with an adequate information system such that the decision are based on reliable and recent information that shows a clear picture of the Health system situation.
- Medical products, vaccine and technologies (Ahmed et al., 2010; Frank, 2010): Here the main point is whether the system is capable of delivering the appropriate group of interventions and technologies to fulfil the needs of the population.
- Financing (Atun et al., 2004; Ahmed et al., 2010; Countdown Working Group on Health Policy and Health Systems, 2008; O'Kane et al., 2008; Pang et al., 2003): This is a key factor since has a major effect on whether the people can have access to the health care and whether they will face financial hardship as a consequence of illness.
- Leadership/governance (Ahmed et al., 2010; Dearani JA et al., 2010; Frank 2010; O'Kane et al., 2008): It is important not only to account with a strength leadership and organization in the system, but also a local and provincial governmental support for the introduction of the new intervention or treatment. A lack of support could hinder the distribution and access of the new intervention.

In addition to the six blocks, two extra elements has been extracted from the literature:

- Public health surveillance and response system (Atun et al., 2004): It is fundamental for the developing countries to account with a system that can detect and prevent the advent of emerging pandemics. In this sense, the

epidemiologic and laboratory capacity of the country are central (Nsubuga et al., 2010).

- The fragility of the country (Goeman et al., 2010; Newbrander et al., 2011): Government instability, armed conflict and natural disasters can change the priorities of the countries in a relatively short time. Although the current situations could appear to be favourable to the introduction of a new treatment, a high probability of facing one of these problems could hinder the benefits of the new health technology. Even if this is a factor that particularly preoccupies decision makers in low income countries (LICs) many of the MICs can also be considered fragile given their government instability or internal conflicts. For instance, during the armed conflict in the region of Chiapas in Mexico studies suggest that the maternal and perinatal mortality rates were higher in the conflict region than in the rest of the country (Brentlinger et al., 2005).

Apart from the current situation, the inclusion of the new interventions should consider the possibility of overcoming some of the obstacle linked to the above mentioned factors. In the case that the new health technology is complemented by improvements in the current health system situation, this would allow the adequate utilization of a new health technology that otherwise would not be offered. In many countries the introduction of a new technology is normally done as part of a health program, such as a Tuberculosis or HIV programs. For instance, the introduction of the decentralization of HIV treatment to the primary health centre has improved the pharmaceutical delivery system of the countries in which has been applied (Embrey et al., 2009). In addition, some technologies are introduced along with additional measures which aim to face the shortages of the system, such as training programs and the support to developing country laboratories, increasing the potential benefit of the intervention (Embrey et al., 2009; Palen et al., 2012). For example, the impressive decline in the unit cost of providing antiretroviral therapy for treatment of HIV explained by an improvement in drug delivery and supply chains, taking advantage of economies of scale in program implementation, and standardization of clinical and LAB monitoring (Countdown Working Group on Health Policy and Health Systems, 2008).

A final group of elements to consider during the decision process are the positive spill-overs related to the introduction of a new treatment. These could be divided into two sub-categories. First, one source of positive spill-overs is the correlation between diseases; an improvement in the health condition of a group of patients could affect the incidence and prevalence of other disease. For instance, it has been proved that the probability of suffer from tuberculosis is higher among those with diabetes. Therefore, many countries that experience serious problems of tuberculosis would benefit from the indirect effect of decreasing the diabetes incidence (Remais et al., 2012). Additionally, the prevention and treatment of many non-communicable diseases are linked with the prevalence of the communicable diseases. For instance, the cancers associated with infectious diseases continue to disproportionately impact LMIC (e.g. hepatitis C, which accounts for one-third of liver cancer cases worldwide) (Remais et al., 2012). The relationship between diseases is a factor rarely taken into account during the decision making process and that could be a key part of the potential benefits of a new health technology, particularly when is related to the priority diseases of the health system.

A second source of positive spill-overs is the non-intended effects of the introduction of a new health technology on the health system current situation. For instance, because the adherence has a central role in the efficacy of ART, HIV programs have supported the

development of medicine counselling skills of pharmacists and pharmacy technicians which have been beneficial for all patients (Embrey et al., 2009). Another example is the public-private partnerships that has emerged from the expansion of efforts to ensure equitable access to ART, including co-formulations designed to support adherence, this has resulted in the development and commercialization of drugs for other diseases that excessively affect LMICs (Embrey et al., 2009). The following list summarizes the positive spill-overs on the health system current situation suggested by the reviewed literature:

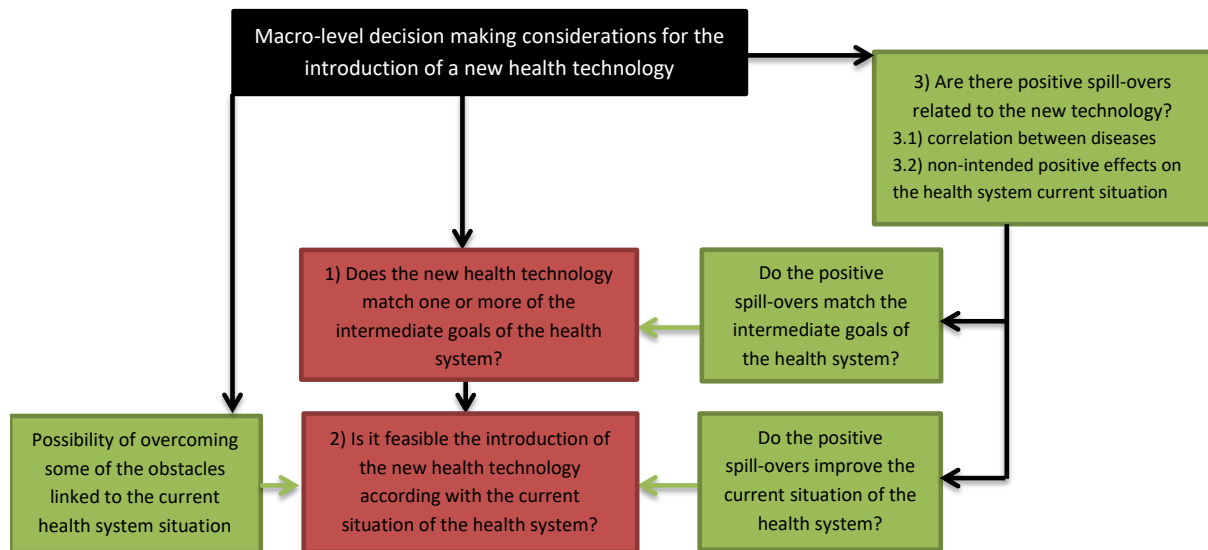
- New interventions that allow the improvement of the health information system, improvement that benefits the monitoring of other non-intended diseases.
- Improvements on the overall situation of the health system (e.g. access to health care).
- Building collaborations whose benefit could be directed to more than one disease (Embrey et al., 2009).
- Improvements in policy, law and regulation: For instance, the decentralization of the HIV treatments generated legislative changes in some countries in order to enable health care staff other than pharmacists to dispense medicines (Embrey et al., 2009). This allowed the health system to deal with the lack of pharmacists and so benefited the treatment of other non-intended diseases.
- Health System Strengthening (HSS): It is common for development partners to provide capacity building support, part of this support is lead to health system strengthened (Palen et al., 2012). It would be desirable to introduce a new treatment accompanied by HSS measures as part of a larger health program. In this sense, Kipiriri and Martin (2010) point out that one of the measures of the success of a priority-setting process is the capacity of improve leadership and governance by increasing internal accountability and reduce corruption.

Increase in fiscal space through both generating additional resources through innovative financing approaches and ensuring optimal use of available resources through efficient allocation and program implementation. It would be recommendable that the introduction of a new treatment includes a plan for increasing efficiency in the allocation of resources as well as the related financing mechanisms (Palen et al., 2012).

As a summary, Figure 5 shows the way in which the three different groups of elements interact during the decision making process. The boxes represent the main elements to be considered (intermediate goals and current situation) and the green boxes correspond to the elements that could modify the decision that would be taken if only the main information is included in the decision process.

Figure 5

Factors related to the Organization of the Health System that should be considered in the decision of including a new treatment in the formulary



Source: Authors' elaboration

6.3. Results of the literature review on micro-level decision making in selected countries

The framework in which the analysis of the information collected in micro-level decision making literature review corresponds in part to the one suggested in Sussex, et al., 2013. The information was broken down into five categories:

- Introduction and Decision-making process
- Brief description of the drug tariff, national formulary, positive/negative list, benefit package
- What are the attributes of value
- How are they measured and aggregated
- Affordability tools/managed entry agreements (MEA)

The decision making process of five countries was analysed. Three MICs (Brazil, Taiwan and Thailand) and two high income countries (Germany and the UK) were included. The consideration of the two high income countries responds to the need of exploring highly structured drug formulary decision making processes and take advantage of the methodologies apply in those countries which could be adapted to the MICs context.

6.3.1. Brazil

Introduction and decision-making process

In 1988, Brazil's constitution granted its citizens the right to universal healthcare and established the Unified Health System (SUS) (Banta and Almeida, 2009). In theory, the SUS public health care system covers 100% of Brazil's population, however, an estimated 21% of the population is covered by the private health care system (Towse et al. 2011). Furthermore, government spending as a percentage of total health expenditures resides at 50%, while private health insurance and out-of-pocket payments

account for 20% and 30% of the total health expenditure, respectively (Rajkumar et al., 2014).

The public health care system is financed by a mix of federal, state, and municipal funds. In 2000, a constitutional reform mandated minimum tax revenue and social contributions to the SUS from each of the three government levels. The minimum percentage contribution of gross tax revenues to the SUS is 6-7% for the federal government, 12% for state governments, and 15% for municipal governments (Rajkumar et al., 2014).

Decentralization within the SUS has resulted in regional and local variations. Table 6 details the types of care, funding sources, and provision levels within the SUS:

Table 6
SUS Decentralization

Level of Care	Type of Service	Level of Government Responsible for Provision	Predominant Form of Service Provision	Funding Source(s)
Primary Medical (Básica)	General outpatient services (preventive, diagnostic and curative)	Municipalities	Public outpatient (ambulatory) facilities, often 'Family Health Clinics'	- Federal transfers (Capitation system and results-based transfers to municipalities) - State transfers to municipalities - Municipality's own funds
Secondary Medical (Média Complexidade)	Specialist outpatient and inpatient	- States and some larger municipalities - Federal Government	- Private sector facilities - MOH referral hospitals - Ministry of Education (MOE) teaching hospitals	- Federal transfers to States and municipalities - States and larger municipalities (using Federal and own funds) contract with Private facilities - Federal funds go directly to MOH and MOE hospitals
Tertiary Medical (Alta Complexidade)	Complex services: Organ transplants, HIV/AIDS treatment, hemodialysis, etc. Diagnostic: MRIs, CT scans, etc.	States Federal Government and States	Public hospitals - MOE teaching hospitals - Private facilities	- Federal transfers to States - State funding of public facilities using Federal and State own funds - Research grants and other private sources - Federal financing for MOE hospitals - Federal transfers to States - State contracts with private facilities (using Federal and state's own funds)

Source: Rajkumar et al., 2014

In 1994, the Ministry of Health (MOH) introduced the Family Health Strategy, (FHS) which relies upon health teams assigned to follow families in geographically-defined health areas. The FHS includes a performance-based financing mechanism associated with federal transfers to municipalities for primary care (called Piso da Atenção Básica or PAB transfers).

Ordinance GM/MS # 204 (2007) established the financing package for the SUS Pharmaceutical Benefit Plan, which is composed of Basic, Strategic, and Specialized, program components. The three components are defined as follows (Figueiredo et al., 2013):

- **Basic:** medicines used in primary health care
- **Strategic:** medicines including those used to treat endemic conditions, such as infectious diseases (e.g. HIV/AIDS, tuberculosis) and specific programs (e.g. lupus erythematosus)
- **Specialized:** medicines used in the high-cost treatment of rare conditions and for second or third-line treatment options of highly prevalent diseases. There is an access strategy at the outpatient level for the specialized component, with diagnostic and therapeutic criteria established by protocols and guidelines developed and updated by the Brazilian Ministry of Health (PCDT).

Additionally, the federal government created a supplementary program - the People's Pharmacy Program of Brazil (Programa Farmácia Popular do Brasil), which aims to increase access to medications for the most prevalent health concerns. This People's Pharmacy Program possesses its own network of public pharmacies and has established a partnership with a private network of pharmacies and drugstores (de Figueiredo, 2012).

The National Essential Drug List (Relação Nacional de Medicamentos Essenciais – RENAME) details the SUS list of medications available under the Basic, Strategic, and Specialized components of the Pharmaceutical Benefits Plan, which includes medications provided by hospitals. Every two years, the Ministry of Health publishes and reviews the RENAME list.

Overview of HTA and National List of Essential Medicines decision-making

In 2004, the Brazilian Ministry of Health created its Department of Science and Technology (DECIT) and approved the National Health Policy for Science, Technology and Innovation. The General Coordination Office for Health Technology Assessment was created in 2005, with the mission of implementing, monitoring and disseminating HTA within the SUS. HTA was formally incorporated in the public health system at a federal level in 2006 and in 2007, the Brazilian Network for Health Technology Assessment (REBRATS) was created to improve the government's regulatory capacity, and its ability to define prioritization criteria and methodology for HTA studies (Ferraz et al., 2011). In 2009, the Institute for Health Technology Assessment (Instituto de Avaliação de Tecnologia em Saúde, IATS) was created to providing technical information to help in decision-making processes. The first national HTA Guidelines for conducting healthcare economic evaluations in Brazil were published in 2009, with revisions also provided in 2011 (Vianna et al., 2009).

In December 2011, Law 12401 was approved which established a new framework for HTA in Brazil and created a new national HTA body, the National Committee for Incorporation of Technologies (Comissão Nacional de Incorporação de Tecnologias no

SUS, CONITEC) in the SUS under the MOH. Law 12401 amended Law 8080 (the main SUS legislation) and now states:

- “ HTA must address efficacy, effectiveness, safety, as well as the impact of implementing technologies;
- the implementation of new technologies must be integrated with the elaboration of national clinical protocols (i.e., critical pathways) and clinical guidelines;
- the process of HTA is to be centrally performed by the Brazilian MOH with technical advice from CONITEC;
- the rules of procedures for HTA must also include its maximum period of duration and a mandatory public consultation and an optional public hearing as part of the process;
- CONITEC is composed of 13 representatives from the following institutions: seven representatives from the Brazilian MOH; one representative from the national regulatory agency for the private health care sector (Agencia Nacional de Saude); one representative from the National Association of the State Secretaries of Health; one representative from the National Association of the Municipal Secretaries of Health; one representative from the National Health Council; and one representative of the Federal Council of Physicians. (Kuchenbecker et al. 2012).”

Brief description of the drug tariff, national formulary, positive/negative list, benefit package

In 1998, the National Drug Policy was approved in Brazil with the purpose of ensuring safety, efficacy, and quality of drugs, as well as the promoting rational use and access for essential medicines, technologies, and supplies (Banta and Almeida, 2009).

The Brazilian National Agency for Sanitary Surveillance (Agência Nacional de Vigilância Sanitária, ANVISA) play a primary role in the approval of pharmaceutical products to enter the Brazilian market. However, the incorporation of medications into SUS is carried out through an evidence-based selection process, involving health authorities at federal, state and municipal government levels. The process results in medicine lists belonging to the three different previously noted funding components of pharmaceutical services (basic, strategic, and specialized) (Figueiredo et al., 2013).

Anvisa’s pricing decisions (2004) have been based on comparative efficacy and cost-minimization analysis, setting premium price for new drugs depending on additional benefits gained (Lemgruber 2013). Category 1 drugs have a valid patent in Brazil and bring gains to treatment (defined as higher efficacy, same efficacy with fewer adverse events, or same efficacy and safety with lower costs). The approved price of Category 1 drugs is the lowest price from nine reference countries. If the drug does not have a valid patent does not show health gains relative to a registered treatment, is considered as Category 2. Category 2 drugs have a maximum price set to the price of a treatment already registered in Brazil that provides equivalent efficacy. For innovative products, after the initial price is set via external reference pricing, it is adjusted subsequently by SUS (Towse et al. 2011).

New drugs must be submitted for HTA evaluation. CONITEC provides recommendations in favour or against the inclusion of new drugs and the Ministry of Health ultimately decides. Generally, a favourable guidance is mandatory for implementation, however,

the government does not publish the rationale behind the recommendations given (for positive and negative guidance) (Towse et al. 2011).

What are the attributes of value

Evaluation of pharmaceutical products in Brazil lead by ANVISA considers the following (Banta and Almeida, 2009; Kuchenbecker et al. 2012):

- epidemiology of the disease(s) related to the product
- alternative treatment options for the disease(s) related to the product
- detailed descriptions of the pharmaceutical to be evaluated
- robust efficacy and safety data of the product under consideration
- economic evaluation in accordance with published guidelines (detailed below),
- budget impact of the product

CONITEC provides key assistance in the economic evaluation of the product under consideration for incorporation to the Brazilian market and SUS. While details on the decision measurement of all criteria are not provided online, economic evaluation guidance has been published for use in Brazil. Furthermore, recommendations for budget impact analysis have been approved but not formally adopted in the evaluation process (<http://www.htai2011.org/documentos/884%20ALFS.pdf>)

How are they measured and aggregated

The following section summarizes Brazilian guidelines (originally published in 2009 and updated in 2011) which provide specific recommendations for health-related economic evaluations conducted in the country (Vianna et al., 2009):

- **Target population** (s) should be described in terms of its demographic and disease characteristics. The population(s) must be also be defined in terms of features such as place of care where technology or intervention falls (outpatient or hospital care), geographic location, adherence rate to the proposed intervention proposal, standards of care, and eligibility/exclusion criteria to use the technology.
- **Study design** should be clearly stated, in addition to whether or not the analysis is based on primary data or modelling. It is recommended that, wherever possible, effectiveness data is used instead of efficacy data.
- **Comparator** should be the most prevalent strategy in use in the SUS. When there is variability in clinical practice among subgroups, analyses should be conducted separately for these subgroups.
- **Study Perspective and Related Costs:** The study perspective should either be the National Health System or societal perspective. From the perspective of the SUS management body as a buyer of public and private health services, all direct costs covered by the public system should be computed. From the perspective of society, all direct costs of producing the service should be included in addition to time lost by patients and their families, and related valuation of lost productivity and premature death (all cost types should be presented separately).
- **Time horizon** should be based on the natural course of disease and the likely impact that the intervention.

- **Quality measures of healthy life** must be calculated with consideration for target population characteristics, disease conditions, the rules for calculating scores and interpretation of the results. The use of expert judgment as a source of weights assigned to quality should be avoided wherever possible and, when used, a sensitivity analysis should be performed. The study should explicitly state the measure being used for quality of life, and justify the selection, methods employed for preference measurement.
- **Benefit measures:** when willingness to pay (WTP) is used, an explanation must be provided for all assumptions, alongside sensitivity analysis.
- **Quantification and costing of resources** involves three stages:
 - (1) Identification of costs relevant to the assessment;
 - (2) the measurement of resources used; and
 - (3) valuation of resources.

When the analytical perspective taken is the SUS, all all costs directly involved in care delivery by the health system should be considered. The use of resources in each health state must be represented relative to their costs. All current and future costs of each intervention, relevant for the chosen time horizon must be included in the analysis. When the societal perspective is adopted, additional costs incurred by patients and their families should be included, as well as those associated with decreased productivity for lost time and premature death, adopting valuation per capita national income.

- **Modelling:** The proper choice of the model to be used depends on the objective of the study. The use of Markov models is recommended when assessing the long term effects of chronic diseases.
- **Discount rate:** When the time horizon of the analysis is more than 1 year, both costs and health outcomes that occur in the future should be discounted To increase the comparability of studies, a standardize cost discount rate of 5% per annum is recommended (with a sensitivity range of 0% to 10%).
- **Results:** Independent programs are ranked in order based on their cost-effectiveness ratios. In evaluating two or more mutually exclusive programs, the initial option is to choose the most cost-effective strategy. Cost-effectiveness should be measured in incremental terms.

The guidelines further emphasize that findings of cost-effectiveness studies should emphasize how choices between non-dominated options can be legitimately applied by managers in their decision process.

Of further note, while guidelines in Brazil do not necessitate the use of the QALY, discussions have continued about whether or not the measure should be adopted uniformly by CONITEC (Machado, 2015)

Affordability tools/managed entry agreements (MEA)

In late 2009, the Ministry of Health launched the Horus Information System – the National System of Pharmaceutical Benefit Program Management (Sistema Nacional de Gestão da Assistência Farmacêutica), which targets managers, health care professionals, public oversight institutions, and health care service users within the SUS.

6.3.2. Taiwan

Introduction and Decision-making process

Starting in 1995, Taiwan launched a single-payer, National Health Insurance program (NHI) with the aim of achieving universal health coverage for its population (Cheng, 2003). The NHI is funded through premium collection and tax revenue, in combination with employer contributions and patient co-payments (Jirawattanapisal et al., 2009). Enrolment is mandatory for the Taiwanese population and coverage is currently estimate to be over 96%. The NHI is managed by the National Health Insurance Administration (NHIA, formerly the Bureau of National Health Insurance), under jurisdiction of Taiwan's Department of Health (DoH).

Health care providers in Taiwan receive revenues from three sources: payments by the NHI, patient user fee/copayments, and the sale of products and services not covered by the NHI. Healthcare providers have traditionally been paid by a fee-for-service retrospective reimbursement system, and there is a list of treatments that specifies those eligible for reimbursement (Jirawattanapisal et al., 2009). More recently, the NHIA explored the use of alternative provider payment mechanisms, such as DRGs, capitation for specified populations, and payment linked to clinical outcomes, in order to control rising NHI costs (Cheng, 2003). In 2002, the NHI ultimately imposed global budgets as a cost control measure.

More than 80% of health providers are private organizations, which provides market competition for the delivery of health services to Taiwanese citizens.

Drug Coverage under NHI

Despite being noted as a successful example of universal health reform, the NHI's greatest challenge remains its financial sustainability. In particular, pharmaceutical costs accounted for approximately 25% of total NHI expenditure in 2012 (approximately USD4.7 billion), consistent with historic drug expenditures as a percentage of NHI expenditures (Cheng, 2009; Hsu and Lu, 2015).

Drug reimbursement and pricing processes have shifted over time under the NHI. Most recently, beginning in 2013, Taiwan's "Pharmaceutical benefits and reimbursement schedule" was established, replacing the "Pharmaceutical Benefits Scheme" which was previously used. The schedule lists all medicines and medical devices reimbursed under NHI (Ministry of Health and Welfare of Taiwan, 2012). Decisions on the new schedule rely more heavily on engaging stakeholders (insurers, scholars, the insured, employers, service providers, etc.) while determining drug listing and reimbursement prices (Hsu and Lu, 2015).

In Taiwan, hospitals are allowed to sell patients drugs at prices above their acquisition cost (negotiated with the pharmaceutical companies) and retain profits (Cheng, 2003).

Role of Health Technology Assessment

The Division of Health Technology Assessment (DHTA) was established in 2007 as a pilot program in the regulatory body, the Centre for Drug Evaluation (CDE), which is a private, not-for-profit, non-governmental organization, fully sponsored by the Department of Health devoted to providing HTA consulting services to government and industry. The purpose of the HTA group is to support the NHIA by providing evidence-based evaluations of the merits or drawbacks of new healthcare technologies. Four types of new drug applications were sent to the HTA division for review: new chemical

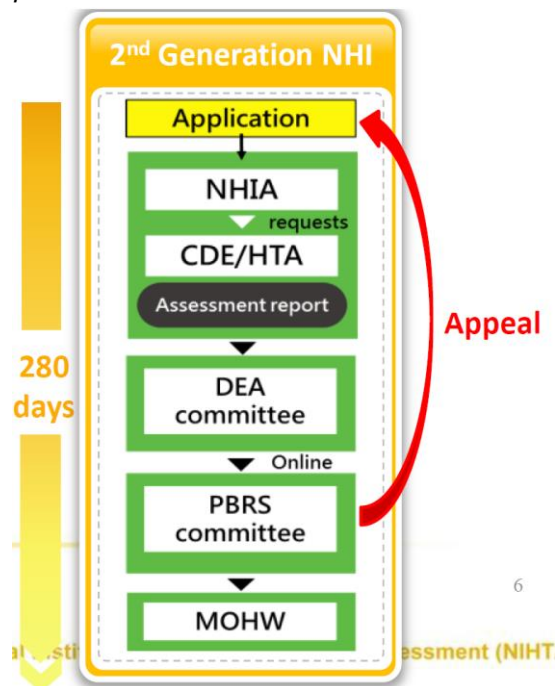
entities, new indications, new dosage forms, and new combinations. The HTA group would then assign each case to two experts who search independently for evidence from CADTH (Canada), NICE (United Kingdom), PBAC (Australia), SMC (Scotland), the Cochrane library, PubMed, EMBASE, etc. Under this system, a typical report is completed and verified within 42 days upon which it is disseminated to the BNHI for the Drug Benefit Committee (DBC) meeting.

After changes to the NHI were implemented starting in 2013, HTA for new drugs is required by law. In practice, this had been the case for most products following the 2008 incorporation of the pilot HTA system into the routine assessment procedure. The new law establishes a separate National Institute for Health Technology Assessment (NIHTA), which is administratively distinct from the CDE. The NIHTA is also outside the jurisdiction of the national health insurance body, the NHIA, though the NHIA does have a role in considering evidence presented by the NIHTA at a joint meeting phase. The NIHTA process will produce a dossier, outlining the relevant evidence, which will then be passed on to the DBC, who will focus on pricing. While the NIHTA will not have direct input into pricing, they may, as part of their review process, provide the DBC with input on the selection of appropriate comparators for use by the DBC in the reference pricing process.

Figure 6 outlines the current decision process related to new drug inclusions in Taiwan.

Figure 6

Drug formulary decision process: Taiwan



Source: Wu, Grace Hui-Min (2014) Presentation. Acronyms: NHIA (National health insurance administration), CDE (Centre for Drug Evaluation), DEA (Drug Expert Advisory), PBRS (Pharmaceutical Benefit and Reimbursement Standard), MOHW (Ministry of Health and Welfare).

Recently, the Director of CDE/HTA noted that in order to achieve the envisioned role of HTA in Taiwan, additional capacity is need in four areas: new staff that conduct HTA analyses, industry professionals who engage directly with the application process, academics that might contribute in research and training for HTA, and government officials who need to be aware of HTA’s use within decision-making (Pwu, 2015).

Brief description of the drug tariff, national formulary, positive/negative list, benefit package

Subject to an annual review, the Pharmaceutical benefits and reimbursement schedule lists all pharmaceuticals and medical devices to be reimbursed by the NHI.

Any item not listed in the schedule can be proposed for inclusion by a license holder or a contracted medical care institution. For any new drug and new category medical device, the submission must include financial impact analysis data and will not be put as a reimbursement item before obtaining approval made by the Joint Meeting of the NHI Pharmaceutical Benefits and Reimbursement Schedule. All drugs must comply with Good Manufacturing Practice for medicinal products of Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (Center for Drug Evaluation of Taiwan, 2006; Chen CL et al., 2008).

Chinese medicines may be submitted for listing consideration if they are new Chinese medicines which have been subject to clinical trial or are Concentrated Chinese medicines.

Taiwan CDE's "Pricing Principles" guidance distinguishes between Category I and Category II new drugs. For a new drug to be in Category I, drug license holders must justify a "substantial clinical improvement" via head-to-head or indirect comparison. Likewise, Category 2A new drugs exhibit at "moderate improvement, while Category 2B new drugs have similar clinical outcomes as therapeutic reference class products (Bureau of National Health Insurance, 2010).

According to Article 51 in the National Health Insurance Act, the NHIA does not reimburse (1) medicines that are approved by the Taiwan Food and Drug Administration (Taiwan FDA) but are not used for disease treatment, such as contraceptive, hair tonic, dark spots detergent, smoking cessation patches; (2) some vaccines (e.g., HPV); (3) over-the-counter drugs and behind-the-counter drugs; (4) drugs for human-subject clinical trials; (5) drugs which are deemed as not essential for medical treatment or not cost-effective; (6) drugs which do not conform to the indication that stipulated in the approved indication for licensing. However, in special cases, an application for prior authorization can be made to the National Health Insurance, and the drug will be reimbursed if authorization is given; and (7) any other drug which the NHIA publicly announces that it will not be reimbursed (Hsu and Lu, 2015).

What are the attributes of value

Evaluation of health technology aims to determine if a medication of interest, compared to a current treatment, can increase monetary benefits and/or effectiveness in achieving health outcomes. Overall, HTA provides evidence to justify the health insurance organization reimbursing a new medication or revising current reimbursement guidance (Center for Drug Evaluation of Taiwan, 2006; Jirawattanapisal et al., 2009).

Additionally, the NHI may also consider budget impact of new additions to the national schedule or revisions of current schedule listings.

How are they measured and aggregated

The Taiwanese pharmacoeconomic analysis guidelines suggest both CEA and CUA as methods of choice, depending on the anticipated outcomes of the drug and associated disease. The guidelines recommend the quantification of marginal costs and health outcomes, expressed in terms of quality-adjusted life years (QALYs), of new

interventions versus standard practice (in an incremental cost–effectiveness ratio [ICER]). The ICER is the ratio between the marginal change in health and the marginal change in costs (adjusted by the savings related to the application of the new technology).

Identification of study audience is important, and largely includes the joint meeting stakeholders (detailed above), DEAA, PBRS, and MOHW when consideration applications for drug inclusion in Pharmaceutical benefits and reimbursement schedule.

Pharmacoeconomic evaluations can be conducted in any phase of a clinical trial for a new medicine (usually in phase II, phase III or phase IV). In 8 principle, the comparator in analyses can be what is most likely to be replaced by the drug in clinical practice (another drug, a surgery, or treatment).

Costs: The Taiwanese pharmacoeconomic guidelines include specific recommendations on the measurement of costs related to health technology (Center for Drug Evaluation of Taiwan, 2006):

- Societal study perspective is strongly recommended, though target sub-analysis may also be presented
- Times horizon recommendation is the period necessary to cover all significant clinical and cost consequences that are directly related to the intervention
- From the societal perspective, direct medical costs, direct non-medical costs, and indirect costs should all be included in cost analysis
- The medical resources used during the treatment period must be shown in their natural units (non-monetary)
- Both incremental use of resources and the total cost of an intervention are considered
- Direct costs from BNHI reimbursement price
- The human capital approach is recommended for calculation of indirect costs

The outcome measure used to quantify an impact on survival or health-related quality of life is quality adjusted life years (QALYs) (one QALY is a year in perfect health and zero QALY is dead). This change in health status, express through change in QALYs, is used as the numerator in the estimation of the cost-effectiveness ratio.

Clinical Effect: The following recommendations are made by the Taiwan pharmacoeconomic guidelines related to effect measurement (Center for Drug Evaluation of Taiwan, 2006):

- Ideally, evaluations are to show the effectiveness rather than the efficacy of a medicine.
- Both life years (the survival years) and health-related quality of life (HRQoL) must be presented. Quality-adjusted life-years (QALYs) are recommended to be used to combine survival years and HRQoL.

Future outcomes and costs should be discounted to their present values by the same discount rate. The discount rate must be included in sensitivity analyses. Sensitivity analysis must be used to demonstrate the relationship between the study results and the assumptions. The basic method is the univariate sensitivity analysis, though multivariate techniques should be used if required. If the purpose of an evaluation is to be used for resource allocation, then any equity assumption, implicit or explicit must be emphasized.

There is no explicit threshold to be applied in the joint meeting's consideration of cost-effectiveness. No evidence was found on the approach adopted during the joint meeting of the PBRS to make reimbursement decisions.

How are they valued

- General population perspective de facto (those preferences are used to value health states used to estimate HRQoL)
- Market prices
- Deliberations of the decision making committees.

Affordability tools/managed entry agreements (MEA)

To assess medicines procurement prices, the NHIA conducted surveys to obtain drug wholesale prices from pharmaceutical companies and procurement prices from hospitals since 1999. Because institutions procure large quantities of medicines, procurement prices are typically lower than the amount reimbursed by the NHIA and the differences constitutes a profit for hospitals. Reimbursements were adjusted if there was a difference of 30% or more between the average procurement price and the NHI reimbursed price. Prices were subsequently monitored and adjusted every two years for patented products, for products whose patent right has expired for more than five years, and for products that have no patent right (Hsu and Lu, 2015).

6.3.3. Thailand

Introduction and Decision-making process

The Thai population is predominantly covered under three health insurance schemes (Jirawattanapisal et al., 2009; Holloway, K., 2012; Yoongthong, W. et al., 2012):

- Civil Servant Medical Benefit Scheme (CSMBS): covers all civil servants, public sector employees, retirees and their dependents. CSMBS is funded entirely from tax revenues and pays providers a fee for service through a retrospective reimbursement system paid directly from the Ministry of Finance (MOF). CSMBS allows for 100% reimbursement of all drugs, whether they are included in the national list of essential medicines (NLEM) or not. In 2008, the CSMBS covered 8% of the Thai population.
- Social Security Insurance Scheme (SSS): covers private employees. SSS is funded by tripartite contributions from tax revenue, employers, and employees. Contributions are paid directly into a fund run by the Ministry of Labor (MOL). Patients pay a co-pay and facilities seek reimbursement directly from the MOL. In 2008, SSS covered 15% of the Thai population
- Universal Health Insurance (UC): covers the remaining ~75% of the population not enrolled under CSMBS and SSS. UC is entirely funded by tax revenue and funds are issued from the Ministry of Finance (MOF) to the National Health Security Office (NHSO). The NHSO was established in 2001 and serves as a purchaser of health services, under the authority of the National Health Security Board (NHSB). The NHSO primarily channels funds using capitation and diagnosis-related group (DRG) methods. The NHSO mandates that funds sent to facilities be mostly spent on UC benefits package services. For 96 items on the NLEM, purchasing occurs at the NHSO level and items are sent to facilities. Patients pay between 0 to 30 Baht in user fees.

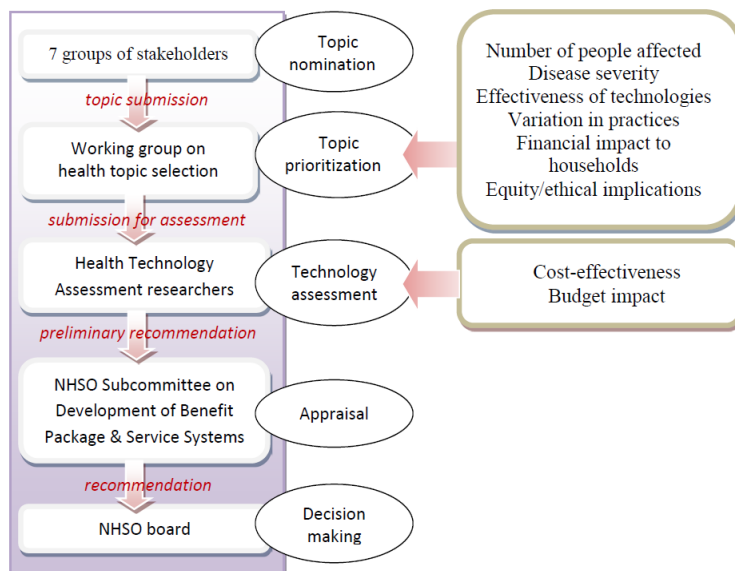
The Antiretroviral Fund and Renal Replacement Therapy Fund are special funds under the UC that were created to cover medical care for HIV/AIDS patients and renal

replacement therapy for end-stage renal disease patients. These funds pay providers based on predefined fee schedules for specialized care. (Hanvoravongchai, 2013).

With new health technologies and interventions, the NHSB Committee on Benefits Package (SCBP) is in charge of revising the benefits package and making recommendations to the NHSB on the adoption of new drugs and technologies. Prior to 2010, there were no systematic and transparent mechanisms to make such decisions (Jongudomsuk, 2012). A guideline was therefore developed and the committee regularly requests the Health Intervention and Technology Assessment Program (HITAP) and the International Health Policy Program (IHPP), two technical agencies working on health technology assessment and health system evaluation under the MOPH, to supply evidence such as the effectiveness and cost-effectiveness of various health interventions that will be considered for benefits package expansion. Financial feasibility, budgetary impact, and ethical considerations are among the important criteria in the decision process. Figure 7 below illustrated the NHSB Committee on Benefits Package (SCBP) decision process:

Figure 7

Schematic of NHSB Committee on Benefits Package Decision Process



Source: Modified from Teerawattananon, 2008

The Health Intervention and Technology Assessment Program (HITAP) was established in 2007 to assist in evidence generation in the context of health technology resource allocation in Thailand (Tantivess, 2009). In addition to strengthening the capacity of Thailand’s health researchers, HITAP has played a key role in developing methodological guidelines, standard protocols and benchmarks for resource allocation which have been adopted in various aspects of policy making.

HITAP was initially launched as a three year program affiliated with the International Health Policy Program (IHPP), a semi-autonomous research arm of the MoPH. Since it was founded in the 1990s, IHPP has conducted studies in a broad range of health systems areas including healthcare financing, human resources for health, and health systems assessment (Tantivess, 2008). One of the primary aims of IHPP was to build capacity in health policy and systems research in Thailand, sending fellows to study abroad through international grants. IHPP continues to build the capacity of Thai researchers in conjunction with HITAP and has recently conducted studies in topics such

as rural retention of health workforce, coverage of migrants in the UC, and the impact of universal coverage on reproductive health practices. (IHPP, 2015).

Brief description of the drug tariff, national formulary, positive/negative list, benefit package

The UC benefits package is comprehensive and includes inpatient and outpatient care, prevention, promotion, and rehabilitation. The benefits package is generally described as categories that will be covered. However, it has a positive list and a negative list that specify specific health conditions or clinical procedures that will be covered or excluded. The benefits package also refers to the National Essential Drug List, which classifies medicines and therapeutics into categories based on effectiveness and cost-effectiveness characteristics (Hanvoravongchai, 2013).

In 1981, a National List of Essential Medicines was introduced in Thailand, which includes the pharmaceutical benefits covered by public health insurance. While the NLEM closely followed WHO guidelines in its initial introduction, it is currently distinct from the WHO list and is used as a tool for promoting rational drug use, drug procurement at public hospitals, and drug reimbursement (Tantivess, 2009).

Medicines Supply and Procurement

Most drugs are procured by facilities using funds allocated centrally by the NHSO. There is a requirement for all health facilities to procure 70-100% essential drug items, costing 60-90% of their individual budgets, according to a 3-year procurement plan at median drug prices, which are monitored by the MOPH (Halloway, 2012). All hospitals have their own formularies that include non-essential as well as essential drugs and use revenue from private insurance, out-of-pocket payments and fee for service activities to purchase non-essential drugs. Consumption data in 2011 revealed that about half of hospital drug budgets were being spent on non-essential drugs (Halloway, 2010). Hospitals can charge a mark-up of 10-30% on drugs dispensed to civil servants and formally employed workers, for which they are later reimbursed by MOF and MOL, respectively. The reimbursement margins form revenue which may be used by the hospitals to purchase more drugs, mostly non-NLEM ones.

Facilities must purchase from the Government Pharmaceutical Organisation (GPO) if it manufactures required item. The GPO supplies about 50-70% items, however, non-GPO drugs may also be purchased. Facilities can only purchase non-GPO drugs at the median price or below as published by Pharmacy Section of the Office of the Permanent Secretary. The Pharmacy Section monitors procurement - through the Drug Management System Information Centre (DMSIC). All hospitals are required to upload volumes and prices of all drugs procured online, allowing the DMSIC to monitor prices. For 19 programs covering high risk high cost drugs, the inventory management is monitored by the GPO directly and each patient prescription is audited.

Drug Regulation

The Thai national Food Drug and Drug Administration, under the MOPH, implements regulations according to the National Drug Act (Hanvoravongchai, 2013). The main activities of the FDA consist of:

- Pre-marketing and post-marketing surveillance
- Surveillance program on product safety
- Surveillance system on advertisement

- International affairs regarding pharmaceuticals
- Database on registered pharmaceuticals

For generic products, registration is required for bio-equivalence studies along with submission of a dossier concerning the specifications and quality assurance of the product. For new brands, ACT/ASEAN technical guidelines for registration are followed. The National Centre for Pharmacovigilance (NHPCV) is situated in the Technical and Planning Division of the FDA. Every hospital Drug and Therapeutic Committee (DTC) is involved in monitoring adverse drug reactions (ADRs).

Thailand has a 2-year temporary market authorization of new drugs, pending the result of a Safety Monitoring Program (Jirawattanapisa, 2009)

What are the attributes of value

Prioritization of health topics in Thailand is conducted by a panel comprising of representatives from four stakeholder groups (health professionals, academics, patient and civic groups). The panel selects at least ten topics yearly for assessment according to six prioritization criteria (Mohara, 2012):

- Size of the affected population
- Severity of problem
- Effectiveness of interventions
- Variation in practice
- Economic impact on household expenditure, and
- Ethical and social implications.

After the selected topics are approved by the SCBP, economic evaluation and budget impact analysis are conducted by two health policy research institutes – the IHPP and HITAP – in collaboration with external experts, following the Thai HTA methods guidelines. Safety of technology remains a key consideration in overall decision processes.

A pilot project was conducted in 2012 to improve the systematic transparency of initial health topic prioritization based on a multicriteria decision analysis (MCDA). The pilot analysis specified assigning a score from one to five for each of the six noted decision criteria (Youngkong, 2012). The literature does not specify if the MCDA measurements noted in the article have fully been adapted in the UC benefit package decisions.

How are they measured and aggregated

After initial topic selection, the Thai HTA guidelines suggest either CEA and CUA as methods of choice (Ngorsuraches, 2008). The guidelines recommend the quantification of marginal costs and health outcomes, expressed in terms of quality-adjusted life years (QALYs), of new interventions versus standard practice (in an incremental cost-effectiveness ratio [ICER]). The ICER is the ratio between the marginal change in health and the marginal change in costs (adjusted by the savings related to the application of the new technology). Specific components of costs and outcomes are measured according to clear guidelines set by HITAP and IHPP.

Costs: The Thai HTA guidelines include specific recommendations on the measurement of costs related to a new health technology (Riewpaiboon, 2008)

- Use of market prices as a proxy for opportunity costs
- Societal study perspective is strongly recommended
- Times horizon recommendations are one year (prevalence-based cost of illness approach) or lifetime (incidence-based cost of illness approach)
- In most cases, direct medical, direct non-medical and indirect costs are included. The guidelines suggest the exclusion of indirect or productivity costs if quality-adjusted life years (QALYs) are the measure of effectiveness, in order to avoid “double counting” the effect of productivity loss in costs and utility scores. However, this exclusion recommendation is not consistently applied in Thai CEAs.
- The incremental use of resources is of interest rather than the total cost of an intervention
- There are two alternative sources of cost of medical services used in the valuation: reference unit cost (using CSMS reimbursement rates) and setting-specific unit cost (based on national guidelines and cost menu)
- Valuation methods for informal care should be conducted using both opportunity cost and replacement cost
- The human capital approach is recommended for calculation of indirect costs

The outcome measure used to quantify an impact on survival or health-related quality of life is quality adjusted life years (QALYs) (one QALY is a year in perfect health and zero QALY is dead). This change in health status, express through change in QALYs, is used as the numerator in the estimation of the cost-effectiveness ratio

Clinical Effect: The following recommendations are made by the Thai HTA guidelines related to effect measurement (Teerawattananon, 2008)

- Clinical effectiveness is recommended to be used in economic evaluation studies rather than clinical efficacy
- Outcome measures to include the final intended effects of the proposed health technology in terms of the ultimate change in health state, while the use of surrogate indicators and number-needed-to-treat (NNT) should be avoided.
- The systematic review and meta-analysis of high quality RCTs is a favored method to synthesize evidence
- The preferred utility methods are standard gamble and time trade off, though the specific application of methods depends on intervention characteristics.

Health technology assessment findings and recommendations are subsequently presented to the SCBP for appraisal. Appraisal criteria may include the assessment results as well as feasibility and social value judgments. In terms of determining exactly what constitutes good value for money, the SCBP considers a threshold of one per-capita gross domestic product per QALY gained. Although the SCBP is not the formal decision-maker, their recommendations on the inclusion or exclusion of assessed interventions are, in practice, endorsed by the NHSO board (Mohara, 2012)

Affordability tools/managed entry agreements (MEA)

- The Pharmacy Section monitors procurement - through the Drug Management System Information Centre (DMSIC). All hospitals are required to upload on-line the

volumes and prices of all drugs procured. In this way the DMSIC is able to monitor prices.

- HITAP's Health Technology Assessment Database
- For the price labeling of over-the-counter (OTC) drugs, the control of the Ministry of Commerce over drug prices are mandatory under the Prices of Goods and Services Act B.E.2542 (1999). The evidence used for price setting of OTC drugs includes information on cost structures and international prices submitted by pharmaceutical companies (Jirawattanapaisal, 2013)
- Prices of non-OTC drugs include in the NLEM procured by public hospitals are controlled by the "Medicine Price Ceiling," which is a list of maximum prices for each drug that sellers are allowed to charge from public hospitals (Jirawattanapaisal, 2013)

6.3.4. Germany

Introduction and Decision-making process

Around 86% of the Germans are affiliated to the public statutory health insurance scheme (SHI) which is operated by more than 140 competing sickness funds (Blümel, 2013). Even if these sickness funds compete between each other to capture the highest number of affiliates, this competition is not based on the package benefit which is the same for each one of the sickness funds, and which is also the based package for the private funds. The benefit package is determined by the Federal Joint Committee (G-BA). The G-BA includes representatives from sickness funds, healthcare providers and patient organizations (Green and Irvine, 2013).

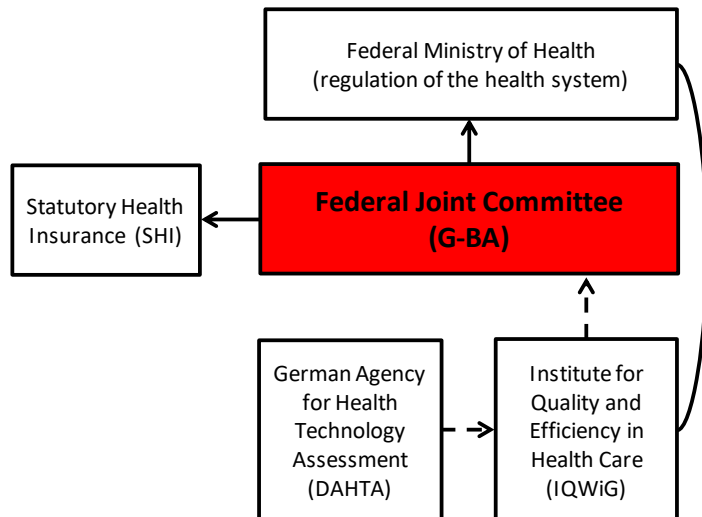
Most pharmaceuticals approved by the EMA or the German Federal Institute for Drugs and Medical Device (BfArM) are automatically included in the benefit package. Nevertheless, there are some exceptions. For instance, drugs for trivial diseases (e.g a common cold) are legally excluded from the benefits' package over 18 years (ISPOR, 2011). Moreover, since the German health care reform of 2011, through the enacting of the new Act to Reorganize the Pharmaceutical Market in the Statutory Health Insurance System (AMNOG), an early benefit assessment is required for all new medicines (Rouf et al., 2014). The pharmaceutical manufacturers have to submit a benefit dossier which is evaluated by the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the IQWiG evaluation and his own evaluation the G-BA decides whether a new medicine prove to have sufficient additional benefit to be reimbursed. Otherwise, when a drugs deemed 'inefficient' (not effective for the desired purpose or effect not certainly evaluated), it is included in a negative list and will not be reimbursed (Gerber et al., 2011; Rouf et al., 2014).

IQWiG evaluates the medical efficiency, quality, effectiveness, and in recent years the cost-effectiveness of the health technologies. Some evaluations of the IQWiG are commissioned to the German Agency for Health Technology Assessment (DAHTA) which is part of the German Institute of Medical Documentation and Information DIMI. DAHTA has two statutory functions: (1) setup and maintenance of a database-supported information system for the assessment of the effectiveness and costs of medical procedures and technologies, (2) assessment of procedures and technologies relevant to health in the form of HTA reports (DIMI, 2013).

Figure 8 illustrates the decision-making process in Germany. The Federal Ministry of Health is the responsible of establishing the legal framework for health-care provisions. The role of the G-BA is to translate this legal framework into practice. In this sense, the

decisions taken by the G-BA are legally binding for providers, payers and persons insured under the SHI (Fricke and Dauben, 2009). The G-BA considers the IQWiG recommendations, but is free to decide independently. For instance, during 2011-2012 in at least five cases related to new drugs, the G-BA final decision diverged from the IQWiG recommendation (Rouf et al., 2014).

Figure 8
Germany Decision-making process



Boxes: Decision-making bodies
Solid Arrows: Required steps in decision-making process
Broken Arrows: May or may not impact decision.
Source: ISPOR, 2015 (ISPOR, 2011)

Brief description of the drug tariff, national formulary, positive/negative list, benefit package

Three instruments regulated the pharmaceutical market in Germany:

- **Reference prices:** Drugs that are judged to be therapeutically equivalents are grouped in a single “cluster” for which a single level of reimbursement is established. In the case that a patented drug is considered a me-too drug with no additional benefit compared to current treatment and the respective original drug is off-patent, both drugs are included in the reference pricing scheme (Drummond et al., 2011).
- **New Medicines early benefit assessment:** In the AMNOG regulation is stipulated that for each new medicine the manufacturer has to submit a dossier to the G-BA in order to prove the added benefits. G-BA commission the IQWiG to conduct a rapid benefit assessment in a three months period. After the IQWiG assessment the G-BA has three months to evaluate the new medicine and issue its decision. After this point two pathways are possible:
 - i. If the G-BA decision is positive, then the price is negotiated between the Federal Association of Sickness Funds and the manufacturer. If after 6 months a price agreement is not achieved, a price is defined by an arbitrary body. Normally, the arbitrary body considers a set of international prices to define the internal price (Gerber et al., 2011; Ognyanova et al., 2011).
 - ii. If the G-BA decision is negative, the new drug will be directly included in the reference pricing system. This applied for all pharmaceutical that do not

demonstrate added value. In case that the new drug cannot be included in any existing therapeutically equivalent group, it will receive the same price as its comparator (Gerber et al., 2011; Ognyanova et al., 2011).

Two important elements of the German system need to be highlighted. First, in Germany after the marketing approval of a new drug the manufacturer can set the price freely and the SHI will pay this price until the process mentioned before is completed (around one year) (Gerber et al., 2011). Second, the early benefit assessment elaborated during the first three months of the process does not include a cost-effectiveness assessment. A cost-effectiveness assessment might be included at a later stage if requested (e.g. if it has not been an agreement during the regular period of price negotiations) (Greiner and Graf von der Schulenburg, 2010; Ivandic, 2014).

- **Negative list for drugs which are not reimbursed:** Specific medicinal products that are not proved to have sufficient therapeutic benefits or which are prescribed in cases of specific minor impairments of health are not reimbursed at all and are set out in a government "negative list". Moreover, prescribing limitations to specific indications, to specific usage requirements (after failed nonmedical treatment, second-line, third-line), can be defined by the G-BA using self-assessment or an IQWiG assessment (ISPOR, 2011).

What are the attributes of value

The G-BA and IQWiG assessments are focused on health benefits based on clinical evidence meeting specific standard (e.g. surrogate outcomes are generally not accepted). Adverse event can also be considered. No other elements of value are reported. More details are provided in the text below.

Orphan Drugs are treated as an exception. In this case, market authorization is considered prove of additional benefit. Therefore, orphan drugs are excluded from the obligation of a benefit assessment. The exceptions are those orphan drugs whose revenues of the past year do exceed 50 million euros. In this case, the IQWiG should only assess the target population size and drug budget impact and G-BA will decide only on the extent of the additional benefit (Ognyanova, et al., 2011; Rémuzat et al., 2014).

Various elements are important during the G-BA and IQWiG early benefit assessment:

- **The selection of the appropriate comparative therapy (ACT):** This is the first element in the process of assessment and it is crucial in the final decision. The ACT is defined by the G-BA, and in most of the cases there is consensus with the manufacturer. However, since the manufacturer defined the therapy earlier during the clinical trials, there are some examples in which the manufacturer selection differs from the G-BA selection. To avoid this, an amendment to the AMNOG was introduced in 2012, now the regulatory bodies need to be involved during early consultations (before phase III trials) (VFA, August 2012).
- **The level of evidence:** IQWiG focuses on randomized controlled trials (RCTs) in its general methods because of their internal validity, which is to demonstrate causal relationships (Fricke and Dauben, 2009). Three characteristics are important, the number of studies, the certainty of the results and the consistency of the direction of the effect between the studies. Based on these three criteria, the evidence presented for each new drug is classified into three categories: (a) proof, (b) indication, and (c)hint (Rouf et al., 2014).

- **Clinical endpoints/outcomes:** Patient-relevant outcomes are not only preferred but required.
- **Adverse event in comparison with the ACT:** The IQWiG considered an additional benefit from the new drug whether fewer adverse events were observed (Rouf et al., 2014). Based on the outcomes and number of adverse effects, the benefit harm ratio is analysed (Ivandic, 2014).

How are they measured The relevant outcomes for each case are defined by the G-BA or the IQWiG and are grouped into three categories: (a)mortality, (b)morbidity, and (c) health related quality of life (HRQoL). Only if patient-relevant endpoints are not available, the assessment is based on other information. Surrogate outcomes are normally not accepted by the IQWiG, only in particular cases such as those related with extremely serious diseases for which there are no other treatment alternative (Ivandic, 2014; Rouf et al., 2014).

How are they aggregated and valued

Based on the information presented by the manufacturer on the dossier and the analysis of the mentioned four factors, the IQWiG classified the additional benefit of the new drugs in comparison with the ACT according with the following categories (Gerber et al., 2011; Rouf et al., 2014):

- Remarkable additional benefit
- Considerable additional benefit
- Minor additional benefit
- Additional benefit not quantifiable
- No evidence of additional benefit
- Less benefit than the comparator

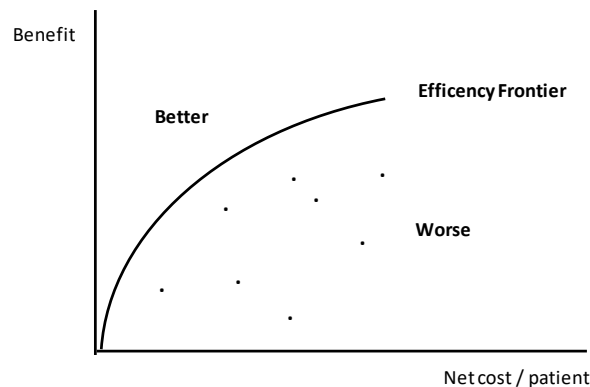
It is common that the G-BA divides the patient population into different groups and assigns different additional benefit scores depending on the sub-populations (Rouf, et al., 2014).

The cost-effectiveness assessment is not part of the initial assessment; however, it has an important role in the determination of the price for innovative drugs that have proved additional benefit and have a high cost. (Greiner and Graf von der Schulenburg, 2010).

The approach applied by the IQWiG to determine the cost-benefit of a new drug is the so called Efficiency Frontier. This is based on the relationship between the total benefit and total costs of all available compounds (Figure 9). If the new medicine has a cost-benefit ratio comparable to efficient existing treatments, then the current price may be reasonable. Nevertheless, the final decision involves additional evaluation; for instance, budget impact analysis. The budget impact analysis examines the impact on the total expenditure of the maximum reimbursable price which is established based on the efficiency frontier analysis. The IQWiG limits the analysis only to the description of the possible financial impact without attempting to make a concrete recommendation regarding the reasonableness of cost coverage (Institute for Quality and Efficiency in Health Care (IQWiG), 2009). The judgment whether the financial burden is acceptable or not is taken by the G-BA.

An important discussion has emerged around this methodology. For instance, the difference in the recommendation depending on the benefit measure (ISPOR, 2011).

Figure 9
Efficiency Frontier



IQWiG has run a number of pilots aimed at eliciting patient preferences on a range of dimensions of value (mainly of clinical nature). Those could in principle be used as weights to determine disease-specific efficiency frontiers. However, the results of the pilot and the methodologies used in the pilot have not implemented in practice.

Affordability tools/managed entry agreements (MEA)

A number of affordability tools and managed entry agreements are applied in Germany (Cassel and Wille, 2007). Some of the most important are:

- In the pharmaceutical sector, negotiated rebates contracts between sickness funds and pharmaceutical manufacturers, along with incentives to lower prices below the reference prices, are now the major instruments of cost restraint (Green and Irvine, 2013).
- Parallel Trade: The pharmacists are required to dispense at least 5% of the total drug dispensations as parallel imported drugs (Fricke and Dauben, 2009).
- Reference price and aut idem: Allows pharmaceuticals to substitute the same active agent from different manufacturers (Gerber et al., 2011).

6.3.5. United Kingdom

Introduction and Decision-making process

Health services in England are largely free at the point of use. The National Health Service (NHS), created in 1948, provides preventive medicine, primary care and hospital services (Thorlby and Arora, 2015). UK residents have the right to use NHS healthcare without charge, apart from some co-payments required for outpatient prescription and dentistry services. The system is financed mainly by general taxation and national insurance (a payroll tax) (Harrison, 2013; Thorlby and Arora, 2015).

The Department of Health (DH) and the Secretary of State for Health are ultimately responsible for the management of the health system as a whole. Nevertheless, after the Health and Social Care Act 2012, some important functions and decision were transferred to the NHS England such as the overall budgetary control. (Boyle, 2011; Thorlby and Arora, 2015).

In this context, the National Institute for Health and Care Excellence (NICE), created in 1999, has the responsibility of setting the guidelines on clinically effective treatments and appraising a selection of new health technologies for their clinical and cost-effectiveness (Thorlby and Arora, 2015). NICE is a Non-Departmental Public Body

(NDPB), which means that it responds to the DH but it is independent from the government.

NICE produces advices and guidelines on a number of areas including: 1) clinical guidelines, 2) public health guidelines, and 3) technology appraisals (TAs) which are recommendations on appropriate use of health technologies, mainly pharmaceuticals, within the NHS.

In the NHS constitution, it formally specifies that patients have the right to receive the treatment recommended by NICE in its health technology appraisal guides. This is in line with the mandatory nature of these NICE recommendations (Cerri et al., 2014; NICE, 2014).

Three other agencies have a role in the provision of health technologies within the English NHS: 1) The National Screening Committee (NSC), 2) the Joint Committee of Vaccinations and Immunizations (JCVI) responsible for vaccinations, and 3) the Health Protection Agency (HPA) which is involved in a number of different matters such as infection diseases, laboratory testing and radiological hazards (Raftery, 2014). These agencies apply some of the methodologies used by NICE during its appraisals.

For instance, the NSC, JCVI and HPA use a cost-effectiveness approach as defined by NICE (Raftery, 2014).

The rest of the note focuses on NICE TAs, which are the only NICE recommendations which are mandatory (i.e. they have to be implemented by local NHS commissioners).

Brief description of the drug tariff, national formulary, positive/negative list, benefit package

In England new medicines are automatically included in the NHS drug tariff (NHS, 2012) and can be prescribed by clinicians unless they are referred to NICE.

The following list corresponds to the mechanisms that regulate the pharmaceutical market in England:

- **Pharmaceutical Price Regulation Scheme (PPRS)**: this corresponds to a voluntary agreement between the pharmaceutical companies and the Department of Health. This agreement regulates the price of the majority of the branded drugs by limiting the price and related to the branded medicines (Department of Health and the Association of the British Pharmaceutical, 2013).
- **NICE TAs focusing on clinical and cost-effectiveness**: NICE does not look at all NHS treatments or drugs. There is a well-established procedure for the topic selection that starts approximately 2 years before a drug is licensed. The possible topics are assessed according to NICE/DH criteria. Some of the criteria are (Godfrey, 2014):
 - i. Population Size.
 - ii. Disease severity: Takes into account life expectancy; how far the individual is away from perfect health and health states that incur social stigma.
 - iii. Potential resource impact of guidance including cost of implementing guidance.
 - iv. Extent to which a new technology claims measurable therapeutic benefit over currently available NHS treatments.

In the case of highly specialised technologies (HST) (which are interventions for very rare conditions), NICE uses an extra group of selection criteria (Godfrey, 2014):

- i. The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS.
- ii. The target patient group is distinct for clinical reasons.
- iii. The condition is chronic and severely disabling.
- iv. The technology is expected to be used exclusively in the context of a highly specialised service.
- v. The technology is likely to have a very high acquisition cost.
- vi. The technology has the potential for life long use.
- vii. The need for national commissioning of the technology is significant.

After NICE, DH and NHS England jointly agree on the topics, they send the selected list of topics to the Minister of Health which makes the final referral to NICE to produce (TA) guidance (NICE, 2014).

Once NICE receives the referral from the Minister, the clinical effectiveness and cost-effectiveness of the selected health technologies are jointly examined during the health technology appraisal (House of Parliament, 2015).

What are the attributes of value

Health effects and Health service cost savings are the most important elements of value considered. The other element of benefits that is considered (and explicitly mentioned in the NICE guide to methods) is the proximity to death of the patient and effect on survival that a new treatment has. The End of Life policy includes three criteria that have to be met (NICE, 2009):

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and;
- The treatment is licensed or otherwise indicated, for small patient populations.

In the case of the clinical effectiveness, NICE considered the evidence from randomised controlled trials and systematic reviews. In that senses the characteristics of the evidence are analysed (Rawlins et al., 2010):

- Strengths and limitations of the systematic evidence review.
- Absence of direct comparisons.
- End-point used in the relevant studies (e.g. the use of surrogate outcomes).
- Time scale of the studies.
- Generalizability of the available data.

Regarding costs, NICE considers the acquisition costs, the administrative costs (e.g. input from nursing), additional costs of monitoring the response and the cost of treating adverse effects (Rawlins et al., 2010).

Other factors that have been indicated as playing a role include: (Rawlins et al., 2010):

- Disease severity.
- Stakeholder persuasion: Patients or their advocates can explain why the evidence analysed (e.g. randomised clinical trials) does not reflect the severity of the disease or its effects.
- Significant innovation.
- Disadvantage population.
- Children.

However, those appear to be taken into account only on a case-by-case basis.

Between 2013 and 2014 approaches for introducing a new value based assessment were proposed by NICE. Those included changing the current NICE methods to consider burden of illness (measured by using the proportional QALY shortfall approach) and wider societal benefit (measured by using the absolute QALY shortfall approach). However, because no agreement was achieved through the public consultation, the NICE methods have remained unchanged.

How are they measured and aggregated

In the case of the cost-effectiveness analysis the analysis is normally based on the estimation of the incremental cost-effectiveness ratio (ICER). This is the ratio between the marginal change in health and the marginal change in costs (adjusted by the savings related to the application of the new technology) (Rawlins et al., 2010).

Measures of health outcomes reflect health benefits and adverse effects that are important to patients. The outcome measures usually quantify an impact on survival or health-related quality of life that translates into quality adjusted life years (QALYs) (one QALY is a year in perfect health and zero QALY is dead). This change in health status, expressed through change in QALYs, is used as the numerator in the estimation of the cost-effectiveness ratio (NICE, April 2013).

Regarding the estimation and measure of the total costs, this required the use of economic modelling. Economic modelling is always based on a series of assumptions that are defined by the modellers and the decision-makers (Rawlins et al., 2010).

Once the most plausible ICER (given the assumptions of the economic model) is estimated, the advisory bodies decided whether the new technology offers good value for money. These decisions are based on a threshold explicitly stated in the NICE method guide. The probability that NICE recommended the use of a new technology with an ICER above £30,000 is considerably low, but not zero. Similarly, the probability that NICE reject the use of a new technology whose ICER is lower than £20,000 is small. However, there is evidence showing that NICE has approved a number of technologies with ICERs greater than the current threshold, as it exercises social value judgements as well as assessing the cost per QALY (including whether the technology is a life-extending treatment at the end of life) (Dakin et al, 2014).

How are they value

- General population perspective de facto (those preferences are used to value health states used to estimate HRQoL)
- Market prices

- Deliberation of the Appraisal Committee members

Affordability tools/managed entry agreements (MEA)

- **Patient Access Schemes (PAS):** When a treatment does not prove to be cost effective (i.e. their ICER is higher than the pre -defined cost-effectiveness threshold), the manufacturer can propose and agree a PAS with the Department of Health (DH). Types of PAS (Department of Health and the Association of the British Pharmaceutical, 2013; Puig-Peiro et al., 2011): financially-based schemes (which have accounted for the majority); and outcome-based schemes.
- The above mentioned **PPRS** (Department of Health and the Association of the British Pharmaceutical, 2013): the current scheme involves
 - Pre-agreed level of allowed growth rate of UK branded medicine bill for each year of the scheme
 - Payments in cash once the allowed growth rate is exceeded

The Cancer Drug Fund (CDF): The main objective of this fund is to enable patients to access drugs that may not be available in the NHS (e.g. drugs that have not been recommended or appraised by NICE). The CDF will cost around £340 million between April 2015 and April 2016 (House of Parliament, 2015).

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7. APPENDIX 2 – INTERVIEW GUIDE

1. Do you have any direct experience of developing a national drug formulary?
 - a. If yes, are there any specific MICs that you have worked in or have interest in?

This interview will first ask you about micro-level decision- making before asking questions about macro level issues

2. What do you think are the three most important principles that should be used when adding a new medicine to a drug formulary in MICs?

Please look at Table 7

Table 7 summarises, based on a review of published evidence, some example factors that may be used in the context of deciding whether to add a new medicine to a national drug formulary.

Table 7

Potential factors to use when assessing the value of a new medicine

Factor	Examples
<i>Intervention-specific</i>	<ul style="list-style-type: none"> • Health effects • Treatment side effects profile • Impact on existing processes of care or care pathways • Patient convenience
<i>Disease-related</i>	<ul style="list-style-type: none"> • Severity of health condition • Size of the population targeted by the treatment
<i>Equity</i>	<ul style="list-style-type: none"> • Stigma • Characteristics of the target population: <ul style="list-style-type: none"> - socioeconomic status - age - ethnicity
<i>Financial</i>	<ul style="list-style-type: none"> • Cost offset (per patient) to the health care system • Indirect costs, including impact on non-health public sectors and impact on individuals/households • Total budget impact

3. Considering the listed factors, which ones do you think should be considered when deciding whether to add a new medicine to a national drug formulary?
4. Are there any additional factors you would like to add to this list or changes you would like to make?
5. What types of evidence should be used when deciding whether to add a new medicine to a national drug formulary?
6. How can these factors be combined to generate an overall view on the 'value' of the proposed new medicine when deciding whether to add it to a national drug formulary?

7. What mechanisms, processes, or methods do you think should be used so that opportunity cost can be taken into account when adding a new medicine to a national drug formulary?
8. Which mechanisms, methods, or processes could be used to take account of affordability in terms of the impact on the healthcare budget when a new medicine is added to a national drug formulary?

Turning now to macro-level decision making

9. In your view, to what extent and how does macro-level decision making that focuses on the health system organisation and its priority setting affect decisions on whether to add a new medicine to a national drug formulary?
 - a. If not, why not?
10. Can you tell me about any proposed changes in a MIC health system that should be considered when thinking about developing a new drug formulary?
11. What mechanisms, processes, or methods should be used to identify and measure the impact of changes in a health care system when making decisions on whether to add a new medicine to a national drug formulary?

Finally, the interviewer will ask you about process issues related to the development of a national formulary

12. Who are the key stakeholders you think should be involved in developing a national formulary?
13. What process should be used to decide which medicines should go through the decision-making process?
 - a. Should all medicines be assessed or should particular medicines be selected for assessment?
 - b. Should there be a separate process for the HTA assessment and the appraisal/pricing/reimbursement decisions?
14. How often should the national drug formulary be updated?
 - a. How should this be done?
15. Is there anything else you would like to add that we have not covered in the questions I have asked you?

8. APPENDIX 3 – SURVEY

8.1. Reading material and tasks to complete before the workshop

To explore the issue of how macro-level factors interact with micro-level factors, we outline one middle-income country archetype (country X).

The health ministry of this country is planning to restructure its current process and approach to identify medicines to include in the national formulary. It also intends to evolve its health care system toward UHC.

Country X

- Has a public health insurance scheme covering around 50% of the population. 25% of the population have a private insurance and the remaining 25% of the population pays out of pocket to access health services and treatments.
- The public health insurance scheme provides a benefits package which refers to a national drug formulary
- There is a process involving mainly clinical and regulatory experts and following some, mostly implicit, criteria to decide whether to include a new intervention into the national drug formulary
- There is an intention to improve the current process to develop the national drug formulary but not necessarily to follow an HTA approach

Task 1

Table 8 summarises macro-level factors that country X may consider when restructuring the process for deciding whether to add a new medicine to a national drug formulary.

Table 8

Macro-level factors

Factors	Examples
Macro-level	<ul style="list-style-type: none">• Disease burden and national disease priorities• Other national health system priorities; political considerations and objectives• Role of disease-specific funds and/or programmes• Role of WHO Model List of Essential Medicines and need for a specific national drug formulary• Current service delivery setting and preparedness of the health care system to provide interventions• Catastrophic effects and financial risk on individuals for not funding certain interventions• Existence of a legal process for patients to access interventions not included in the formulary

Question 1: Considering the macro-level factors listed in Table 8, what are the three most important factors that country X should consider when restructuring the process for deciding whether to add a new medicine to a national drug formulary?

Question 2: What are the three least important factors?

Question 3: Are there important factors not listed in Table 8 that country X should consider instead?

Task 2

Country X intends to introduce a new approach to determine the overall value generated by medicines (e.g. how important is it? how well does it work?) and that could ultimately inform national formulary decisions. This implies a combination of available evidence on macro-level factors (listed in Table 8) and micro-level factors (listed in Table 9 below).

*Table 9
Micro-level factors*

Factors	Examples
Intervention-specific	<ul style="list-style-type: none"> • Health effects (including life extension and quality of life improvements) • Treatment side effects profile • Impact on existing processes of care or care pathways • Patient convenience
Disease-related	<ul style="list-style-type: none"> • Severity of health condition • Size of the population targeted by the treatment
Equity	<ul style="list-style-type: none"> • Characteristics of the target population: Socioeconomic status, Age • Ethnicity • Stigma
Financial	<ul style="list-style-type: none"> • Cost offset (per patient) to the health care system • Indirect costs, including impact on non-health public sectors and impact on individuals/households • Total budget impact

The following are examples of some of the approaches to aggregate macro-level and micro-level factors that country X is considering:

1. Focus on health effects measured by clinical outcomes to develop a “therapeutic added value” index of the intervention as compared to standard of care.
2. Consider an incremental cost per health outcome of the intervention as compared to standard of care and take into account other non-health benefits via a deliberative process.
3. Develop a “therapeutic added value” index of the intervention as compared to standard of care reflecting clinical benefits of the treatment as part of a multi-country evaluation process (similarly to the WHO Model List of Essential Medicines which is relevant to multiple countries and can be adapted to meet national needs and health priorities) and make formulary decisions based on that at the country or local level.
4. Develop a multi-criteria decision analysis (MCDA) approach where selected attributes of value are weighted according to their relative importance (based on the decision maker’s or multiple stakeholders’ preferences); each medicine is scored against the selected attributes and a final score is determined.
5. Recommendations for formulary inclusion are based on the deliberations of an expert body that is grounded in the clinical evidence, but considers the full range of other

factors, such non-health benefits, disease severity, equity, etc.. However, no mathematical formula or explicit weighting is used for combining the attributes.

Question 4: Considering the approaches listed above, what is the most useful approach to implement in country X to develop a decision on adding medicines to the national formulary?

Question 5: What is the least useful approach?

Question 6: Are there important approaches not listed above that country X should consider instead?

Task 3

Country X is considering policy implementation options to take account of budget impact as well as value, and to manage use in clinical settings when developing a decision on adding new medicines to the national formulary.

The following are the policy options under consideration:

1. Rebate schemes involving volume caps
2. "Appropriate use" rules and other means of targeting treatments
3. Alignment with clinical guidelines, if available

Simple forms of managed entry agreements such as outcome-based schemes appropriate to the data and monitoring capabilities of the country health system

Question 7: Considering the policy options listed above, what is the most useful option to implement in country X to develop a decision on adding new medicines to the national formulary?

Question 8: What is the least useful option?

Question 9: Are there important policy options not listed above that country X should consider instead?

8.2. Results of the survey (pre and at the workshop)

Which macro-level factors should affect the development of a national formulary for medicines?

Table 10

The most and least important macro-level factors

	Before workshop (8 responders)		At workshop (7 responders)	
	Least Important	Most Important	Least Important	Most Important
1) Disease burden and national disease priorities		✓ ✓		✓ ✓
2) Other national health system priorities; political considerations and objectives	✓	✓	✓ ✓	✓
3) Role of disease-specific funds and/or programmes	✓ ✓	✓	✓ ✓	
4) Role of WHO Model List of Essential Medicines and need for a specific national drug formulary	✓ ✓	✓	✓	
5) Current service delivery setting and preparedness of the health care system to provide interventions		✓ ✓		✓ ✓
6) Catastrophic effects and financial risk on individuals for not funding certain interventions	✓	✓		✓ ✓
7) Existence of a legal process for patients to access interventions not included in the formulary	✓ ✓		✓ ✓	

Source: Authors' elaboration

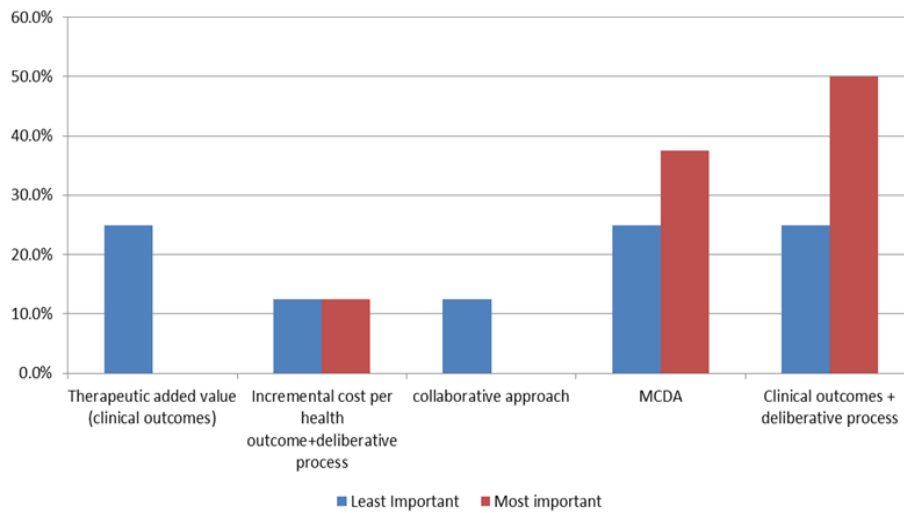
Main Results:

- Consensus that financial risk protection is a very important factor ("healthcare systems provide peace of mind because you are covered"). Example of catastrophic effect of dialysis in Thailand.
- Little role for the WHO list of essential medicine ("it is just a general guidance"). It is much more applicable to low income countries than middle income countries.

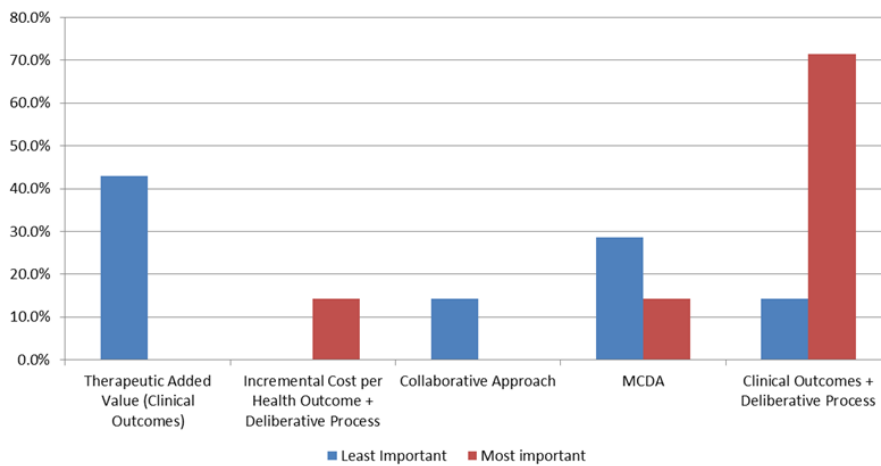
Figure 10

How to consider or combine both macro-level and micro-level factors to determine the overall value of medicines?

A. Voting before workshop



B. Voting at workshop



Source: Authors' elaboration

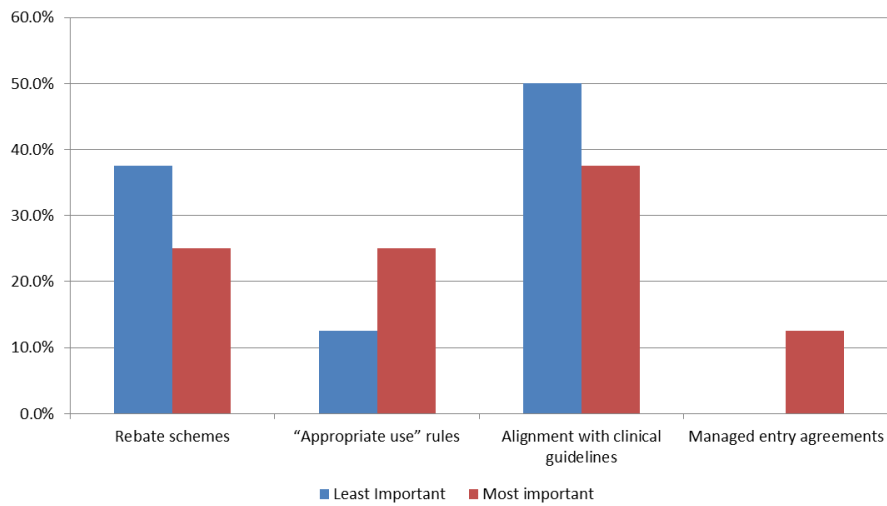
Main Results:

- Consensus that only considering clinical effects would not be a satisfactory option
- Other factors, including “contextual issues”, are important but can be quantified to different degrees
- This is probably why MCDAs option lost support in favour of the deliberative process
 - Label effect?

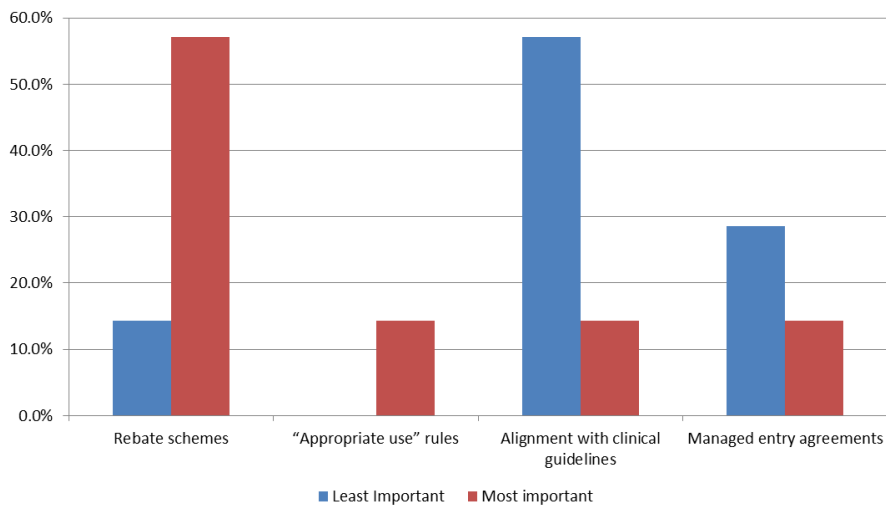
Figure 11

What are the viable policy implementation options to take account of budget impact as well as value, and to manage use in clinical settings?

A. Voting before workshop



B. Voting at workshop



Source: Authors' elaboration

Main Results:

- More support was gained by schemes affecting price (rebate schemes)
 - In MICs schemes affecting volumes ("appropriate use" rules, and clinical guidelines) might be more difficult to enforce
 - Complex MEA/pay for performance schemes can also be problematic in practice (Taiwan example)
- Clinical guidelines lost support and seen as one of the least useful/viable option