

**Sharing Knowledge on Innovative Medicines for Non-Communicable Diseases:  
A Compendium of Good Practices for Sustainable Access**

**-Promoting a Dialogue among Payers and Manufacturers-**

**Management Sciences for Health, RTI International, & Global Health Insights**  
**Project on *Strengthening Global Knowledge on Access Solutions for Innovative Medicines***

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## EXECUTIVE SUMMARY

### Introduction

Non-communicable diseases (NCDs)—including cardiovascular disease (CVD), cancers, strokes, chronic respiratory infections, and diabetes—presently contribute to 70% of worldwide mortality (GBD, 2018). NCDs represent a significant and growing contribution to disability-adjusted life-years (DALYs) in low- and middle-income countries (LMICs) and many of these countries are confronted with a dual challenge since a substantial burden of infectious diseases and NCDs coexist in these settings. The 2013 Global NCD Monitoring Framework aims for a 25% reduction in premature death from NCDs by 2025 (25x25) and Sustainable Development Goal (SDG) 3.4 targets an additional 5% (or 30% overall) reduction of NCDs by 2030. Both 25X25 and SDG 3.4 place emphasis on preventing the causes of NCDs but also highlight the critical role that access to medicines must play in achieving national and global goals.

Equitable, sustainable access is needed for existing NCD medicines, as well as for new, breakthrough NCD innovations that show potential for therapeutic effect and long-term cost reduction. These innovations are increasingly being rolled out in high-income countries, but their availability in most LMICs remains limited due to high prices, fragmentation of sources of funding, and uncertainties about their clinical effectiveness and cost-effectiveness. Moreover, there are a range of health systems constraints including those related to rational selection of medicines, development and use of evidence-based clinical practice guidelines, capacity amongst health professionals to manage NCDs, health information systems, and procurement and distribution systems. The constraints in each country differ, as do the appropriate range of strategies for addressing them, due to varying contexts across LMICs with respect to a wide range of factors including income level, population, disease burden, health expenditure and financing, and pharmaceutical policies.

**This compendium is a global knowledge resource that provides stakeholders with information and tools about access strategies for innovative NCD medicines in LMICs. It is intended to promote dialogue among governments, other payers, and manufacturers in LMICs, as well as additional stakeholders involved in providing access to medicines. In particular, the compendium focuses on formal, negotiated agreements between pharmaceutical companies and payers (government payers, private insurers, or donors) referred to as managed access strategies (MASs). MASs include “compassionate need” and non-profit access programs, voluntary licensing, and confidential agreements known as managed entry agreements (MEAs). In the access to medicines literature, relatively less attention has been given thus far to MEAs, and these arrangements are therefore a particular focus of the compendium. Based on research carried out by Management Sciences for Health (MSH), the compendium includes a literature review of the published and grey literature on MEAs and semi-structured interviews with key informants in three LMICs (Colombia, Kenya, and Ukraine). It is also based on the development and testing of three decision analytic models by Research Triangle Institute (RTI) International in cooperation with MSH. The compendium was compiled and written by Global Health Insights (GLOHI) in partnership with MSH and RTI.**

### **Access to innovative NCD medicines in segmented markets**

Fragmentation or segmentation of pharmaceutical markets within the health sector is present in many countries. In high-income countries where fragmentation of funding sources for healthcare tends to be much less than in lower income settings, most financial resources come from the public sector (either from taxes or national health insurance). Nonetheless, the private sector—such as through private insurance (complementary, supplementary, or substitutive)—adds to the pot of available resources for pharmaceutical products. In these settings, out-of-pocket (OOP) payments usually play a less important role, especially after universal health coverage (UHC) has been achieved.

On the contrary, LMICs are at a range of different levels of development, and their systems may therefore have varying degrees of fragmentation. Many low-income countries rely heavily on donor assistance and OOP payments as main sources of healthcare financing, with limited availability of public resources for healthcare. High OOP payments are a threat to ensuring access and affordability of medicines in countries. At the same time—for those segments of the population with more financial resources—OOP payments are an opportunity for patients to choose preferred providers and medicines. Middle-income countries, on the other hand, are faced with a double challenge since they are not eligible or have transitioned from donor assistance, but many of these countries remain constrained by limited public funding for healthcare. In many middle-income countries, private funding remains substantial and linked to the ability of individuals to pay. The role of private insurance varies in different settings and high levels of OOP payments expose the population to the risk of catastrophic expenditure and impoverishment.

Thus, many health systems in LMICs have multiple payers and/or fragmented delivery systems. The segment of the population in many countries with the ability to pay for NCD medicines may be very limited because of the scarcity of financial resources as well as the high costs of innovative medicines and the chronicity of treatment. In these contexts, it is necessary to identify more nuanced market segments within countries and to establish different MAS arrangements for these different segments to ensure greater reach of and access to innovative NCD medicines. The engagement of the private sector may be required—including the harnessing of private-sector technological innovations—since demand in multi-payer contexts can often not be fully met through public sector provision alone.

### **Managed entry agreements (MEAs)**

MEAs are **formal arrangements between pharmaceutical companies and payers that seek to share risk with respect to the introduction of new health technologies**. These arrangements are referred to by a variety of other names including risk-sharing agreements, performance-based agreements, patient access schemes, and special pricing arrangements. MEAs involve two key stakeholders: a payer (either a government or public fund holder, or a private holder of pooled resources such as an insurer) and a pharmaceutical company that manufactures and commercializes a new drug. A number of additional stakeholders may be involved in the negotiation and implementation of MEAs, including other regulatory

bodies, Health Technology Assessment (HTA) agencies, and health providers involved in implementation. MEA arrangements have three objectives: 1) to reduce high costs and uncertainties about expenditure on a new medicine; 2) to address uncertainties about a new medicine's clinical effectiveness and cost-effectiveness in a particular setting; and 3) to manage a medicine's utilization in order to optimize performance (Kanavos et al., 2017).

MEA agreements generally fall into two categories: financial schemes and performance-based agreements. Financial schemes focus on targeting the financial impact of new drugs to patients and/or health systems. Financial schemes leverage instruments such as discounts, price/volume agreements, patient/dose dependent discounts, and utilization-based price capping. Performance-based agreements address the uncertainty with respect to evidence on clinical outcomes or eligibility of patient populations. Instruments include outcome guarantees, patient eligibility requirements/registries, and coverage with evidence development. Hybrid models also exist, combining financial- and performance-based instruments.

Research carried out for the compendium identified 285 documented MEAs, with most of these present in high-income countries. The majority of these MEA arrangements focus on treatments for NCDs, particularly different types of cancer, with financial schemes slightly more common than performance-based agreements. Documentation on MEA implementation in LMICs is extremely limited and requires more study.

MEAs may provide multiple advantages to stakeholders seeking to improve access to innovative NCD medicines. While potentially promoting earlier access to patients, MEAs may help payers to address budget- and clinical-related uncertainties while also allowing them to respond to social pressure for expanding access to innovation. For pharmaceutical companies, MEAs may provide some predictability about initial price conditions and potential market size estimations. MEAs could also help create a more collaborative environment between payers and pharmaceutical companies. Finally, MEAs may bring an opportunity for policy action, allowing stakeholders to explore a wide range of different types of instruments to address context-specific needs and markets.

Despite these advantages, MEAs may also bring challenges and limitations. One key challenge relates to the burden they place on the health system, in terms of administration, cost, and the need for data collection and analysis. MEAs also require enabling legal and policy frameworks. In addition, if implemented under strict confidentiality requirements, these arrangements may limit the ability of some stakeholder groups to know about and participate in MEA processes. Moreover, the lack of publicly available information may prevent learning across countries about what works and what does not in the implementation of MEA arrangements. Negative perceptions about MEAs by some relevant stakeholders may make it unlikely for these arrangements to be considered as a policy tool. A final limitation of MEAs is the possibility that key stakeholders may "game the system" in regard to skipping robust HTA to inform coverage decisions.

The compendium's case studies in Kenya, Ukraine, and Colombia identified a set of nine factors that could help or hinder the use of MEAs in these settings. These factors require further testing in other LMICs.

1. *Contextual characteristics* of the country including income level, market size, political stability, levels of corruption, structure of the health system (centralized or decentralized), previous local successes, international cooperation, and levels of coordination.
2. *Characteristics of the drug and its evidence and uncertainties*: sufficiency and quality of available evidence about a new drug in a particular country, including real-world evidence, cost-effectiveness, and patient eligibility criteria; the possibility of generalizability/extrapolation of clinical results to the local population.
3. *Capacity of the health system to regulate and negotiate, as well as collect, monitor, and evaluate data* (for financial schemes, health systems require capacity to estimate volumes, and for performance-based schemes, health systems need to be able to assess outcomes).
4. *Existence of enabling legal and policy frameworks* on MEAs, including legal requirements about transparency of pricing or confidential agreements.
5. *Existence of clear rules, roles, responsibilities, and implementation plans* within the health sector, particularly in terms of payers and pharmaceutical companies.
6. *Understanding of the use and limitations of MEAs* by key stakeholders, including perceptions of complexity of MEA implementation, feasibility, and market attractiveness.
7. *Support for MEAs as a policy solution* from key stakeholders, including consideration of the policy process, coalitions and networks, financial support, and policy champions.
8. *Level of trust among payers and pharmaceutical companies*, and willingness to dialogue.
9. *Risk attitudes of payers and pharmaceutical companies* (neutral, averters, and seekers), including risk attitudes toward uncertainty, noncompliance with agreement, effects on international or portfolio revenues, and the need for assurance that heavy losses would be compensated.

Bearing in mind their limitations and challenges, MEAs have the potential for promoting constructive dialogue among payers and manufacturers and facilitating earlier, sustainable access to innovative NCD medicines in LMICs. Decision makers in LMICs can approach MEA arrangements incrementally and start with simpler financial schemes while developing a health system strengthening pathway for the selection, adoption, and monitoring and evaluation required for more sophisticated MEAs in the future. This incremental approach recognizes that time and resources need to be devoted to establishing legal and policy environments.

The minimum health system capabilities needed for the negotiation and implementation of MEAs in LMICs may prevent the use of this strategy in those LMICs heavily dependent on donor assistance. However, there is an opportunity to establish international cooperation for developing the foundations for MEAs in the future. In those LMICs where capacities allow and where stakeholders have conducted a comprehensive decision-making process and in-depth risk assessment about the potential use of MEAs for a specific innovative NCD product, a key initial step is bringing payers and pharmaceutical companies together for dialogue.

We developed three decision analytic models to guide communication between payers and pharmaceutical companies by allowing stakeholders, prior to MEA negotiations, to familiarize themselves with the terms and concepts, options for various instruments, and tradeoffs:

1. A Decision Tree Model
2. A Continuum or “Bridge” Model
3. A Quantitative Spreadsheet Model

The overall goal of these models is to help stakeholders navigate the options as to what form of MEA agreement would be most adequate, plausible, feasible, cost-effective, and beneficial to the parties.

The first two models are qualitative and guide decision makers to a determination of whether an agreement is feasible. They are built around two key variables: 1) the amount of public, generalizable information regarding the medicine; and 2) the institutional capacity of the health system and payer. When the outcome from the first two models is positive, a third model—the Quantitative Spreadsheet Model—may be used to calculate expected values and confidence intervals for key metrics (such as overall budget impact and cost-effectiveness) under different price and coverage scenarios. The purpose of this third model is to help payers decide on next steps toward specific terms of a likely MEA agreement, and to help stakeholders understand the impact on key outcomes of pricing and coverage decisions, taking into account uncertainty around factors like efficacy and safety, the size of the eligible patient population, physicians’ prescribing behavior, and patients’ adherence to prescribed treatment. The compendium provides a detailed user guide for all three models.

### **Conclusions and future considerations**

Improving access to innovative NCD medicines is challenging and requires a combination of access strategies at different levels of the health system and an architecture of individuals and organizations who partner in the design and implementation of these strategies. In those LMICs in which the budget impact, effectiveness, and cost-effectiveness of innovative NCD treatments are not yet fully established, this compendium demonstrates that negotiated solutions in the form of MEAs are a potential policy action. The consideration and implementation of MEAs can encourage capacity building and the establishment of institutional arrangements for sustainable decision making about NCD medicines in LMICs that may lead to wiser, more structured allocation decisions. This compendium recommends strategies for those stakeholders considering MEAs and offers recommendations for further research and practical guidance.

***Recommendations for countries with limited previous experience and capacity for implementing MEAs:***

- Learn from the experiences of other countries—particularly other LMICs—in negotiating and implementing MEAs.
- Collaborate with organizations providing technical assistance related to pharmaceutical policy and pricing in order to access support and existing knowledge on MEA arrangements.
- Assess the potential for an MEA pilot for an innovative NCD medicine.
- Build individual and organizational capacities required for understanding MEA arrangements.
- Work with pharmaceutical companies to initiate policy dialogue. For low-income countries with limited fiscal space, support from external funders would be required.
- Prioritize one or two disease areas that could be part of an implementation pilot on MEAs.
- Consider financial schemes as the best potential MEA arrangement, dependent on the setting.
- Ensure sufficient resources for pilot implementation.
- Implement the pilot and assess the experience to identify capacity-building requirements for potential future use of MEA schemes.
- Publish and disseminate results of the pilot as a case study.
- Consider the initiation of other MEA pilots.

***Recommendations for countries with limited previous experience but higher capacity for MEAs (enabling environment, infrastructure, political will):***

- Learn from the experiences of other countries—particularly other similar LMICs—in negotiating and implementing MEAs.
- Collaborate with organizations providing technical assistance related to pharmaceutical policy and pricing in order to access support and existing knowledge on MEA arrangements.
- Create a strategy of starting small with MEA arrangements and incrementally expanding.
- Prioritize a small set of disease areas that could be part of an implementation pilot.
- Identify and choose the best MEA instrument according to the setting.
- Work with pharmaceutical companies to implement pilot(s) and assess implications for future MEAs.
- Assess the experience from the MEA pilot to identify regulatory and capacity-building requirements (both individual and organizational) for potential MEA scale up.
- Strengthen additional resources for MEA implementation (HTA, PBMs, and other tools).
- Publish and disseminate results of the pilot as a case study.
- Review policies within the health sector and across other relevant sectors to identify potential barriers to long-term implementation of MEA arrangements.
- Leverage reform processes in health and other relevant sectors, drawing from the experiences of the MEA pilots, to institutionalize enabling legal and policy reforms.

***Recommendations for additional research and practice guidance on MEAs in LMICs:***

- Research and publish case studies on MEAs that have been negotiated and implemented in LMICs to build evidence on processes, facilitators and barriers, outcomes, and lessons learned.
- Examine the findings from the compendium's case study countries in other LMIC settings, involving focus groups and workshops with targeted audiences in order to better identify potential uses of MEAs.
- Test and refine the compendium's decision models and analytical framework in a set of LMICs to further explore how to reach certain market segments, assess barriers and facilitators, and identify synergistic access strategies that can work with MEAs to reach more patients.
- Develop practical guidance for LMIC governments, as well as development partners, regarding the steps required to build an enabling policy and legal environment, capacity in negotiation and implementation of MEAs, and rational decision making on NCD medicines more generally.

## ACRONYMS

AIFA	Agenzia Italiana del Farmaco
ATM	Access-to-medicines
AU	African Union
BCCOE	Butaro Cancer Center of Excellence
CED	Coverage with evidence development
CEPS	Comité Economique des Produits de Santé
CVD	Cardiovascular disease
CR	Contributory Regime
DAH	Development assistance for health
DALY	Disability-adjusted life year
DMT	Disease-modifying treatment
EBM	Evidence-based medicine
EML	Essential Medicines List
EPS	Entidades Promotoras de Salud
ERP	External reference pricing
EU	European Union
GDP	Gross Domestic Product
GNI	Gross National Income
HAI	Health Action International
HCPD	High-cost prescription drug
HPV	Human papilloma virus
HTA	Health technology assessment
ICT	Information and communication technology
IETS	Instituto de Evaluación Tecnológica en Salud
IHME	Institute for Health Metrics and Evaluation
KEMSA	Kenya Medical Supplies Authority
LMIC	Low- and middle-income countries
MAS	Managed access strategy
MEDS	Mission for Essential Drugs Supply
MOH	Ministry of Health
MS	Multiple Sclerosis
MS RSS	Multiple Sclerosis Risk-Sharing Scheme
MSH	Management Sciences for Health
NCD	Non-communicable disease
NEML	National Essential Medicines List
NGO	Non-governmental organization
NHIF	National Health Insurance Fund

NICE	National Institute for Health and Care Excellence
NMP	National Medicines Policy
NRA	National medicines regulatory agency
OOP	Out-of-pocket
PMPA	Pharmaceutical Manufacturing Plan for Africa
SDG	Sustainable development goal
SDI	Socio-demographic index
SR	Subsidized Regime
STG	Standard Treatment Guideline
TBT	Technical Barriers to Trade
TRIPS	Trade-Related Aspects of Intellectual Property Rights
UHC	Universal health coverage
UK	United Kingdom
UNCITRAL	United Nations Commission on International Trade Law
VAT	Value added tax
WHO	World Health Organization
WTO	World Trade Organization

## SECTION 1: INTRODUCTION

### 1.1 The problem

*“Imagine if an epidemic threatened to kill 41 million people every year. It’s already happening. This year. Last year. Next year, too. Non-communicable diseases are the global biggest killers...”*

Dr. Tedros Adhanom, Director General of the WHO, 2018

Non-communicable diseases (NCDs)—including cardiovascular disease (CVD), cancers, strokes, chronic respiratory infections, and diabetes—presently contribute to 70% of worldwide mortality (GBD, 2018). As of 2015, an estimated 40 million deaths have been attributed to NCDs (WHO, 2015a), an increase from 31 million in 2000 (WHO, 2014a). This includes 17.7 million deaths from CVD, 8.8 million from cancer, 3.9 million from respiratory disease, and 1.6 million from diabetes (WHO, 2015a).

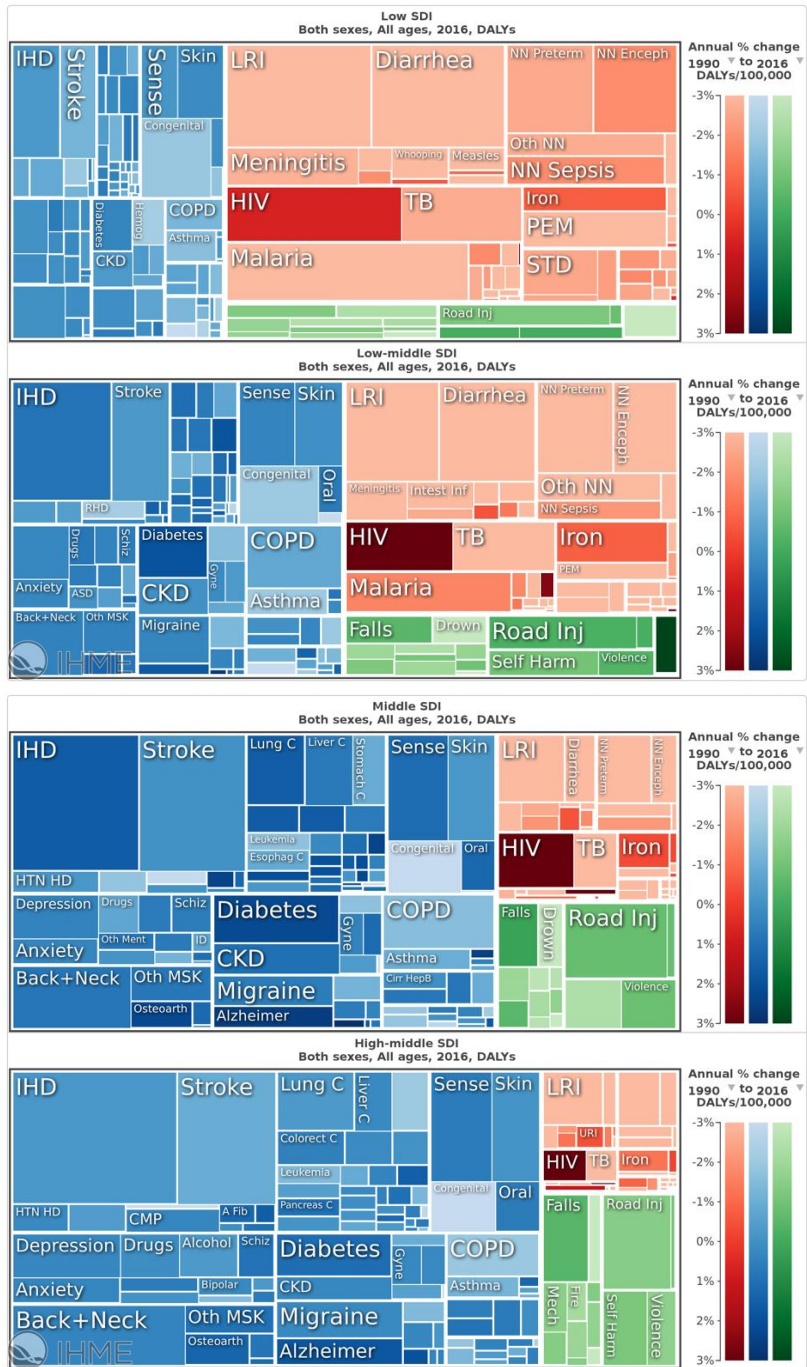
For decades, the prevailing theory was that NCDs were primarily diseases of affluence. With demographic and epidemiological transition, populations should become richer, fertility decline, sanitation and hygiene improve, and access to public health interventions increase, thereby shifting the epidemiological burden from infectious disease to “man-made” and/or chronic diseases (such as those based on lifestyle, aging, and environmental stress) (McKeown, 2009).

In practice, however, this theory has not been born out. While low-income countries do bear a disproportionate share of infectious disease, NCDs still represent a significant and growing contribution to disability-adjusted life-years (DALYs) in these countries (IHME, 2016). Countries classified by “low,” “lower-middle,” and “middle” socio-demographic index (SDI) in the Global Burden of Disease Study clearly struggle with a dual burden of infectious diseases and NCDs (Figure 1).

Moreover, in many instances, infectious diseases serve as important contributors to NCDs (Mercer, 2014). As a consequence, 80% of deaths from NCDs occur now in low- and middle-income countries (LMICs) (WHO, 2015a). As importantly, trends with respect to overall improvement in global adult NCD mortality that are clearly evident in high- and upper-middle income countries are happening at a much slower rate in low- and lower-middle income countries (Nugent et al, 2018).

The social, economic, political, and health systems burden of NCDs first received high-level attention in 2011 when the UN General Assembly issued a declaration stating that NCDs are now one of the major challenges of the twenty-first century, serving to undermine social and economic development and threatening the achievement of internationally agreed development goals (UNGA, 2012). After this declaration, the 2013 Global NCD Monitoring Framework was established which aims for a 25% reduction in premature death from NCDs by 2025 (25x25) (Beaglehole et al, 2014). The Framework was followed by the incorporation of NCDs into Sustainable Development Goal (SDG) 3.4 which targets an additional 5% (or 30% overall) reduction by 2030 (WHO, 2015b).

**Figure 1: Global Burden of Causes of Disability-Adjusted Life Years (DALYs), 2016<sup>1</sup>**



Notes: **Blue** = Non-communicable diseases; **Red** = Communicable, maternal, neonatal, and nutritional diseases; **Green** = Injuries  
Source: Institute for Health Metrics and Evaluation (IHME) (2016). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington ([http:// vizhub.healthdata.org/gbd-compare](http://vizhub.healthdata.org/gbd-compare), accessed July 29, 2018).

<sup>1</sup> Countries are classified based on a socio-demographic index (SDI) of low, lower-middle, middle, upper-middle, and high. SDI is a summary measure of income, educational attainment, and fertility rates.

While both 25X25 and SDG 3.4 place emphasis on preventing the causes of NCDs, they also highlight the critical role that access to medicines must play in achieving national and global goals. The 25X25 framework, for example, sets targets for: 1) 80% availability of the affordable basic technologies and essential medicines, including generics, required to treat major NCDs in both public and private facilities; and 2) at least 50% of eligible people accessing drug therapy and counselling (including glycemic control) to prevent heart attacks and strokes (WHO, 2013a). Meanwhile, SDG 3.4 includes sub-goals aimed at: 1) supporting the research and development of vaccines and medicines for NCDs that primarily affect developing countries; and 2) providing access to affordable essential medicines and vaccines for NCDs (WHO, n.d.).

Recent research has clearly demonstrated an investment case for improved prevention and treatment of NCDs, arguing that—for an additional US \$1.50 per capita per year—15 million deaths would be averted, including eight million incidents of ischemic heart disease and 13 million incidents of stroke, with an average benefit-cost ratio of 5.6 for strictly economic returns on investment, and 10.9 if social returns are included (Bertram et al, 2018).

With respect to treatment, though, such an investment case is primarily focused on existing basic or essential medicines. But what of new, breakthrough innovations for NCDs? Many innovative NCD medicines exhibit great promise for therapeutic effect and potential long-term cost reduction and are increasingly being rolled out in high-income countries, resulting in improved access to new health technologies for NCD patients.

However, their availability in most LMICs remains limited due to high prices, fragmentation of sources of funding, uncertainties about their clinical effectiveness and cost-effectiveness, and other constraints at subnational, national, and global levels. These access barriers to NCD medicines in LMICs exist at five different levels of the health system, as shown in Table 1: 1) individual, household, and community; 2) health service delivery; 3) health sector; 4) public policies cutting across sectors; and 5) international and regional level.

Addressing these access barriers to NCD medicines in these settings is an urgent priority. Modeling has estimated the probability of dying from one of the four main NCDs as ranging from 19% in the Americas to 29% in Southeast Asia for men, and 13% in Europe to 21% in Southeast Asia for women (Kontis et al, 2014). The probability of dying prematurely from NCDs is projected to decrease in every region over time, except in Africa where it is projected to increase (Kontis et al., 2014). To confront these challenges to regional equity, it is imperative that NCD patients in LMICs not be denied access to the innovations from which their fellow patients in higher income settings increasingly benefit.

**Table 1: Access Barriers to NCD Medicines at Different Levels of the Health System, and Strategies for Addressing these Barriers<sup>2</sup>**

Level of the health system	Access barriers to NCD medicines	Strategies for addressing access barriers, by level of health system
<p><b>1. Individual, household, and community</b></p> <p>Demand-side barriers and strategies; health-seeking behaviors and attitudes pertaining to NCDs and NCD medicines, related technologies, and services are influenced by individual preferences as well as the cultural and social constraints of households and communities</p>	<ul style="list-style-type: none"> <li>• Perceived quality of NCD medicines and health services</li> <li>• Cost of NCD medicines, related technologies (diagnostics and monitoring tools), and services (clinic visits and hospital stays)</li> <li>• Perceived opportunity costs – time spent traveling, lost earnings while seeking care.</li> <li>• Irrational health-seeking behavior, demand for, and use of medicines</li> <li>• Social and cultural barriers (stigma related to poverty, ethnicity, and gender)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Raise individual, household, and community awareness about NCDs and available NCD medicines and services</li> <li>▪ Strengthen patient linkages along the continuum of care, from NCD diagnosis to treatment</li> <li>▪ Financial risk protection schemes (subsidized services, enrollment in health insurance)</li> </ul>
<p><b>2. Health service delivery</b></p> <p>Supply-side barriers and strategies at the subnational and national levels pertaining to the delivery of NCD medicines, related technologies, and services</p>	<ul style="list-style-type: none"> <li>• Irregular availability of NCD medicines and related technologies in clinics, hospitals, pharmacies, and shops</li> <li>• High prices of NCD medicines, related technologies, and services</li> <li>• Irrational prescription and dispensing of NCD medicines by providers</li> <li>• Low quality/substandard and counterfeit NCD medicines</li> <li>• Low quality of health services</li> <li>• Competition between public and private health service delivery</li> </ul>	<ul style="list-style-type: none"> <li>▪ Train healthcare workforce in public and private sectors to improve quality of service delivery (appropriate prescribing, dispensing, and use of NCD medicines and related technologies, as well as appropriate supervision and monitoring of patients)</li> <li>▪ Separate prescribing and dispensing functions to avoid conflicts of interest</li> <li>▪ Improve health facility infrastructure</li> </ul>

<sup>2</sup> Table 1 was adapted for the specific case of NCD medicines from Bigdeli et al (2013) who analyzed access-to-medicines (ATM) constraints at different levels of the health system and developed an ATM framework from a health system perspective. Bigdeli et al (2013) built on the five-level framework of the health system first conceptualized by Hanson et al (2003), as well as previous ATM frameworks (see Centre for Pharmaceutical Management, 2003; WHO, 2004; Frost and Reich, 2009).

<p><b>3. Health sector</b></p> <p>Supply-side barriers and strategies at the national level in the health sector</p>	<ul style="list-style-type: none"> <li>• Exclusion of NCD medicines, related technologies, and services from insurance coverage in many countries where such coverage is available to the population</li> <li>• Lack of public resources for NCD medicines and related technologies, due to underfunding or underbudgeting</li> <li>• Inaccurate demand forecasting and quantification</li> <li>• Inefficient public sector procurement, storage, supply, and distribution systems</li> <li>• Fragmentation of service delivery and procurement systems that leads to overlap and duplication of distribution functions</li> <li>• Lack of data and information necessary for planning, forecasting, and budgeting for NCD medicine/related technology needs</li> <li>• Insufficient pharmaceutical workforce, both in terms of numbers and skill mix</li> <li>• Lack of, or inefficient, systems for selecting NCD medicines and related technologies, and controlling prices</li> <li>• Insufficient evidence base for NCD medicines (particularly new, innovative medicines) in real-life settings</li> <li>• Weak health sector governance affecting all health system building blocks</li> <li>• Health sector pluralism and stewardship over private sector</li> </ul>	<ul style="list-style-type: none"> <li>▪ Establish systems to centralize procurement of NCD medicines</li> <li>▪ Strengthen national regulatory authorities for effective regulation of the quality and safe use of medicines; ensure it is adequately resourced and staffed, and has legal powers</li> <li>▪ Conduct generic promotion policies including preferential registration procedures, quality assurance, generic substitution, and financial incentives</li> <li>▪ Establish and/or strengthen systems for rationally selecting NCD medicines (ie through HTA processes)</li> <li>▪ Independently develop evidence-based clinical guidelines to enhance appropriate use</li> <li>▪ Update national essential medicines lists and formularies based on guidelines</li> <li>▪ Implement UHC policies, including those that reduce out-of-pocket spending and promote financial protection through risk pooling</li> <li>▪ Develop a strategy for adequate and equitable financing and budgeting for NCD medicines. Where health insurance exists, ensure that NCD medicines and related technologies are covered. Ensure budget includes procurement of NCD medicines for vulnerable populations not covered by insurance.</li> <li>▪ Assess and implement strategies through dialogue and negotiation with manufacturers to promote affordable NCD treatment in public and private sectors, including voluntary licensing for local production,</li> </ul>

		<p>differential pricing, negotiated confidential agreements, and donation programs.</p> <ul style="list-style-type: none"> <li>▪ Consider the utilization of Trade-Related Aspects of Intellectual Property Rights (TRIPS) flexibilities (ie compulsory licensing), analyzing advantages for public health, as well as disadvantages for health and other sectors, and potential alternative strategies</li> <li>▪ Improve and sustain an adequate pharmaceutical workforce</li> <li>▪ Ensure that “expert” patients with long experience of NCD conditions are fully represented in policymaking</li> <li>▪ Review national drug control policies and legislation and conduct regulatory reform, awareness raising, health professional training, and coordination with suppliers to improve procurement and distribution of controlled medicines for pain relief and symptom control</li> <li>▪ Establish systems for collecting, monitoring, and using data on NCD and other medicines in real life settings, including availability, price, expenditure, usage, quality and safety for evidence-based policymaking</li> </ul>
<p><b>4. Public policies cutting across sectors</b></p> <p>Supply-side barriers and strategies at the national level in non-health sectors but which influence policies related to NCDs and NCD medicines, related technologies, and services</p>	<ul style="list-style-type: none"> <li>• Low public accountability and transparency</li> <li>• Low priority attached to social sectors</li> <li>• High burden of government bureaucracy</li> <li>• Conflict between trade/economic goals and public health goals (ie taxes and tariffs on imported NCD medicines, as well as markups in the supply chain, both of which contribute to high prices)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Control markups through initiating dialogue with agents along the supply chain and regressive markup schemes</li> <li>▪ Exempt essential NCD medicines from import duties and taxes (including VAT)</li> </ul>

<p><b>5. International and regional level</b></p> <p>Supply-side barriers and strategies at international and regional levels; encompasses issues related to international markets and regulations</p>	<ul style="list-style-type: none"> <li>• International donors’ agenda (and funding) which has emphasized infectious diseases more than NCDs</li> <li>• Patents and intellectual property rights</li> <li>• International treaties (specifically, international drug control treaties which limit availability of controlled medicines for pain relief and symptom control)</li> </ul>	<ul style="list-style-type: none"> <li>▪ Raise political priority for NCDs in global health</li> <li>▪ Expand existing global health initiatives to include NCDs (i.e. Medicines Patent Pool, advanced market commitments, Unitaid)</li> <li>▪ Mobilize and sustain financing for NCD medicines and related technologies, as well as public-private collaborations involving NCDs (such as GAVI’s rollout of HPV)</li> <li>▪ Pool procurement regionally and/or globally</li> <li>▪ Invest in operational research to strengthen the evidence base to support treatment strategies that are feasible and appropriate in all resource settings</li> <li>▪ Continue dialogue across key stakeholder groups on “unifying principles” for research and development and build trust between these groups</li> <li>▪ Develop an NCD stakeholder framework, including ground rules for stakeholder involvement in provision of NCD medicines, related technologies, and services</li> </ul>
<p>Sources: Bigdeli et al., 2013; Hanson et al (2003), Abegunde (2011), The NCD Alliance (n.d.b.), Access Observatory, 2018.</p>		

## 1.2 Access strategies for NCD medicines

There are multiple strategies that governments, pharmaceutical companies, and development partners can use to overcome barriers to accessing innovative NCD medicines in LMIC, as also shown in Table 1. These strategies were drawn from access-to-medicines frameworks (Centre for Pharmaceutical Management, 2003; WHO, 2004; Frost and Reich, 2009; Bigdeli et al., 2013) and a taxonomy of access strategies for NCD medicines (which includes demand, systems, production, and price strategies) developed for the Access Observatory by Boston University's School of Public Health in partnership with the Access Accelerated Initiative (Access Observatory, 2018). Access strategies for innovative NCD medicines are not mutually exclusive but rather complementary and work together to improve access, as government and partner initiatives often deploy a mix of approaches at various levels of the health and broader system. Section 2 provides more information about and examples of access strategies in LMICs.

The World Bank supports governments in developing health systems capacity necessary to purchase, distribute, and utilize medicines effectively and efficiently. This includes technical assistance on HTA, pricing strategies, and negotiation strategies for innovative medicines.

In summary, there are a range of different access strategies that are being utilized by governments, pharmaceutical companies and development partners to ensure that NCD patients in LMICs have access to life-saving or life-extending medicines, related technologies, and services for CVD, diabetes, cancers, and other chronic diseases.

One set of pricing strategies involves negotiated agreements between pharmaceutical companies and payers in the public, private, or donor sectors. These agreements are referred to in this compendium as managed access strategies (MASs) to emphasize that the ultimate goal of these arrangements is to improve access to innovative medicines for patients. Depending on the type of MAS, they can also be used to bring costs down and expand the clinical and health system evidence base. MASs involve two key stakeholders: a payer (such as a government or public fund holder, a private holder of pooled resources such as an insurer, or a donor) and a pharmaceutical company that manufactures and commercializes a new drug. MASs include "compassionate need" and non-profit access programs, voluntary licensing, and confidential agreements known as managed entry agreements (MEAs). MEAs have been increasingly used in high-income countries for new, promising treatments for NCDs for which their effectiveness, cost-effectiveness, availability, and acceptability are surrounded by uncertainty. They have been less commonly used in LMICs, though are increasingly being considered by decision makers (Carlson et al., 2014). There are major gaps in the knowledge and skills required for countries to plan, negotiate, implement, and measure MEA impact. If these gaps can be filled, MEAs have the potential to be an important access strategy to address the problems of high price and uncertainties related to innovative NCD medicines.

### 1.3 Focus of this compendium

This compendium is a global knowledge resource that provides stakeholders with information and tools about access strategies for innovative NCD medicines in LMICs. It is intended to promote dialogue among governments, other payers, and manufacturers in LMICs, as well as additional stakeholders involved in providing access to medicines. The compendium focuses in particular on one type of managed access strategy (MAS)—managed entry agreements (MEAs). It describes MEAs and how they have been used in different contexts, presents advantages and limitations, and offers tools and good practices. The compendium is not meant to advocate for MEAs as the *only* strategy to access new medicines for NCDs. Rather, it seeks to describe how, when, where, and why MEAs might be an appropriate strategy to add to stakeholders' access toolkit.

The compendium is based on research carried out by Management Sciences for Health (MSH), including a literature review of the published and grey literature on MEAs and semi-structured interviews with key informants in three LMICs (Colombia, Kenya, and Ukraine). It is also based on the development and testing of three decision analytic models by Research Triangle Institute (RTI) International in joint cooperation with MSH. The compendium was compiled and written by Global Health Insights (GLOHI) in partnership with MSH and RTI. Annex I provides more information about these research activities.

The compendium consists of four sections. Following this introductory section, Section 2 describes the health systems context in LMICs in which access strategies for innovative NCD medicines are implemented. Section 3 then presents MASs as a strategy for improving access to innovative NCD medicines in LMICs, including in those countries with multiple payers. The section places a particular emphasis on MEAs and describes the range of instruments, demonstrates how these have been used in different countries for a range of medicines, and discusses advantages and limitations. This section also includes an analysis of where MEAs might be most productive in LMICs, given the context outlined in Section 2, and presents three decision analytic models that can be used by governments, other payers, and pharmaceutical companies to explore the potential use of this strategy and terms of agreements. Finally, Section 4 concludes with some considerations for future research and action.

## SECTION 2: CONTEXTUAL CONSIDERATIONS FOR IMPROVING ACCESS TO NCD MEDICINES IN LOW- AND MIDDLE-INCOME COUNTRIES

LMICs are often grouped together under a single conceptual heading due to certain shared characteristics with respect to drivers of ill health, constraints on health systems, challenges with respect to equity, and processes by which healthcare is planned, financed, delivered, and regulated. However, despite some similarities, in practice many of these characteristics vary dramatically across LMICs. This section describes key contextual considerations for improving access to NCD medicines in LMICs in three areas: 1) income level, population, and disease burden; 2) health systems structure and sources of funding; and 3) pharmaceuticals and pharmaceutical policies. Throughout the section, and summarized in Boxes 1-3, we refer to the context and experiences in three case study LMICs: Kenya and Ukraine (both lower middle-income countries), and Colombia (an upper middle-income country). These three countries were chosen purposively to represent different geographical settings, levels of income, socio-political contexts, and healthcare systems (see Annex I for more information on methodology).

### 2.1 Income level, population, and disease burden

The World Bank classifies LMICs by three separate categories based on a country's gross national income (GNI) per person: low-income, lower middle-income, and upper middle-income.<sup>3</sup> For the 2018 fiscal year, *low-income economies* are those with a GNI per capita of under US \$1,006. This low-income group includes 31 countries that represent 9% of the world's population (see Table 2).

Communicable and neonatal diseases remain the leading causes of early death and disability in low-income countries—specifically diarrhea and lower respiratory infections, neglected tropical diseases and malaria, HIV/AIDS and tuberculosis, and neonatal disorders. These diseases represent 59.43% of total disability-adjusted life years (DALYs) in low-income countries (IHME, 2017). However, as mentioned in Section 1, cardiovascular diseases (CVD) and other NCDs are increasing as causes of early death and disability in these countries, and make up 32.08% of DALYs. The remaining DALYs are caused by injuries (8.49%) (IHME, 2017).

Middle-income countries represent 75% (5.5 billion) of the world's population (est. 7.4 billion people). As of 2018, the World Bank classifies *lower middle-income countries* as having a GNI per capita of between US\$1,006 and US\$3,955, and this group includes 53 countries and represents 40% of the world's population (see Table 2). India—the country with the second largest population of 1.32 billion people—lies in this lower middle-income group, along with two of this compendium's case study countries, Kenya and Ukraine (see Boxes 1 and 2). *Upper middle-income countries* are those with a GNI per capita between US\$3,956 and US\$12,235, involving 56 countries and 35% of the world's population. China, the world's largest population with 1.38 billion people, falls into this category and so does Colombia, the compendium's third case study country (see Box 3).

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<sup>3</sup> For more information, see <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>.

**Table 2: World population, by income group**

Income group	Population, in millions (2016)
Low-income	659.3 (9%)
Lower middle-income	3,014.8 (40%)
Upper middle-income	2,580.0 (35%)
High-income	1,190.0 (16%)
	7,444.1 (total population)
<p><i>Source:</i> <a href="https://data.worldbank.org/">https://data.worldbank.org/</a>. (1) United Nations Population Division. World Population Prospects: 2017 Revision. (2) Census reports and other statistical publications from national statistical offices, (3) Eurostat: Demographic Statistics, (4) United Nations Statistical Division. Population and Vital Statistics Report (various years), (5) U.S. Census Bureau: International Database, and (6) Secretariat of the Pacific Community: Statistics and Demography Programme.</p>	

Countries that attain middle-income status begin to confront new challenges that reflect their stage of development, including ageing populations. As infectious diseases are successfully addressed and populations age, NCDs account for a greater part of a country's disease burden. This provides new prevention and treatment challenges for health-care systems. Tables 3 and 4, and Figure 1 (in Chapter 1), demonstrate this increasing burden of cardiovascular diseases and other NCDs in both lower and upper middle-income countries.

In many lower middle-income countries, however, communicable diseases including diarrhea, lower respiratory infections, HIV/AIDS, tuberculosis, and neonatal disorders, continue to be major causes of early death and disability. In these countries, the percentage of DALYs due to NCDs is 49.83%; communicable, maternal, neonatal, and nutritional diseases is 39.51%; and injuries is 10.65% (IHME, 2017), though there is large variation across countries in this group. In Kenya, for example, NCDs represent 29.88% of total DALYs and several infectious diseases continue to account for 63.35% of total DALYs (Table 3). In India, diarrhea, lower respiratory tract infections, and neonatal disorders are a leading cause of death and disability (32.74% of total DALYs), but NCDs account for 55.41% of total DALYs. In comparison, as demonstrated in Tables 3 and 4, Ukraine has characteristics of upper-middle income countries and NCDs represent a higher proportion at 82.55% (IHME, 2017).

In upper-middle income countries as a group, NCDs account for a larger proportion of the disease burden at 79.34%, while the percentage of total DALYs due to communicable, maternal, neonatal, and nutritional diseases is 8.55% and injuries is 12.11% (IHME, 2017). This high burden of NCDs in upper-middle income countries can be seen through the case of Colombia, where NCDs represent 70% of total DALYs.

**Table 3: Leading causes of early death and disability, 2016, in low- and lower middle-income countries including Kenya, India, and Ukraine (all ages and genders)**

	Low-income	Lower middle-income	Kenya	India	Ukraine
1	Diarrhea, lower respiratory, and other common infectious diseases	Diarrhea, lower respiratory, and other common infectious diseases	Diarrhea, lower respiratory, and other common infectious diseases	Cardiovascular Disease	Cardiovascular Diseases
2	Neonatal disorders	Cardiovascular diseases*	HIV/AIDS + Tuberculosis	Diarrhea, lower respiratory, and other common infectious diseases	Neoplasms
3	Neglected tropical diseases and malaria	Neonatal disorders	Neonatal Disorders	Neonatal Disorders	Mental Disorders
4	HIV/AIDS and tuberculosis*	Other non-communicable diseases	Other Non-Communicable Diseases	Other Non-Communicable Diseases	Musculoskeletal Disorders
5	Cardiovascular diseases*	Mental disorders*	Mental Disorders	Chronic Respiratory Disorders	Other Non-Communicable Diseases
6	Other non-communicable diseases	HIV/AIDS and tuberculosis	Cardiovascular Diseases	Diabetes, urogenital, blood, and endocrine diseases	Unintentional Injuries
7	Nutritional deficiencies	Neoplasms*	Unintentional Injuries	Mental Disorders	Neurological Disorders
8	Unintentional injuries	Diabetes, urogenital, blood, and endocrine diseases*	Nutritional Deficiencies	Unintentional Injuries	Self-Harm & Violence
9	Mental disorders*	Unintentional injuries	Neoplasms	Neoplasms	Cirrhosis
10	Neoplasms*	Chronic respiratory diseases	Neglected Tropical Diseases & Malaria	Nutritional Deficiencies	Diabetes, urogenital, blood, and endocrine diseases

*Notes:*

-- \* Causes that have a higher ranking than in 1990.

-- Orange represents communicable, maternal, neonatal, and nutritional diseases; Blue represents non-communicable diseases; and Green represents injuries.

*Source:* Institute for Health Metrics and Evaluation (IHME) (2018). GBD Compare Data Visualization. Seattle, WA: IHME, University of Washington, 2017 (<http://vizhub.healthdata.org/gbd-compare>, accessed May 4, 2018).

**Table 4: Leading causes of early death and disability, 2016, in upper middle-income countries, including Colombia and China (all ages and genders)**

	Upper middle-income	Colombia	China
1	Cardiovascular diseases	Other Non-Communicable Diseases	Cardiovascular Disease
2	Neoplasms	Cardiovascular Diseases	Neoplasms
3	Mental disorders*	Self-Harm & Violence	Mental Disorders
4	Other non-communicable diseases	Neoplasms	Other Non-Communicable Diseases
5	Musculoskeletal disorders*	Mental Disorders	Musculoskeletal Disorders
6	Diabetes, urogenital, blood, and endocrine diseases*	Musculoskeletal Disorders	Diabetes, urogenital, blood, and endocrine diseases
7	Neurological disorders*	Neurological Disorders	Chronic Respiratory
8	Unintentional injuries	Diabetes, urogenital, blood, and endocrine diseases	Neurological Disorders
9	Transport injuries	Neonatal Disorders	Transport Injuries
10	Chronic respiratory diseases*	Unintentional Injuries	Unintentional Injuries

## 2.2 Health systems in LMICs, fragmentation, and access to NCD medicines

A country's health sector is comprised of the resources, organizational structures, managerial relationships, financing, and services that enhance a population's health (Roemer 1993). The World Health Organization (WHO) conceptualizes the health system in terms of six building blocks that when functioning well, ensure increased access to safe, high quality health services and technologies. This ultimately leads to improved health outcomes, equity, financial risk protection, efficiency, and responsiveness to the population. The health systems in LMICs have some similarities but also vary in size, form, sources of funding and comprehensiveness, depending on political and economic trajectories and global and national contexts, as well as class dynamics and societal values (Birn et al., 2009). Thus, health coverage, including NCD care and treatment, is variable and heavily influenced by the capacity and effectiveness of the health system building blocks.

Access barriers for NCD medicines at five levels of the health system were identified in Table 1 (in Chapter 1). In the following sub-sections, we outline how these barriers at each level of the health system impact access to NCD medicines and LMICs' capacity to address them.

### **2.2.1 International and regional level policies and regulations**

Trade-Related Aspects of Intellectual Property Rights (TRIPS), initiated in 1995 by World Trade Organization (WTO) member states, is an international public law that has had an important impact on global access to medicines (Sell, 2007). TRIPS stipulates a 20 year patent period for innovative products and processes in support of manufacturers' innovation with the aim of fostering and compensating for research and development. It is binding and if violated, TRIPS allows countries to initiate sanctions against those that have violated it (Sell, 2007). In 2001, WTO members agreed to incorporate certain flexibilities for public health often referred to as the Doha Declaration (Huang, 2013). These flexibilities allow LMICs to issue compulsory licenses for public health emergencies and epidemics as they have "a right to protect public health and, in particular, to promote access to medicines for all" (Hogerzeil et al 2013). Additionally, they allow for countries to import and receive differential (often reduced) pricing from those countries that have issued compulsory licenses and produce generic versions of medicines for public health emergencies (Huang, 2013). Countries like India, Brazil, and South Africa have taken advantage of these flexibilities and issued compulsory licenses for infectious disease medicines to tackle large scale epidemics of HIV/AIDS and tuberculosis (Huang, 2013).

In recent times, there has been a rise of bilateral or multilateral treaties between high-income countries and LMICs such as the Trans-Pacific Partnership, the Central America, Dominican Republic and United States Free Trade Agreement, and the European Union (EU)-Thailand Free Trade Agreement. These have provided a platform for global pharmaceutical manufacturers to push tighter intellectual property regulations in LMICs as conditions for more favorable trade conditions. These conditions, broadly known as TRIPS Plus, include regulations such as delayed entry for generics through data exclusivity for clinical data, linking product registration and market authorization to product patent status, and patent extension for alternative uses of the same medicine (Sell, 2007).

There has been significant debate and legal battles on how TRIPS flexibilities can be applied to medicines for NCDs. Countries have reacted differently based on their buying power—determined by their capacity to negotiate pricing, national trade and health priorities, and local production capacity. Countries with a large pharmaceutical industry have leveraged the TRIPS flexibilities to issue compulsory licenses for cancer drugs in the last few years. For example, this was done in India where a stricter definition of "innovation" was included as not just reformulation but increased efficacy with the alternatives in the market (Hogerzeil et al 2013). Talks between the EU and India for a trade agreement have long been stalled with TRIPS Plus measures as one of the sources of conflict. Being a significant exporter of infectious disease medicines to other LMICs, India has a substantial opportunity to do the same for NCD medicines as LMICs shift their focus to address the growing NCD epidemics in their countries.

In another example, Thailand issued compulsory licenses in 2008 for key cancer drugs docetaxel, letrozole, erlotinib, and imatinib. However, Novartis designed a mutually agreeable access program for imatinib and the compulsory license was taken back (Lopes et al, 2013). Brazil and Colombia have effectively utilized the threat of compulsory licensing in the past but have now shifted to voluntary licensing with guaranteed volume purchase by the national health insurance scheme as an incentive for lowered pricing (Cherian, 2016 and Vyas, 2016). Nevertheless, given their local manufacturing capacity and focus on the fundamental right to healthcare, both still retain significant buying power and capacity to issue compulsory licenses in the future.

China, which also has a large pharmaceutical and vaccines manufacturing industry, in contrast has not issued as many compulsory licenses, opting to focus on encouraging foreign investments and collaborations (Huang, 2013). Still, China remains a price sensitive market with payers opting to issue tenders based on prices rather than medicine quality (Mossialos et al, 2016). This has led to a highly fragmented market open to low quality producers that could limit market growth for innovator NCD manufacturers (Mossialos et al, 2016). All of this highlights the need for active negotiation of mutually beneficial purchasing agreements between LMICs and pharmaceutical companies (such as voluntary licensing and negotiated MEAs).

In addition to intellectual property, other aspects of global trade impact the progression of the NCD disease burden and subsequently, the need for NCD medicines. NCDs can be prevented by reducing the risk factors or modifying the lifestyles associated with them, including exposure to high sugar, fat, salty, and processed foods, lack of physical activity, excessive alcohol consumption, and smoking (NCD Alliance, n.d.c). However, LMICs are growing markets for multinationals that manufacture products such as sugar-sweetened drinks, unhealthy snacks, cigarettes, and alcohol. WHO has made many recommendations to curb consumption of these products including “sin” taxes on such imports, improved labelling regulations that highlight the risks associated with the products or their ingredients, warning labels on tobacco products, and limiting the advertising of alcohol and cigarettes (Barlow et al., 2018).

Exporting high-income countries have often challenged such measures by leveraging conditions set in trade agreements. One key instrument has been the Technical Barriers to Trade (TBT) Agreement, which is binding for all WTO members. This agreement stipulates that new trade measures introduced by members for issues such as public health must not add unnecessary trade costs if there are less expensive options available (Barlow et al., 2018). In 2009, Colombia initiated a regulation that would require the prominent labeling of risks associated with alcohol consumption on alcohol packaging. The E.U. and the U.S. disputed this regulation using the TBT Agreement, stating that it would entail costly changes for their exporting alcohol producers. Faced with continued pressure, Colombia made considerable amendments to the legislation where many alcohol products were exempt from needing the health warning (Barlow et al., 2018).

Another barrier at the global level that has limited access to NCD medicines has been the low prioritization of NCDs on the global health agenda. Access to vaccines and medicines for infectious diseases in LMICs

has been driven by sizable development assistance from governments in high-income countries, private foundations, multilateral organizations, and large financing vehicles and programs such as Gavi, PEPFAR, and others. As mentioned in Section 1, NCDs have gained prominence on the global health agenda since 2010, beginning with the UN Political Declaration on NCD Prevention and Control in 2011 (UNGA, 2012). Heads of state and other leading stakeholders will be meeting September 2018 at the UN General Assembly to discuss actionable measures and commitments to address NCDs in the third High-level Meeting of the UN General Assembly on NCDs (NCD Alliance, n.d.d). That said, development assistance and financing for NCDs has yet to see a significant increase. In 2017, of the \$37.4 billion dollars in development financing for health, HIV/AIDS received 24.2%, whereas NCDs received only 2.20% (a large portion of which went to tobacco control programs) (IHME, 2018). Additionally, the Global NCD Action Plan and the recent “Time to Deliver” set of recommendations by the WHO Independent High Level Commission on NCDs emphasize commitment of domestic resources and inclusion of NCD related commodities in Universal Health Coverage (UHC) programs (WHO, 2018). Thus, there is an urgent need for innovative strategies in LMICs, in collaboration with the private sector, for attaining these access goals.

### **2.2.2 National multi-sectoral policies**

The WHO constitution identifies health as a fundamental right of every human being and this has influenced many member states to adopt a human rights based approach to health. For example, in 2010, Kenya enshrined a human rights framework in its constitution stating in Article 21(4) of Chapter 4—*The Bill of Rights*—that, “The State shall enact and implement legislation to fulfil its international obligations in respect of human rights and fundamental freedoms.” The subsequently developed National Health Policy 2012 – 2030 by the Ministry of Health (MOH) recognizes the need to meet human rights obligations and thus aims for “equitable, affordable and quality health and related services at the highest attainable standards to all Kenyans” (Government of Kenya, 2014). Similarly, Colombia treats access to healthcare as a fundamental right after at least two decades of heavy judicialization of healthcare access and the enactment of a higher hierarchy Law from 2015 (1751). Ukraine recently passed bill no. 6327 on financing the healthcare system from the country’s budget, which stipulates that a minimum of 5% of the GDP will need to be spent on healthcare through national health insurance programs (Verkhovna Rada of Ukraine, 2017). These policies not only demonstrate how governments respond to their populations’ health demands but also have considerable impact on the health access decisions of governments. For example, Section 2.2.1 referred to how civil society in countries like Brazil have leveraged the right to healthcare to increase access to infectious disease medicines through compulsory licensing.

The right to health and resource allocation notwithstanding, achieving policy coherence across sectors is a complex task. Conflict between trade, economic development, and industrial policies often arises and this can constrain efforts to provide access to medicines. A key example is taxation on pharmaceuticals. LMICs raise most of their tax revenues through indirect taxes such as sales tax, value added tax (VAT), and import tariffs rather than direct taxes (WHO and HAI, 2014). Due to smaller formal sector economies and limited capacity for tax collection, direct tax revenues such as income or corporate tax revenues are lower compared to indirect tax revenues. Thus, Ministries of Finance in LMICs are not supportive of providing

exemptions on goods, including medicines (WHO and HAI, 2014). A study by WHO and Health Action International (HAI) in 2014 showed that VAT revenue from pharmaceuticals in 57 countries averaged \$11.6 million (WHO and HAI, 2014). India earned close to \$1 billion in VAT revenues from pharmaceuticals and Brazil close to \$123 million. For high priced innovative NCD medicines, these policies will likely have a direct impact on price negotiations.

### **2.2.3 National health sector governance and policies**

Health sector governance encompasses measures such as national health policies, treatment guidelines, pharmaceutical policies, regulatory policies and infrastructure, health financing, and the overall institutional structure of the healthcare system. These policies define the selection, procurement, and distribution processes for NCD medicines and other health technologies but also how they are financed, priced, and used. In this section, we explore some key health sector governance and policy issues. Pharmaceutical governance and sector policies and their influence on access to NCD medicines are outlined in detail in Section 2.3.

Health spending in countries varies significantly between LMIC income groups. In 2015, upper middle-income countries spent on average \$949 per person on health; lower middle-income countries spent \$266 per person; and low-income countries spent \$110 per person (IHME, 2018). In addition, large variations exist within these income groups. For example, within the low-income category, health spending per person in 2015 ranged from \$28 to \$481; from \$90 to \$849 in the lower-middle income group; and from \$241 to \$1,850 in the upper middle-income group (IHME, 2018).

Countries' health spending has various sources, including: 1) government health spending, derived from domestic sources; 2) prepaid private spending, such as private health insurance and services provided for free by non-governmental organizations (NGOs), 3) out-of-pocket (OOP) spending, involving payments made at the time of healthcare delivery including copayments or payments for deductibles; and 4) external financing known as development assistance for health (DAH), involving financial and in-kind resources given by health development agencies (IHME, 2018). In general, the sources of countries' health spending transforms with economic development, as shown in Table 5. As countries move into the upper middle-income group, they source a larger proportion of health spending from domestic resources, and they no longer have access to development assistance for health since eligibility criteria for many donors is tied to income levels. OOP spending remains high, however, in many low-income *and* middle-income countries.

Figure 2 further demonstrates this point and shows that countries with lower gross domestic product (GDP) per person on average finance their healthcare with DAH and OOP spending. As countries become more economically developed, DAH decreases significantly and countries transition to funding their health sector domestically (IHME, 2018). In Kenya, for example, health spending is accounted for equally by government spending (31%), OOP spending (30%), and DAH (27%) (IHME, 2018). In Ukraine, sources of total government spending are primarily from the government (48.3%) and OOP expenditures (46.8%),

with a limited role for DAH (IHME, 2018). In upper middle-income Colombia, the main source of total health spending is the government (70.1%), and the country does not receive significant DAH.

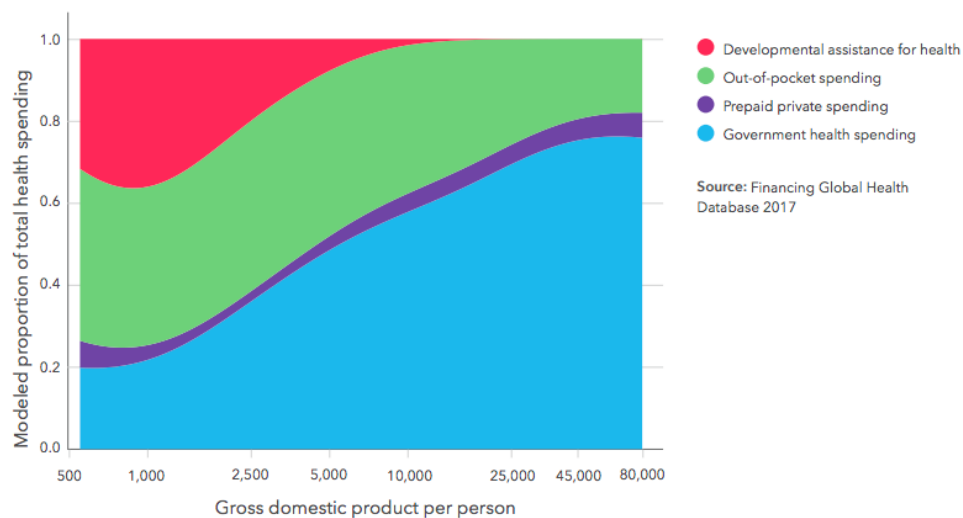
**Table 5: Total health spending and health spending by source, 2015**

World Bank income group	Total health spending per person	Government health spending per total health spending	Prepaid private spending per total health spending	Out-of-pocket spending per total health spending	Development assistance for health per total health spending
High-income	\$5,551	64.2%	21.7%	14.1%	0%
Upper middle-income	\$949	57.7%	10.1%	32%	0.2%
Lower middle-income	\$266	31.9%	7.4%	57.7%	3.1%
Low-income	\$110	21.6%	7.1%	39%	32.3%

Source: IHME, 2018

**Figure 2**

Health spending composition by source and GDP per person, 2015



Source: IHME, 2018

Health sector reform is currently underway in many countries to address gaps in healthcare coverage. In many countries, these reforms focus on the problem of high OOP spending which can lead to catastrophic health expenditures—especially in the context of NCDs which are often chronic and involve care and treatment over an extensive period of time. The majority of these reforms are focused on achieving universal health coverage (UHC), a priority objective of WHO that ensures that “all people have access to needed health services (including prevention, promotion, treatment, rehabilitation, and palliation) of sufficient quality to be effective while also ensuring that the use of these services does not expose the user to financial hardship.”<sup>4</sup> While Colombia’s health system undertook reforms years ago (in 1993) through the establishment of a mix of contributory and subsidized healthcare system, in other countries such as Kenya and Ukraine these reforms are just beginning. In Kenya, UHC is one of four pillars of President Uhuru Kenyatta’s final term and the country plans to begin health reforms focused on increasing coverage through public and private insurance (see Box 1). Ukraine is currently undergoing a massive reform effort towards UHC, including a guaranteed package of services for all citizens, funded by general taxation (see Box 2). For these and other countries embarking on health reforms, NCDs will need to be effectively addressed in order to achieve UHC (NCD Alliance, n.d.a.).

For those lower and upper middle-income countries in transition from a high dependence on DAH to a government-funded health system, there may be gaps in healthcare coverage and medicines availability and continued high OOP payments. For example, transition of middle-income countries from Global Fund and PEPFAR support for HIV/AIDS, tuberculosis, and malaria in recent years has shown mixed results (Burrows et al., 2016). The experience of Costa Rica is a case of successful transition where, in anticipation of its graduation from Global Fund funding, the government created policies and mechanisms that allowed HIV NGOs and key populations to access government funds and social security to continue their programs. In contrast, Romania, Bulgaria, and Serbia—countries with large drug injecting key populations—saw a drop in harm reduction and needle exchange programs and the governments did not step in to fill the funding gaps (Burrows et al., 2016). There are many lessons to be learned for NCD stakeholders from the transition experience of the Global Fund, PEPFAR, Gavi, and bilateral donors in the infectious disease and vaccine space. Effective planning that links to government financing mechanisms such as UHC schemes, phased transition over five to seven years, and the development of specific targets for transition have been crucial in successful transitions (Burrows et al., 2016). Taking a cue from the Global Fund experience, Gavi has developed a detailed transition planning approach in collaboration with countries as many have graduated from its vaccine funding in recent years (Gavi, n.d.). A key outcome of global funding mechanisms for infectious diseases and vaccines has been reduced pricing and pooled high volume procurement of commodities. Thus, LMICs have experience with Global Fund and Gavi with respect to price/volume based agreements and investments have been made for sustainable implementation. These factors need to be kept in mind to negotiate and build similarly sustainable agreements and programs for NCD medicines.

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<sup>4</sup> For more information, see [http://www.who.int/healthsystems/universal\\_health\\_coverage/en/](http://www.who.int/healthsystems/universal_health_coverage/en/).

## 2.2.4 Priority setting and the use of HTA in LMICs

As LMICs transition from international aid and move toward achieving UHC, there is growing concern about the financial sustainability of the provision of health services (Glassman et al., 2012), particularly in the context of limited resources for health, uncertainty around donor funding, and widespread wastage and inefficiencies within the health sector. To effectively manage and allocate finite resources for health, particularly in the context of a growing burden of NCDs, there is an increasing need to improve the rationing of scarce resources for health and institute explicit methods for priority setting (Glassman et al., 2012). Explicit priority setting in health refers to “...making explicit choices about what to fund and weighing the trade-offs between the various options in the process” (Chalkidou et al., 2016). Unlike ad-hoc, implicit priority setting (e.g. through waiting lines, low quality, and inequities), explicit priority setting at the national level most commonly refer to the development of essential medicines lists, health benefits plans or lists, and HTA agencies (Glassman et al., 2012).

HTA provides decision makers, funders, health professionals, and health consumers with evidence on the benefits and comparative value of health technologies to inform policy, funding, and clinical decisions, as well as assisting with consumer decision-making. As a multi-disciplinary process, HTA systematically evaluates the properties and effects (safety, efficacy, and effectiveness) alongside the economic implications of health technologies such as pharmaceuticals, devices, procedures, and organizational systems (INAHTA, n.d.). Moreover, HTA addresses the direct and intended effects of a health technology, as well as its indirect and unintended consequences to inform decision making and has become an issue of great interest in many settings and a means for transitioning from Essential Medicines Lists (EML) to evidence-informed and more dynamic Benefits Packages.

Over the past decades, the establishment of HTA agencies has increased as countries seek to systematically use HTA in support of achieving UHC and facilitating evidence-informed decision making (WHO, 2015c). Although well-established in high-income countries, the use and institutionalization of HTA in LMICs has been more recent and has built on the experiences of these high-income settings. HTA institutions vary according to setting, and some of them use the principles of comparative safety, efficacy and effectiveness, and economic analyses to inform coverage, reimbursement, procurement, quality, and more recently pricing decisions. This means that “one size does not fit all” and there is need to consider key procedural principles for their robust operation while bearing in mind the local context in which they will operate.

HTA has been particularly useful for supporting evidence-based rationing for NCDs, which represent a significant and growing disease burden globally. Although an increasing number of innovative medicines have become available to treat these conditions, many of them are expensive, and payers are confronted with the challenge of how to ensure that expenditures on these and other competing priorities fit within finite budgets while also providing citizens with the treatment they need (Dunlop, 2018). For many of these innovative medicines, there are also uncertainties about their effectiveness in real world conditions because of limited data at the moment of entering the market.

### **2.2.5 Health service delivery strategies**

Strategies at the level of health service delivery involve investing in human resources and service delivery for NCD case finding and case management, improving facility infrastructure and logistics, and separating the NCD medicines prescribing and dispensing functions to avoid conflicts of interest. For example, Takeda's program on Cancer Education for Primary Healthcare Professionals in Kenya provides courses in cancer control and care to primary healthcare providers identified by Kenya's county governments (Access Accelerated, 2018a). This program seeks to address the shortcomings in primary healthcare training on cancer management topics such as screening, early diagnosis, timely referral, and palliative care (Access Accelerated, 2018a). In Rwanda, recognizing the limited infrastructure for cancer care amongst poor, rural-based patients, the Ministry of Health, Partners in Health, and the Dana-Farber/Brigham and Women's Cancer Center collaborated in 2012 to establish the Butaro Cancer Center of Excellence (BCCOE)—a public, rural-based facility. At BCCOE, doctors and nurses receive foundational didactic training in cancer care and long-term capacity building. Furthermore, cancer medicines used at the hospital are selected from the WHO Essential Medicines List (EML) and procured through the public supply chain through stock orders every 6-12 months (Tapela et al., 2016). Following its establishment, the BCCOE experienced large patient volumes—2,326 patients presented to the hospital for cancer evaluation or care related to cancer, compared to 21 patients presenting to Butaro hospital for cancer evaluation or care in the previous 12 months (Tapela et al., 2016).

Strategies at this level of the health system recognize that reducing prices of innovative NCD medicines is insufficient in achieving access in the absence of a trained workforce and infrastructure to actually deliver these medicines. Indeed, many analyses of health systems in LMICs point to critical service delivery, supply chain, and human resources bottlenecks as the primary downstream barriers that impede access to even inexpensive and long-proven essential health technologies, along with demand-side awareness and utilization issues (Dickson et al, 2014; Frost and Reich, 2008).

### **2.2.6 Strategies at the individual, household, and community level**

These demand-generation strategies focus on raising personal, household, and community awareness about either the NCDs targeted by the medicines or the medicines themselves, ensuring patients and communities receive adequate information, education, and communication in order to make informed choices. Additionally, demand-generation strategies seek to strengthen patient linkages along the continuum of care, from diagnosis to treatment (BUSPH, 2017).

For example, to improve hypertension control in the peri-urban Lower Manya-Krobo District in Ghana's Eastern Region, a public-private partnership involving the Ghana Health Service, FHI 360, and the Novartis Foundation is conducting the Community-based Hypertension Improvement Project that links community members to the private sector, community health workers, and the public health system, using information and communication technologies (ICT). The intervention involves: community-based education on cardiovascular disease risk factors and healthy lifestyles; community-based blood pressure

screening, monitoring, and dispensing of anti-hypertension drugs by licensed chemical sellers; telemedicine consultations between community-based nurses and physicians and the referral of patients; ICT messages about healthy lifestyles, treatment adherence support, and treatment refill reminders; and a cloud-based health records system (Lampthey et al., 2017).

An example more specific to innovative NCD medicines is Roche's Breast Cancer National Access Program. To improve access to Herceptin (trastuzumab) by patients in Kenya with human epidermal growth factor receptor 2 (HER2) positive+ breast cancer, the program includes a community component, supporting the Kenyan Ministry of Health's efforts to raise awareness of breast cancer and roll out breast cancer screening campaigns (Access Accelerated, 2018b). Launched in 2016, the program has engaged First Lady Margaret Kenyatta as a program champion, ensuring her presence at high profile events such as the launch of Roche's public-private partnership with the Kenyan Ministry of Health and Kenyatta National Hospital via the Beth Mugo Cancer Foundation (PSCU, 2016). The Breast Cancer National Access Program, therefore, combines demand generation in communities with systems strengthening activities including training of health workers and improvement and upgrading of diagnostic infrastructure, and a pricing strategy based, in part, on a cost-sharing agreement with the Ministry of Health to provide Herceptin free of charge to public sector patients (Access Accelerated, 2018b).

Demand generation strategies at the individual, household, and community levels are vital for scaling access to medicines for NCDs, since awareness of risks and symptoms of NCDs alongside knowledge and availability of screening activities serve as patients' gateway to treatment. At the same time, these strategies alone are insufficient and can impede access if services, supplies, and medicines are persistently unavailable or unaffordable and patients subsequently lose motivation to follow up on treatment.

### **2.3 Pharmaceuticals and pharmaceutical policy in LMICs**

Over the last 35 to 40 years, many countries have created a National Medicines Policy (NMP) which is a key reflection of its approach to access to medicines and health technologies. Based on recommendations from experts after the Conference on Rational use of Medicines in 1985, WHO has promoted the concept of NMP as a systematic approach towards ensuring access to and rational use of medicines (Hoebert et al, 2013). Prior to this, pharmaceutical sector policy was developed in a fragmented manner with different parts of the government responsible for disparate parts such as regulatory policy, rational use policy, procurement policy, and others (Hoebert et al, 2013). NMPs have become a means of bringing cohesion and coordination between stakeholders across the spectrum of manufacturing, marketing, pricing, selection, distribution, coverage and reimbursement, quality, and rational use of medicines (SIAPS, n.d.). Based on a survey of 165 countries by WHO in 2011, 81% of countries have an NMP, although only 62.6 % have an associated implementation plan (Hoebert et al, 2013). Additionally, NMPs need to be updated every few years to align with changing environments. However, LMICs have had a lower frequency of updates compared to high-income countries (Hoebert et al, 2013). In this section, we explore various components of an NMP and its impact on access to medicines.

### 2.3.1 Local production

Local production of pharmaceuticals has often been debated as a viable option for increasing the availability and access to medicines in a country. However, empirical evidence on linkages between the two is limited from LMICs (WHO, 2011, Kaplan et al., 2016). As we mention earlier, policy makers may often have competing priorities when it comes to pharmaceutical access and industrial policy. Ideally, local production would increase availability, competition, and reduce prices. However, LMIC manufacturers may not have the economies of scale to achieve these goals. In the interest of access to affordable medicines, governments may subsequently choose to import lower cost medicines over promoting its local manufacturing industry (WHO 2011). Thus, while some middle-income countries have a significant domestic pharmaceutical industry, most LMICs import the bulk of their medicines (Birn et al., 2009).

Kenya, for example, is the strongest producer of pharmaceuticals in East Africa but these companies only supply one-fourth of the domestic market and largely manufacture generics and over the counter products (Banda et al., 2016) (see Box 1). In another example, India has a large pharmaceutical and vaccine manufacturing capacity, and exports a significant number of these to other LMICs (WHO, 2011). However, this has not translated to universal access to quality assured medicines for its own population as exports are more profitable for the domestic pharmaceutical industry (Mackintosh et al, 2016). In fact, Indian pharmaceutical manufacturers' investments have steadily shifted to improving quality production of generics (including for NCDs) for larger and profitable high-income markets. Colombia also has a significant local manufacturing capacity that supplies 67% of the domestic market and also exports regionally (Barbosa et al., 2016). Healthcare reform in 1993 included increasing the quality standards related to manufacturing of pharmaceuticals, strengthening the country's ability to compete with exports (Barbosa et al., 2016). However, the business environment has changed in recent times with unfavorable exchange rates and supply chain costs of importing raw materials as well as local distribution. This has somewhat limited the industry's growth and ability to innovate to produce complex medicines which would include those for NCDs (Barbosa et al., 2016).

In sub-Saharan Africa, the African Union (AU), in collaboration with UNIDO and several other agencies, launched the Pharmaceutical Manufacturing Plan for Africa (PMPA) in 2007 (AU, n.d.). Many countries in Africa have a history of local production of pharmaceuticals but the industry in most countries suffered during the period of structural adjustment in the 1990s (Mackintosh et al 2016). The PMPA stems from a renewed focus on self-sufficiency and industrial development on the continent. Since the announcement, the AU, its affiliates, UNIDO, and other have been working with countries to build capacity on local production. For example, Ethiopia has a national plan for promoting local manufacturing and is heavily investing in creating an enabling environment to support its industry. While this may not serve as immediate competition to international manufacturers of NCD medicines, the move towards self-sufficiency may have long term market impact. For example, as mentioned in the earlier section, the local manufacturing capacity has allowed the governments in India, Thailand, Brazil, South Africa, and other countries to have significant bargaining power and ability to issue compulsory licenses if required.

### **2.3.2 Selection and rational use of medicines**

WHO estimates that over half the medicines sold globally are prescribed or used inappropriately, and close to half the patients they are prescribed to do not take them properly (SIAPS, 2015). Irrational use contributes to adverse consequences such as anti-microbial resistance, adverse reactions, and wastage. The cornerstone of rational use is the development of evidence-based and regularly updated Standard Treatment Guidelines (STGs) and National Essential Medicines Lists (NEMs). In total, 156 countries have NEMs which serve as the basis of national, regional, and facility formularies (SIAPS, n.d.). Additionally, NEMs determine which medicines will be reimbursed by national or private health insurance schemes and/or provided for free through government financing. Since 1977, WHO has developed a model Essential Medicines List (EML) that serves as the foundation for NEMs for many countries (WHO n.d.). These model EMLs are updated regularly every two years to include newer and more efficacious medicines (WHO n.d.). The most recent update in 2017 added eight new NCD medicines to the list.

The process for updating EMLs by individual countries varies widely. Most LMIC do not update their NEMs systematically or as regularly as the WHO due to several reasons, including limited technical capacity and funding (SIAPS, 2015). Over the past decades, various countries have established specialized health technology assessment (HTA) organisations aimed at better informing healthcare policies and clinical practice. According to the International Network of Agencies for HTA, HTA bodies exist in certain LMICs like Brazil, Colombia, Iran, Mexico, Thailand, Tunisia, and South Africa that have progressively transitioned from NEM to more dynamic benefit packages.

In the case of infectious diseases, especially those funded by donors, governments in LMICs have often chosen to revise disease specific STGs and formularies rather than initiate a full NEM review. However, given the limited funding for NCDs, governments may not update their NEMs or STGs to include many NCD medicines, thus restricting access (Quintiles IMS, 2016). A recent study on selection of essential medicines for CVD in LMICs noted that of the 34 countries studied, most had the main classes for CVD medicines listed in their NEMs but corresponding STGs were not developed (Bazargani et al, 2018). Furthermore, the WHO/HAI baseline survey on the availability of NCD medicines conducted in 2016 shows low availability and/or poor affordability of NCD medicines in many LMICs.

### **2.3.3 Financing for pharmaceuticals and its fragmentation**

Globally, pharmaceuticals are a significant and increasing proportion of total health spending. Data from 2006 suggest that pharmaceutical spending as a percentage of total health spending ranges from an average of 30.4% in low-income countries to 19.7% in high-income countries, with variance within these income groups (see Table 6). In some low- and lower middle-income countries, pharmaceutical expenditures were as much as 67.6% of total health expenditure in 2006.

**Table 6: Total pharmaceutical expenditure, as proportion of total health expenditure, 2006 (%)**

Income group	Mean (%)	Minimum (%)	Maximum (%)
High-income	19.7	8.7	32.4
Upper middle-income	23.1	10.4	36.8
Lower middle-income	27.6	9.8	67.6
Low-income	30.4	7.7	62.9

Source: Lu et al, 2011

Fragmentation or segmentation of pharmaceutical markets within the health sector is common in all income groups. In high-income countries, where fragmentation of funding sources for healthcare tends to be much less than in lower income settings, most financial resources come from the public sector (either from taxes or national health insurance). Nonetheless, the private sector—such as through private insurance (complementary, supplementary, or substitutive)—adds to the pot of available resources for pharmaceutical products. In these settings, out-of-pocket payments (OOP) usually plays a less important role, especially after universal health coverage (UHC) has been achieved.

On the contrary, LMICs are at a range of different levels of development, and their systems may therefore have varying degrees of fragmentation. Many low-income countries rely heavily on donor assistance and OOP as main sources of healthcare financing, with limited availability of public resources for healthcare. High OOP is a threat to ensuring access and affordability of medicines in countries. At the same time—for those segments of the population which are wealthier—OOP is an opportunity for patients to choose preferred providers and medicines. Middle-income countries, on the other hand, are faced with a double challenge since they are not eligible or have transitioned from donor assistance, but many of these countries remain constrained by limited public funding for healthcare. In many middle-income countries, private funding remains substantial and linked to the ability of individuals to pay. The role of private insurance varies in different settings and high levels of OOP expose the population to the risk of catastrophic expenditure and impoverishment.

In the majority of high-income countries, most medicines are funded by the government, such as through insurance schemes or social security systems. However, in LMICs, at least two-thirds of pharmaceutical expenditures are funded through private sources (see Table 7) (Lu et al., 2011). As mentioned previously, private spending in LMICs is primarily through OOP payments, making this also the main source of pharmaceutical spending in these countries (Lu et al., 2011).

The fact that many people in LMICs must pay for medicines through OOP payments has multiple consequences for patients, their families, and their communities. For instance, patients may have to forego treatment or may have to interrupt treatment. Households may go into debt to afford payment or

have to go without purchasing other important items, because of the high cost of medicines. Communities may become divided because of the problem of inequitable access within and across populations (Bigdeli et al., 2014). The segments of the population in many countries with the ability to pay for medications for NCDs may still be very limited because of the scarcity of financial resources as well as the high costs of innovative NCD medicines and the chronicity of treatment.

**Table 7: Composition of per capita total pharmaceutical expenditure by income group, 2006**

Income group	Total pharmaceutical expenditure (%)	
	Public	Private
High-income	61.3	38.7
Upper middle-income	38.8	61.2
Lower middle-income	33.5	66.5
Low-income	23.1	76.9

Source: Lu et al, 2011

In addition to the problem of high OOP spending for medicines in many LMICs, there is also limited availability of many medicines in both public and private sectors. A study conducted in 40 LMICs through facility-based surveys found that the availability of widely-used generic medicines was suboptimal across these countries, even more so in the public sector (57%) than in the private sector (65%) (Cameron et al., 2011; Bigdeli et al, 2014). In both the public and private sectors, medicines for acute conditions were more available than those for chronic conditions that require ongoing management (Cameron et al., 2011). Availability of innovative medicines for treating NCDs is even more limited in these contexts.

#### **2.3.4 Procurement and distribution policies and processes**

Access to NCD medicines is also influenced by distribution and procurement processes. The distribution of medicines in many LMICs is a government-run process from procurement to distribution through central medical stores and a government transport fleet, a complex process that can lead to continual delays and stock-outs (Yadav et al., 2011). Procurement and distribution functions are often separate which leads to limited flow of information, compounding the delays and stock-outs (Yadav et al., 2011). This model of distribution is often found in African countries, the majority of which are low-income and lower middle-income countries. Funding constraints in these countries mean that in most cases it is impossible to hold adequate quantities of safety stock (Yadav et al., 2011). Some countries are experimenting with different distribution models including decentralized medical stores, quasi-private, or private drug distribution systems (Yadav et al., 2011).

Moreover, in their health system reforms focused on UHC, many LMICs are trying to shift pharmaceutical spending toward pooled financing sources such as public budgets, external financing sources, and social

or community-based health insurance (Yadav et al., 2012). The shift toward pooled funding reduces reliance on OOP and the related burden on patients, households, and communities, and allows for pooled procurement which can lead to lower costs and better supply (Yadav et al., 2012).

Procurement and distribution policies are also highly influenced by the national legal framework with respect to procurement. In 1994, the United Nations Commission on International Trade Law designed the Model Law on Procurement of Goods, Construction and Services (UNCITRAL Model Law) to support governments in developing their public procurement systems and regulations (Arney et al., 2014). Over 30 countries have used the UNCITRAL Model Law to serve as a basis for their procurement systems (Arney et al., 2014). The 1994 Model Law focused on open tendering, restricted tendering, the request for quotations, and single-source procurement as key methods of procurement (UNCITRAL, 2011). Competitive tenders are codified as the key methods of procurement and there is limited flexibility for price negotiations with pharmaceutical companies. The UNCITRAL Model Law has been updated in 2011 to include newer and flexible procurement mechanisms. However, as with NEMLS, many LMICs have not updated their legislation accordingly (Arney et al., 2014).

### **2.3.5 Pricing policies**

In addition to effective processes for procurement and distribution, pricing policies across the procurement and distribution value chain impact access to NCD medicines. WHO published guidelines for pharmaceutical pricing in 2015 that emphasize that policies should be selected based on country context and priorities. There are many options for influencing prices for pharmaceuticals ranging from direct interventions such as setting price ceilings and stipulating statutory discounts on large volume purchases. There are also indirect approaches such as regulating profit margins across the manufacturing, procurement, and distribution value chain or using HTA for determining the added value of an innovative medicine and its budget impact for price negotiation. Competitive bidding, therapeutic and external reference pricing (ERP), negotiating prices for groups of medicines (bundling), and value-based pricing, are additional approaches that countries have used for influencing pharmaceutical pricing. There is substantial data on the nuanced utilization of these strategies in high-income countries to reduce out of pocket expenditure and regulate prices. However, due to limited system capacity and constrained budgets, LMICs lag in implementing a mix of context-specific strategies to increase affordability and access (Nguyen et al., 2015).

In the context of health reforms, some LMICs are building capacity in HTA—the “systematic evaluation of properties, effects and/or impacts of health technologies and interventions”—to inform policy and decision making on how to allocate limited funds to pharmaceuticals, other health technologies, and interventions. HTA and its policy utilization is well instituted in high-income countries; however, while HTA initiatives might exist in LMIC, the linkage between evidence and policy in many countries remains weak (Tantivess et al., 2017). Nevertheless, the demand for HTA capacity in LMICs is increasing as part of broader efforts to reach UHC. In Kenya and Ukraine, for example, no HTA processes currently exist but discussions and initiatives are underway (see Boxes 1 and 2). Colombia established its HTA Institute in

2012 and quickly institutionalized the approach; its focus is currently on establishing a system of value-based pricing of innovative drugs (see Box 3).

Pricing strategies are a necessary ingredient in ensuring equity in access to NCD medicines, particularly for innovative, patented treatments that are unaffordable for many governments and patients in LMICs. At the same time, these strategies alone are often insufficient for long-term, sustainable access for all patients in a population, and this requires consideration of other, synergistic strategies in health and other sectors (Frost and Reich, 2009).

### **2.3.6 Regulation of pharmaceuticals**

Ensuring the quality of medicines in countries requires effective regulatory systems, including National Medicines Regulatory Agencies (NRAs) that are responsible for registration of pharmaceuticals and post-marketing surveillance, amongst other functions (WHO, 2010). Within LMICs, there is a wide range of capacity amongst NRAs to handle product regulatory filings and this means that gaining regulatory approval for medicines can be costly, complex, marked by delays, and unpredictable. WHO estimates that at least 30% of NRAs worldwide have insufficient capacity to carry out essential regulatory functions—many NRAs suffer from insufficient funding and recognition.<sup>5</sup> A study of NRAs in Africa found that every country has a NRA though functionalities vary across countries, with varying levels of growth, maturity and expertise (Ndomondo-Sigonda et al., 2017). Strategies that have been shown to improve the effectiveness of NRAs including harmonizing regulatory standards across countries, work and cost sharing arrangements, and collaboration between NRAs.

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<sup>5</sup> For more information, see <http://www.who.int/medicines/regulation/fact-figures-qual-med/en/>.



only an estimated one-fourth of the domestic pharmaceutical market and most medicines continue to be sourced internationally (Banda et al., 2016).

The regulatory agency for pharmaceuticals in Kenya is the Pharmacy and Poisons Board. Fast-track applications take up to three months for approval, and other applications have an approval time of between 6-12 months. There is currently no formal HTA process for priority setting in Kenya, though discussions are underway about how to move forward in designing and operationalizing such an initiative.

The two key pharmaceutical procurement agencies are the Kenya Medical Supplies Agency (KEMSA), a public wholesaler, and the Mission for Essential Drugs Supply (MEDS), a non-profit wholesaler that supplies the faith-based sector. Until recently, KEMSA had the mandate to procure, store, and distribute medicines to all government health facilities. Together with the Ministry of Health at the national-level, the management and supply of medicines was conducted through a pull system that often led to delays in the fulfillment of orders and stockouts in facilities (Tsofa et al, 2017).

This system changed as a result of the devolution process in Kenya (provided for in the 2010 Constitution) that gave sole responsibility for procurement to county governments. Devolution led to the improvement of drug supply in some counties but not in others. While counties now have autonomy over procurement processes, they do not benefit from the economies of scale associated with centralized procurement (Tsofa et al., 2017). In addition, many donors continue to use parallel procurement systems for vertical programs, leading to a fragmented medicines market.

Within this context, a key challenge for patient access to NCD medicines in Kenya is cost, since so many patients continue to pay for medicines out-of-pocket. Additional access barriers include the lengthy drug registration process, remoteness and inaccessibility of many rural communities, and other health systems challenges.

Pharmaceutical companies have established a range of access programs with the government and other partners for NCDs in Kenya, including:

- The Novartis Access program rolled out in 2016 that offers a portfolio of 15 NCD medicines at US\$1 per treatment per month;
- The Takeda-supported palliative care training project;
- The Celgene-supported project on education about multiple myeloma and anticoagulation care;
- The Roche partnership with the Kenyan Cancer Association for improving access to breast cancer medicines (trastuzumab);
- Healthy Heart Africa by AstraZeneca that focuses on cardiovascular disease and cancer;
- Asthma and diabetes mellitus programs led by GlaxoSmithKline and Novo Nordisk;

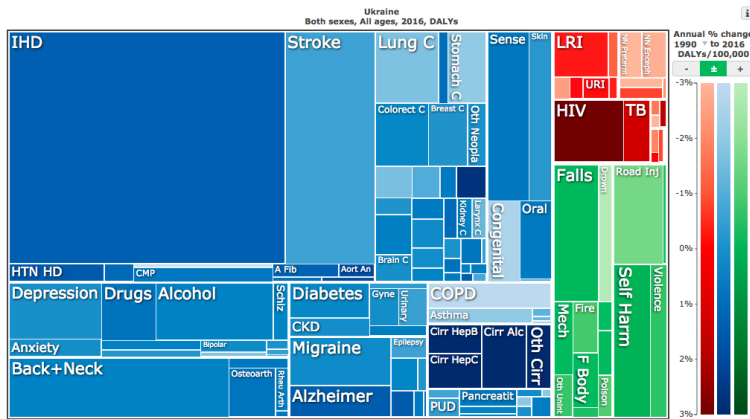
(Access Accelerated, 2018c; MSH, 2018).

Access Accelerated, a cross-industry collaboration on NCDs in LMICs, launched pilot programs in two Kenyan counties with the World Bank in 2017 targeting early screening, diagnosis, and treatment for NCDs (Access Accelerated, 2018c). In addition, international NGOs and donors have provided funds and support for health systems strengthening programs such as the Health Commodities and Supply Chain program (implemented by MSH and funded by USAID).

**Box 2: NCD burden, the health system, and access to NCD medicines in Ukraine**

Ukraine is a lower middle-income country with a population of 45 million in 2016 (World Bank Data, 2018). In 2015, the country allocated approximately 6.1% of its GDP to health and had total health spending per person in 2015 of US\$598 (IHME, 2018; World Bank Data, 2018). Sources of total government spending are primarily from the government (48.3%) and OOP expenditures (46.8%), with prepaid private spending and DAH contributing only 3.5% and 1.4% respectively (IHME, 2018).

**Figure 4: DALYs in Ukraine, by cause, in 2016 (IHME, 2018)**



As Figure 4 shows, NCDs account for the bulk of the disease burden in Ukraine, representing 82.55% of total DALYs (IHME, 2017). However, infectious diseases are still critical public health issues. Ukraine has the second-largest HIV epidemic in Eastern Europe and Central Asia, concentrated in key populations, and the second highest TB burden in Europe, with high numbers of multidrug resistant TB. The percentage of total DALYs due to communicable, maternal, neonatal, and nutritional diseases is 5.97% and injuries is 11.47% (IHME, 2017). The health sector in Ukraine is further challenged by the humanitarian needs and lack of access to health services in conflict-affected areas of eastern Ukraine. Even before the conflict began, this area was amongst those with the highest prevalence of HIV and TB (UHC Partnership, n.d.; Twigg, 2017).

Following independence in 1991, Ukraine was left with a centralized public sector health system and a small private sector, primarily consisting of pharmacies, diagnostic facilities, and some private physicians (Lekhan et al., 2015). The centralized system provided few incentives for rational use of resources or cost control (Lekhan et al., 2015). And while Ukraine established universal access to a guaranteed basic package of health services in the public sector, free to citizens and registered long-term residents, there were continued challenges with funding shortfalls, and “a sweeping gap between people’s expectations, built on the Constitutional promise, and reality” (Twigg, 2018, p. 3).

A very high percentage of medicine costs are paid by patients, and many medicines are unavailable. It is estimated that because of corruption, the Ministry of Health has lost \$100 million of its \$250 million budget for pharmaceuticals (Twigg, 2018). The country’s essential medicines list was not modernized until mid-2017, and patients have been treated with old medicines based on outdated treatment protocols. State procurements have suffered from duplication, inefficiency, and conflicts of interest. An MSH study of public procurement in 2015 found that more than 4,630 medicines were procured using public funds the prior year, but only seven medicines accounted for 20% of the expenditure (Konduri and Lebega, 2015).

In this context, international procurement agencies tend to engage in direct negotiations with manufacturers, with the government normally playing a minimal role. One exception is the negotiations the government conducted with Gilead Sciences in 2017 that led to extension of the voluntary license and the subsequent price reduction of sofosbuvir for the treatment of hepatitis C.

Ukraine is currently undergoing a five-year National Health Reform Strategy to work towards UHC. In July 2016, Dr. Ulyana Suprun, a Ukrainian-American with no affiliation to a political party, became acting health minister and quickly pushed ahead reforms (Twigg, 2017). Key components of the reform include: a guaranteed package of services for all citizens, funded by general taxation; restructuring of clinics and hospitals to become autonomous institutions with patients choosing their providers; implementation of a reference pricing approach for state procurement of medicines; implementation of a new e-health platform; and the development of a HTA initiative (supported by MSH with USAID funding).

The main barriers to accessing innovative NCD medicines are their limited availability and high cost. Currently, patients access new NCD medicines through clinical trials; medicine donations by manufacturers on a case-by-case basis; third parties (e.g. donor funds, international mechanisms); and appeals to manufacturers for humanitarian aid (MSH, 2018).

Patient associations in Ukraine have pressured the government to provide access to innovative NCD medicines in the past. One example is the partially successful “right to life” program in which the government covered 35% of medicine needs while the rest was covered by the manufacturer as humanitarian need (MSH, 2018). There is also a new reimbursement program established in mid-2017 for 21 essential medicines for the treatment of cardiovascular disease, type 2 diabetes, and asthma, which led to an 85% increase in daily defined dose consumption of medicines (MSH, 2018). Negotiated managed entry agreements are currently being considered for orphan diseases, certain types of cancer, and hepatitis C (MSH, 2018). These will be facilitated by legislation which is currently being amended by the Ministry of Health to include long-term agreements with manufacturers through a planned central procurement body (MSH, 2018).

### **Box 3: NCD burden, the health system, and access to NCD medicines in Colombia**

Colombia is an upper middle-income country with a population of 48.7 million as of 2016 (World Bank Data, 2018). The country allocated 6.2% of its GDP to health in 2015, and had total health spending per person of US\$861 (IHME, 2018; World Bank Data, 2018). The main source of total health spending in Colombia is the government (70.1%), followed by OOP expenditures (18.6%), and prepaid private spending (11.1%) (IHME, 2018). Like many other upper middle-income countries, Colombia does not receive significant DAH. As Figure 5 shows, NCDs make up the bulk of the disease burden in Colombia at 70% of total DALYs, while the percentage due to communicable, maternal, neonatal, and nutritional diseases is 12.16% and injuries is 17.79% (IHME, 2017).

Colombia’s health system was reformed in 1993 (through Law 100 of the Constitution). Through this system, Colombians have access to a package of health services granted through health insurers known as *Entidades Promotoras de Salud* (EPS). Citizens are entitled to enroll in one of the public or private EPS entities through two major insurance regimes: 1) the Contributory Regime (CR), which is for the employed and pensioners who contribute a percentage of their income to healthcare; 2) the Subsidized Regime (SR) which is for low-income people and is funded by the national government, local government, and the CR. These two schemes currently cover 95% of its population. In the early 1990s, the health center was also decentralized, with responsibility for delivering health



## SECTION 3: MANAGED ACCESS STRATEGIES

The previous section described a set of challenges that many LMICs face when seeking to improve access to NCD medicines. This section introduces a set of agreements that can be used to address these challenges—referred to in this compendium as managed access strategies (MASs).

### 3.1 What are managed access strategies (MASs)?

MASs are formal, negotiated agreements between pharmaceutical companies and payers (including government payers, private insurers, or donors) that seek to improve access to medicines for patients. Depending on the type of agreement, MASs can also help bring costs down and expand the clinical and health system evidence base. MASs consist of a range of different types of agreements including product donations and non-profit access programs, as well as managed entry agreements (MEAs).

Charitable access programs, involving product donations and non-profit models, have long been implemented in LMICs. A well-known example is Merck's decision in 1987 to donate ivermectin for the treatment of onchocerciasis for as long as it might be needed (Frost et al., 2002). Donation programs have focused particularly on neglected tropical diseases (NTDs) but companies have also donated products for communicable diseases, usually targeted to specific groups and tailored to particular country contexts (Access to Medicines Foundation, 2016). Donation programs and non-profit access programs are often implemented with the support of NGO partners. For example, Merck partnered with the Task Force for Child Survival and Development, an Atlanta-based NGO, for the implementation of its ivermectin donation program. Donation programs have been shown to improve access to medicines in certain contexts such as during humanitarian emergencies when health systems have been damaged or inaccessible (Access to Medicines Foundation, 2018). Donation programs can also provide access to medicines for the poorest households with limited ability to pay (Access to Medicines Foundation, 2018). However, questions have been raised about the long-term sustainability of product donations, and this is of relevance to chronic diseases that require care and treatment over an extended period of time. Therefore, non-profit models with limited co-pays provide a more sustainable alternative.

Another type of MAS are confidential agreements between companies and payers known as managed entry agreements (MEAs). These agreements are formal arrangements between pharmaceutical companies and payers that seek to share risk with respect to the introduction of new health technologies. They are also referred to by a variety of other names including risk-sharing agreements, performance-based agreements, patient access schemes, and special pricing arrangements (Kanavos et al, 2017; Ferrario et al., 2017).

### 3.2 Utilizing MASs to improve access to innovative NCD medicines in LMICs

In Section 2, we emphasized that while LMICs are often viewed as a relatively homogenous group due to certain shared characteristics, in reality there is a high degree of variability across LMIC markets. The Global Fund, Gavi, Unitaid, and other global financing mechanisms for infectious disease commodities have successfully utilized MASs such as price/volume agreements in LMICs. These agreements are largely based on market segmentation by income status as low, lower middle, and upper middle-income countries (which is intrinsically linked to the level of donor funding countries receive, another market segmentation strategy).

For MAS agreements, the contextual factors outlined in Section 2 within each of these countries have a significant impact on the utilization of these strategies as an access tool. At the same time, these factors provide the opportunity to identify more nuanced market segments at the country level and also within the country. Stakeholders operating in LMICs with multiple payers—for example, those countries with high OOP spending and/or fragmented health systems—can use a combination of MASs to maximize both reach of and access to innovative NCD medicines. Box 4 provides a potential approach for how stakeholders can utilize MASs to improve access to an innovative NCD medicine. Additionally, Box 5 describes two innovations in Kenya that are examples of private-sector, technological innovations that can be utilized in LMICs to reach more patients with innovative NCD medicines.

#### **Box 4: Potential approach for the utilization of MASs to improve access to an innovative NCD medicine in a multi-payer LMIC context**

Novel, synergistic use of MASs can be used in LMICs with multiple payers to ensure greater reach of and access to an innovative NCD medicine. Such an approach would involve different arrangements to reach different segments of the population, for example:

- A. The pharmaceutical company and the government payer (which covers workers in the formal sector) may agree on a managed entry agreement (MEA) (see section 3.3 for more information about MEAs). The MEA's goal would be to limit budget impact while providing access to patients in the formal sector. The country's health system would provide clinical capacity for diagnosis and management.
- B. The pharmaceutical company may partner with NGOs that provide treatment to the population in the informal sector, either through a donation or with a limited co-pay (to cover marginal costs of manufacturing plus the costs of handling and program management). For patients who are unable to pay, options could include financing through a loan or payment by impact investors, crowdfunding, or other innovative options.
- C. Stakeholders may harness technological innovations in the LMIC's health sector to reach those patients who pay for NCD medicines out-of-pocket at a cost that is more affordable to patients. These technology platforms provide the opportunity to collect quality, needed health data on patients for which no health information would otherwise exist (see Box 5 for examples of these technological innovations in Kenya).
- D. The pharmaceutical company may partner with private sector hospitals to offer treatment packages to patients in higher wealth quintiles, with the NCD medicine priced comparably to international prices.

For this approach to work, confidentiality of agreements would be necessary to allow cross-subsidization from the wealthier to the less wealthy. This goes against an increasing call in the global health community for more transparency on drugs prices so these trade-offs would need to be fully considered before proceeding with such an approach. More discussion about the drawbacks of confidential agreements can be found in Section 3.3.4.

**Box 5: Technological platforms in Kenya: M-TIBA and Mydawa**

Safaricom, PharmAccess, and CarePay in Kenya launched a health payment product in December 2015 called M-TIBA. This product is a “health wallet” on a mobile phone that allows an individual, and their friends and relatives, to send and save funds for use on medical treatment when it is needed. The funds must be spent to pay for healthcare in facilities within the nationwide M-TIBA network; the funds are managed by UAP Insurance. Individuals can transfer funds to their own or their friends’ and family members’ M-TIBA accounts for free from Kenya’s mobile money platform M-PESA. In addition, donors and insurers can utilize M-TIBA for products like vouchers and low-cost health insurance for particular segments of the population. As of April 2017, M-TIBA had a network of 350 providers around the country, had registered 500,000 users, and had recorded 60,000 clinic visits and over Ksh 100 million in medical payments. An important component of M-TIBA is that the platform provides transparency and accountability to donors (both individuals and organizations) since the funds can only be used for healthcare and transactions can be tracked and audited (Moodley et al., 2017).

A second technological innovation in Kenya is Mydawa, a digital platform launched in March 2017, with start-up funding from the Irish private equity firm Ion Equity. Mydawa provides a mobile application through which patients can purchase medicines and wellness products. These products are then delivered to patients’ homes or they can choose to pick-up the products from local, participating pharmacies. Mydawa seeks to provide value for money by cutting out middlemen in the supply chain and does not charge for service fees, or transaction or delivery costs. It also seeks to address the problem of counterfeit medicines and products by enabling consumers to track the entire supply chain process and authenticate products through a QR code tracking system. Finally, Mydawa enables monitoring of patient outcomes and dissemination of healthy lifestyle messaging.

### 3.3 Managed entry agreements (MEAs)

In the access to medicines literature, relatively less attention has been given thus far to MEAs, and this access strategy is therefore the focus of the remainder of the compendium. MEAs are designed specifically to ensure access to medicines for which there is still uncertainty with respect to their cost-effectiveness, optimal and real-life clinical and health system utilization, access pathways, and impact on health sector expenditure (Ferrario et al., 2017). Specifically, MEAs have three objectives: 1) to reduce high costs and uncertainties about expenditure on new medicines; 2) to address uncertainties about a new medicine’s clinical effectiveness and cost-effectiveness in a particular setting; and 3) to manage a medicine’s utilization in order to optimize performance (Kanavos et al., 2017). Box 6 shows the types of uncertainties that can be addressed through MEAs.

Establishing MEAs involves two key stakeholders: the *payer*—either a government or public fund holder, or a private holder of pooled resources such as an insurer) and the *pharmaceutical company* which holds market authorization for the medicine and is also its manufacturer (although there may be separate entities for these two functions). A number of additional stakeholders may be involved in the negotiation and implementation of MEAs, including regulatory authorities, an HTA agency, and health providers involved in implementation (necessary for certain types of MEAs) (Rotar et al., 2018).

From payers' point of view, MEAs are a strategy for limiting the budget impact of new, high-cost medicines and for ensuring that value for money estimates are accurate (Rotar et al., 2018; Wonder et al., 2012). This focus on value for money fits within the current trend toward value-based pricing, which began in the early 2000s, in which payers request that medicines be priced according to the benefits they offer as a way to efficiently allocate limited resources in the context of increasing healthcare costs (Piatkiewicz et al., 2017).

**Box 6: Uncertainties that can be addressed by Managed Entry Agreements (MEAs)**

- Uncertain efficacy and safety of a new drug
  - Can clinical trial results be generalized to this country's patient population?
  - For drugs that treat chronic conditions, is there sufficient long-term data?
- Uncertain cost-effectiveness
  - Given uncertainties about efficacy and safety in a specific country, what is the cost-effectiveness?
  - Additionally, who are the patients who are likely to benefit most?
- Uncertain budget impact
  - How many patients are eligible?
  - For which patients will physicians prescribe?
  - How well will patients adhere to prescribed dosing?

Source: RTI International (2018)

Government payers may have additional reasons for engaging in MEAs. In high-income New Zealand, for example, in addition to wanting to limit budget impact, the government also sought to use these arrangements with companies to ensure a sufficient supply of medicines for their small and isolated country. The contracts specified that if a drug shortage occurred, pharmaceutical companies were required to compensate the government (Morgan et al., 2013).

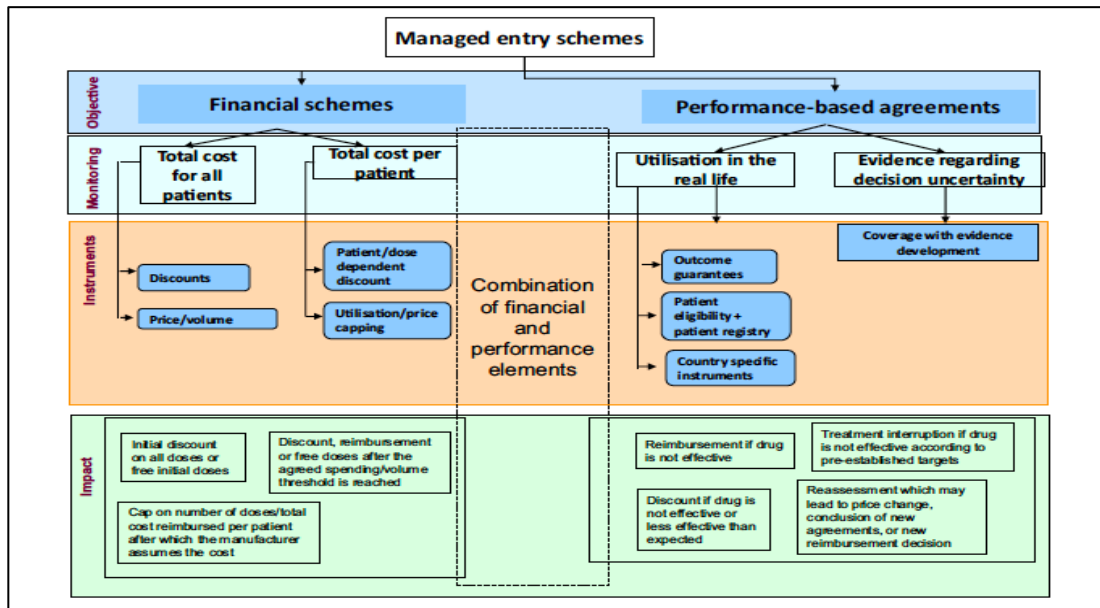
From pharmaceutical companies' perspective, MEAs are a way to extend access to their innovations in countries with restricted budgets or where there

remains some uncertainty about an innovation's performance in real-life conditions. MEAs are also a means for price differentiation in the context of a growing interest in external reference pricing (ERP). ERP, also called international reference pricing, is a practice in which the price of a medicine in a country is set or negotiated on the basis of the ex-factory or manufacturer's selling price in other, similar countries (WHO, 2013b). MEAs allow pharmaceutical companies to determine prices with each individual country in a confidential arrangement, thereby disrupting the reliability of ERP published data because the list price will not actually reflect the real price faced by the payers (Pauwels et al., 2017).

In this compendium, the term MEA serves as a general umbrella term under which many such arrangements can be classified; however, it is also important to recognize that the boundaries as to what constitutes an MEA are not fixed and that many countries differ in their understanding of what an MEA is and when the term should be applied (Ferrario et al., 2017). Ferrario et al (2017) note that the names which countries, payers, and companies apply to such arrangements relate to their objectives, nature, and mode of reaching agreement and sit on a spectrum of informal-to-formal with respect to their institutionalization.

A variety of taxonomies for these arrangements exist, but most taxonomies roughly classify arrangements as falling under two main categories, as shown in Figure 6: financial schemes and performance-based agreements (Kanavos et al., 2017).<sup>6</sup> Financial schemes focus on targeting the financial impact of new drugs to patients and/or health systems. These arrangements leverage instruments such as discounts, price/volume agreements, patient/dose dependent discounts, and utilization-based price capping (Kanavos et al., 2017). Performance-based agreements address the uncertainty with respect to evidence on clinical outcomes or eligibility of patient populations. Instruments include outcome guarantees, patient eligibility requirements/registries, and coverage with evidence development (Kanavos et al., 2017). Hybrid models also exist, combining financial- and performance-based instruments. Additionally, MEAs are not infrequently combined with other access strategies—for example, they may be combined with other price strategies (such as donation programs for certain population groups) as well as demand and health delivery and health sector strategies. Multiple approaches are effective as long as they strengthen and reinforce each other (Kibicho and Pinkerton, 2012).

**Figure 6: A framework of financial schemes and performance-based agreements**



Sources: Kanavos et al, 2017; Ferrario and Kanavos, 2015

<sup>6</sup> For other taxonomies, see Carlson JJ et al. (2010); Klemp et al. (2011); Bouvy et al. (2018).

### 3.3.1 Financial schemes

The objective of financial MEAs is to address the high costs of medicines for patients and/or health systems and uncertainties about financial impact. These schemes address budget uncertainties, though do not address uncertainties related to outcomes (these are the focus of performance-based agreements described in Section 3.3). Agreements can employ a number of financial instruments as shown in Table 8. This type of MEA may seem most appropriate for medicines that are likely to have a significant impact on budgets because of high cost or potential large volumes (Lu et al., 2015).

**Table 8: Instruments for financial schemes**

<b>Instruments</b>	<b>Definitions</b>	<b>Examples</b>
<b>Discounts</b> <i>and free medicines</i>	Pharmaceutical companies agree with payers to provide discounts on medicines or free medicines for a period of time.	In 2010, Merck agreed with the Rwandan Ministry of Health to provide free Gardasil® HPV vaccine for three years, followed by concessional pricing for future doses (Binagwaho et al, 2012).
<b>Price/volume agreements</b> <i>also called budget-impact schemes</i>	Payers and pharmaceutical companies agree on a price based on a forecast volume of sales. If the actual sales volume exceeds the forecast, the price of the medicine may be revised downwards or the company may be asked to pay a rebate.	In France, two price/volume agreements were negotiated with BioMarin and Alexion Pharmaceuticals in 2008 for two orphan drugs respectively: Naglazyme® (galsulfase), a treatment for mucopolysaccharide type IV disease, and Soliris® (eculizumab), a treatment for paroxysmal nocturnal haemoglobinuria (Morel et al, 2013). A price was agreed to up to a budget ceiling; sales made beyond the ceiling required the companies to pay back any turnover made.
<b>Patient/dose dependent discount</b>	Payers and pharmaceutical companies agree on a maximum number of cycles of treatment or dose of drug reimbursed per patient. The pharmaceutical company pays for the drug beyond this agreed amount.	In the UK, an agreement with Celgene in 2009 stipulated that the NHS will fund Revlimid® (lenalidomide) for the treatment of multiple myeloma for 26 cycles (typically 2 years), after which time Celgene will fund the cost for patients (Guardian, 2009).
<b>Utilization/price capping</b>	Payers and pharmaceutical companies agree on a maximum amount spent for a medicine per patient. The pharmaceutical company pays for the drug beyond this agreed amount.	In 2008 in China, Bayer offered Nexavar® (sorafenib), for the treatment of unresectable or metastatic hepatocellular carcinoma, at \$7,000/month per patient, capped at three months of use (Lineberry et al., 2011).

Source of definitions: Cheema et al, 2012.

Financial schemes have been implemented in many high-income countries around the world. For example, in 2008 the French *Comité Economique des Produits de Santé* (CEPS) negotiated price/volume agreements for two orphan drugs with BioMarin and Alexion Pharmaceuticals respectively: Naglazyme® (galsulfase), a treatment for mucopolysaccharaïde type IV disease, and Soliris® (eculizumab), a treatment for paroxysmal nocturnal haemoglobinuria which is one of the most expensive drugs in the world (Morel et al., 2013). In these agreements, which were in effect until 2013, a price was determined up to a maximum budget ceiling. The companies were to supply the medicine to all patients who required it and then paid back to the payer any net sales made above the maximum budget ceiling (Espin et al, 2011).

Another example of a financial MEA in a high-income country is in the United Kingdom (UK), where the National Institute for Health and Care Excellence (NICE) reached a dose dependent agreement with Celgene in 2009 in regards to its product Revlimid® (lenalidomide) for the treatment of multiple myeloma. In the agreement, the UK funds Revlimid® for third-line use for patients for 26 cycles of treatment (typically two years), and any further costs are covered by Celgene (*The Guardian*, 2009).

Financial MEAs to improve access to NCD pharmaceuticals are also being used in some LMICs, though there is currently limited documentation about these schemes. One example is in Rwanda, in regards to its national cervical cancer prevention strategy, where an agreement was made between Merck and the Rwandan Ministry of Health in December 2010 that guaranteed free Gardasil® human papillomavirus (HPV) vaccine for three years, with future doses at concessional pricing (Binagwaho et al, 2012). This arrangement assisted Rwanda in reaching 93.23% coverage following the initial three-dose course of vaccination (Binagwaho et al, 2012). Subsequently, Gavi began including HPV vaccines—which had been introduced in high-income countries as early as 2006—to eligible countries with a price offered by Merck at less than \$5 per dose.

Another example of a financial MEA in an LMIC is Nexavar® (sorafenib) for the treatment of unresectable or metastatic hepatocellular carcinoma. Nexavar® was approved in China in 2008, and Bayer offered a price per dose of approximately \$7,000/month which was similar to the price offered in high-income markets (Lineberry et al., 2011). In China, the patient's cost was capped at three months of use (Lineberry et al., 2011).

### **3.3.2 Performance-based agreements**

Payers in many countries are willing to pay high prices for innovative medicines if they provide value for money. However, for some new products, the evidence remains limited right after registry as to how these medicines will perform in real-world circumstances (Wonder et al., 2012). The objective of performance-based MEAs is to address this problem by focusing on patient and health system outcomes and uncertainty in regards to clinical and health system utilization. These schemes thus provide more opportunity than financial MEAs for risk sharing between payers and pharmaceutical companies (Pauwels et al., 2017). Agreements can employ a number of instruments as shown in Table 9.

In general, these agreements are most appropriate for innovative medicines that require more evidence—as is the case for many new medicines that treat chronic NCDs since it is unlikely that they will have long-term data at the time of submission for approval (Wonder et al., 2012). Additionally, these schemes are most effective for products that have: a) simple methods for measuring effects of treatment, and b) well-defined outcomes (Carlson et al., 2010). Box 7 presents five questions that can guide decision making about whether performance-based agreements are appropriate for a particular product and context.

**Table 9: Instruments for performance-based agreements**

Instruments	Definitions	Examples
<b>Outcome guarantees</b>	<p>The pharmaceutical company provides rebates, refunds, or price adjustments if their product does not meet pre-agreed outcomes after launch in real world settings.</p>	<p>An agreement was negotiated in 2008 between Health Alliance Medical Plans in the U.S. with Procter and Gamble and Sanofi-Aventis for Actonel (risedronate) for treating osteoporosis. The agreement states that the manufacturers will help pay the cost of treating nonvertebral fractures among patients who experience them despite taking Actonel (Neumann et al 2011; Pollack, 2009).</p>
<b>Patient eligibility + patient registry</b>	<p>Patient eligibility criteria is linked to a registry to evaluate utilization in clinical practice and to collect additional data.</p>	<p>Italy utilizes a monitoring registry with 78 therapeutic indications to track patient eligibility, assess utilization in the context of clinical practice, and collect safety and other data (Ferrario and Kanavos, 2013).</p>
<b>Coverage with evidence development (CED)</b>	<p>The payer agrees to cover the drug under certain conditions that facilitate the development of additional evidence on a medicine’s performance in real life, in order to have definitive evidence on the product’s clinical or cost-effectiveness impact. (Trueman et al., 2010).</p> <p><i>CED with negotiation</i> involves the renegotiation of pricing and coverage based on the evidence developed, but not explicitly tied to prespecified outcomes.</p> <p><i>CED with prespecified agreement</i> involve agreements in which future pricing and coverage are explicitly tied to pre-specified outcomes of evidence development.</p>	<p>In the UK in 2002, a scheme was set up to improve access for patients with multiple sclerosis (MS) to disease-modifying treatments (DMTs). In the scheme, if patient outcomes were less than what was required for cost-effectiveness, the UK would be able to reduce the price paid for DMTs (Faulkner et al., 2016).</p>

<p><b>Country-specific instruments</b></p>	<p>Instruments vary by country</p>	<p>Country-specific instruments in Italy include AIFA notes for conditional reimbursement, and therapeutic plans to limit access (Ferrario and Kanavos, 2013).</p>
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Sources of definitions: Kanavos et al, 2017; Coulton et al., 2012; Faulkner et al., 2016; Carlson et al., 2010; Trueman et al., 2010; Ferrario and Kanavos, 2013.

**Box 7: Guiding questions for performance-based agreements**

- Is there uncertainty about the clinical or economic benefits of the technology that can be reduced by further study?
- Can the relevant clinical or economic outcomes be clearly defined and measured in a satisfactory manner?
- Are the timelines for beginning and implementing the scheme reasonable?
- Will the arrangements for data collection and analysis be easily implementable and affordable?
- Can clarity be reached on the likely decisions following the data collection and analysis?

Source: Drummond (2015)

Performance-based agreements have primarily been implemented in high-income countries, as they require more capacities for data collection and monitoring and evaluation, hence are reliant on the wider health system for data gathering and implementation. In the U.S. in 2008, a health insurer called Health Alliance

Medical Plans negotiated an outcome guarantee with Procter and Gamble and Sanofi-Aventis, who jointly sell Actonel (risedronate) for the treatment of osteoporosis. At the time, Actonel costed an estimated \$100/month per patient (Pollack, 2009). In the agreement, the companies agreed to help pay for the cost of the treatment of non-vertebral fractures among patients compliant to treatment through rebates—for example, \$30,000 for a hip fracture and \$6,000 for a wrist fracture (Pollack, 2009). In return, Health Alliance has kept Actonel on a favorable tier of its drug list, with lower copayments for patients than competing brand-name drugs (Neumann et al., 2010; Pollack, 2009).

An example of a coverage with evidence development arrangement was set up in the UK to improve access for patients with multiple sclerosis (MS) to disease-modifying treatments (DMTs). The Multiple Sclerosis Risk-Sharing Scheme (MS RSS) was established in 2002 and followed a decision by the UK's NICE that the cost-effectiveness of the DMTs was dependent on the short-term disability benefits shown in clinical trials being maintained over a sustained period of time. The MS RSS stipulated that if patient outcomes were less than what was required for cost-effectiveness, determined through the monitoring of a patient cohort, the UK would be able to reduce the price paid for DMTs. The scheme led to better access for patients to DMTs, increased investment in healthcare for MS patients, and the development of a MS patient registry (Faulkner et al, 2016). However, problems were encountered with the governance of the scheme, as well as its methodology and data collection (Raftery, 2010). Notably, in the first report of the scheme in 2009, outcomes were worse than what was predicted, but the decision to move ahead with price reductions did not occur as it was deemed too early to make those adjustments (Faulkner et al, 2016). Additionally, the study team and methods used to determine the outcomes and cost-effectiveness

of the DMTs were both changed throughout the period of study, highlighting the difficulties with evaluating performance-based schemes and the need to define a clear methodology from the beginning (Faulkner et al, 2016).

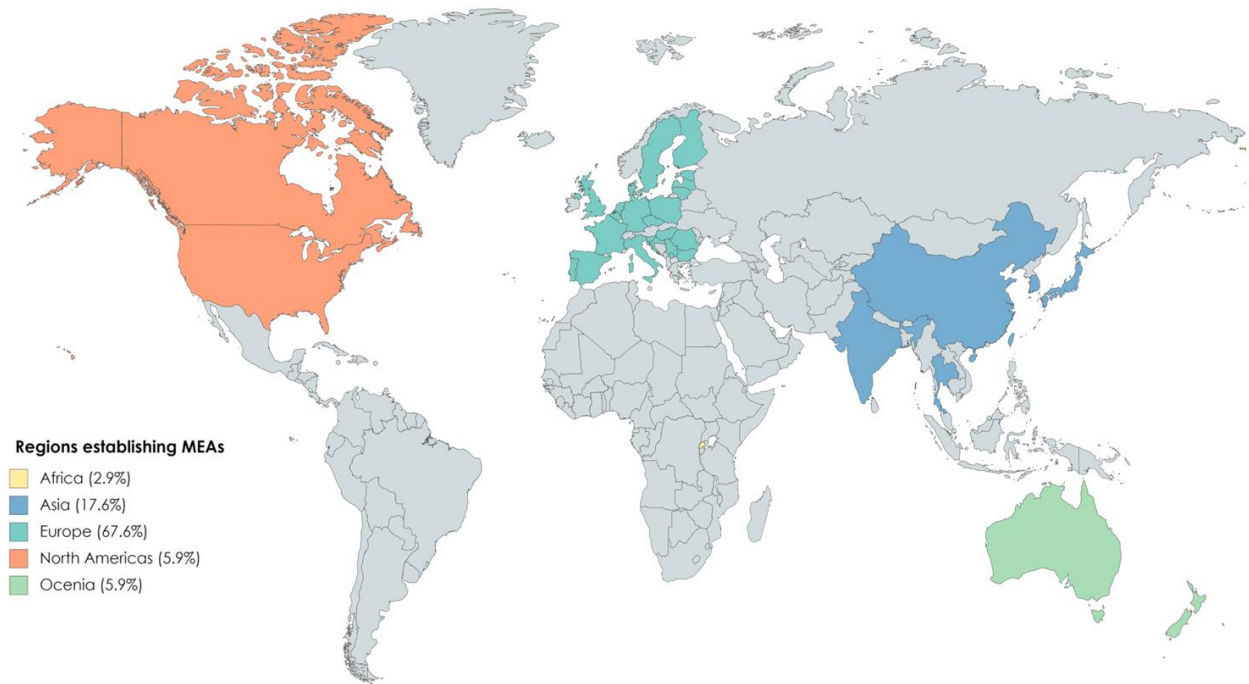
In Italy, performance-based agreements have been used since 2006 and are centrally managed by *Agenzia Italiana del Farmaco* (AIFA) (Upton, 2018). Several different instruments are utilized in Italy, including a registry to monitor patient eligibility, assess utilization in the context of clinical practice, and collect safety and other data (Ferrario and Kanavos, 2013). As of the end of 2011, the monitoring registry included 78 therapeutic indications (Ferrario and Kanavos, 2013). Of these, 28 had conditional reimbursement agreements including cost-sharing, risk-sharing, and payback schemes (Ferrario and Kanavos, 2013). Italy also uses two additional country-specific instruments: 1) AIFA Notes, which limit reimbursement only to specific indications, and in so doing seek to improve the appropriateness of prescription; 2) Therapeutic Plans, which allow prescription and reimbursement only for those indications for which there is reported clinical evidence (Kockaya and Wertheimer, 2018).

### **3.3.3 Where are these financial- and performance-based schemes being implemented?**

A systematic search of the literature for MEAs, conducted for this compendium, identified 285 documented schemes, with most of these present in high-income countries (MSH, 2018). In Europe, 23 countries (67.6%) implemented one or more types of MEA, while there were MEAs in six countries in Asia (17.6%), two countries in North America, two countries in Oceania, and one country in Africa (see Figure 7). The search found no documentation of MEAs in Latin America or Africa, apart from the financial scheme for vaccines in Rwanda referred to in Section 3.2. It is likely that MEAs exist in many LMICs, particularly financial schemes, but these are not documented or perhaps use different terminology. Thus, the documentation on MEA implementation in LMICs is extremely limited, and requires more study. Box 8 provides information about the awareness of MEAs in the compendium's three LMIC case study countries, and the factors that might facilitate or limit the use of MEAs in these three contexts.

The majority of the 285 schemes found in the systematic search cover NCDs and their treatment, particularly different types of cancer. Financial schemes were slightly more common (50.2%) than performance-based agreements (44.9%), and the remaining schemes were hybrid agreements (4.9%). This finding was corroborated by a recent study of schemes in the Middle East and North Africa that found that financial schemes were more frequent, particularly discounts and price/volume agreements, than performance-based schemes (Maskineh and Nasser, 2018). Financial schemes predominate in many countries because their implementation tends to be less complex than performance-based agreements. A general trend over the past decades has been toward MEAs with less administrative burden (Carlson et al, 2014; Bouvy et al., 2018). Generally, performance-based agreements were more prominent in North America, while financial-based schemes were more common in Europe, Asia, and Oceania. Italy, however, has a well-established system of performance-based agreements.

**Figure 7: Implementation of MEAs by region**



Source: MSH, 2018

As discussed throughout this section, MEAs have several advantages for stakeholders. For patients, they provide early access to novel treatments. For payers, MEAs are a means for granting earlier access to new medicines that will have high budget impact due to high-cost and/or high volumes while helping them address uncertainties about effectiveness and budget impact. And for pharmaceutical companies, MEAs may provide some predictability about the initial price conditions and potential market size estimations, and in so doing, advance further innovation (Kanavos et al., 2017). MEAs could also help create a more collaborative environment between payers and pharmaceutical companies (Upton, 2018). Finally, MEAs have the advantage of including a range of different types of instruments to address different needs and markets. Financial schemes can improve budget uncertainties for innovative medicines, and performance-based mechanisms can assist with the collection of information on real-world effectiveness. These different types of MEA can be combined and schemes can also be used along with complementary access strategies.

#### **Box 8: MEAs in Kenya, Ukraine, and Colombia**

A study of MEAs in the three LMIC case study countries found that stakeholders had some experience with utilizing MEAs to improve access to innovative NCD medicines, though this experience was limited. In Kenya, pharmaceutical companies have worked with the government through public-private partnerships to improve access to medicines for infectious diseases and NCDs and these programs have involved both discounts and price/volume agreements. In addition, global partnerships have negotiated price/volume agreements for the benefit of Kenya and other countries, such as Gavi for vaccines (see Box 1). In Ukraine, MEAs are currently being considered for orphan diseases, certain types of cancer, and hepatitis C (see Box 2 in Section 2). Similarly, in Colombia, there is a growing awareness of and interest in MEAs and insurers have recently initiated pilot MEA projects for NCD disease treatment (see Box 3 in Section 2).

Few of the respondents in the three case study countries were aware of MEA terminology and the range of available instruments, but most had an interest in learning more about this policy tool. This limited knowledge of MEAs contrasted with their knowledge of other access strategies, such as the use of TRIPS flexibilities.

The case studies identified a set of factors that could help or hinder the use of MEAs in these three LMICs:

1. *Contextual characteristics* of the country including income level, market size, political stability, levels of corruption, structure of the health system (centralized or decentralized), previous local successes, international cooperation, and levels of coordination.
2. *Characteristics of the drug and its evidence and uncertainties*: sufficiency and quality of available evidence about a new drug in a particular country, including real-world evidence, cost-effectiveness, and patient eligibility criteria; the possibility of generalizability/extrapolation of clinical results into local population.
3. *Capacity of the health system to regulate and negotiate, as well as collect, monitor, and evaluate data* (for financial schemes, health systems require capacity to estimate volumes, and for performance-based schemes, health systems need to be able to assess outcomes).
4. *Existence of enabling legal and policy frameworks* on MEAs, including legal requirements about transparency of pricing or confidential agreements.
5. *Existence of clear rules, roles, responsibilities, and implementation plans* within the health sector, particularly in terms of payers and pharmaceutical companies.
6. *Understanding of the use and limitations of MEAs* by key stakeholders, including perceptions of complexity of MEA implementation, feasibility, and market attractiveness.
7. *Support for MEAs as a policy solution* from key stakeholders, including consideration of the policy process, coalitions and networks, financial support, and policy champions.
8. *Level of trust among payers and pharmaceutical companies*, and willingness to dialogue.
9. *Risk attitudes of payers and pharmaceutical companies* (neutral, averters, and seekers), including risk attitudes toward uncertainty, noncompliance with agreement, effects on international or portfolio revenues, and the need for assurance that heavy losses would be compensated.

Source: MSH, 2018

### 3.3.4 Challenges and limitations of MEAs

Despite their advantages, the use of MEAs as an access strategy comes with a number of challenges and limitations. One key challenge is that some stakeholders have negative perceptions about MEAs, and therefore are unlikely to consider their use as a policy tool. Payers in some countries are suspicious that schemes amount to marketing activities by pharmaceutical companies (Adamski, 2010). Others are concerned that through performance-based schemes, governments rather than companies are funding a portion of a drug's development costs (Adamski, 2010). Sometimes these concerns are fueled by a general lack of understanding and trust between payers and pharmaceutical companies (Bouvy et al., 2018). Others are influenced by the fact that what amounts to an MEA differs across countries, leading to confusion about its role as a strategy to improve access and its synergy with other initiatives (Kanavos et al., 2017).

An important limitation of MEAs relates to the burden on the health system, in terms of administration, cost, and data collection and analysis. This is particularly the case for performance-based agreements which require an infrastructure of data collection and analysis, are reliant on the health system for patient tracking, lead to extra costs for evidence collection, and necessitate agreement between parties on the details of the scheme including what will be measured, by whom, and how (Faulkner et al., 2016; Garrison et al., 2013). Given these financial- and system- requirements, fewer performance-based schemes have been implemented than financial schemes (Coulton et al., 2012; Neumann et al., 2011; Garrison et al., 2013). While financial schemes involve less burden on the health system than performance-based agreements, all types of MEAs need to be renegotiated periodically (Ferrario et al., 2017). The health system requirements related to MEAs are, therefore, an important consideration for stakeholders as they assess the tradeoffs of MEAs versus other access strategies.

Another challenge related to MEAs is that they can only be used in countries with enabling legal and policy frameworks. For example, laws or regulations might prohibit coverage with evidence development schemes. Moreover, some countries have laws in place that do not allow negotiated prices to be confidential; pharmaceutical companies are reluctant to enter into MEAs in these contexts since they value confidentiality in the context of the ERP system. The legal framework in countries may encompass different laws for how pharmaceutical companies can negotiate with government payers as compared to private sector payers. Legal frameworks, however, are not a precondition for entering into MEAs. For example, while the Czech Republic has no formal, national legislation on MEAs, schemes have been implemented in the country since 2013 (Rotar et al., 2018). Moreover, in Poland, the 2011 Reimbursement Act established a legal basis for MEAs; however, before that time, arrangements between payers and companies occurred but were generally informal and described as "gentlemen's agreements" (Ferrario and Kanavos, 2013; Kawalec et al., 2016).

Confidentiality is at the core of MEA agreements, and thus the details of negotiations and agreements are not made public. But this lack of information has implications. It limits the ability of some stakeholder

groups, most importantly patients, to know about and participate in MEA processes (Kanavos et al., 2017). It also prevents learning across countries about what works and what does not in regards to the implementation of MEAs (Kanavos et al., 2017). There are few published evaluations of MEAs, making it difficult to substantiate their claimed benefits (Kanavos et al., 2017; Adamski et al., 2010). The lack of information also makes it difficult to assess equity in who has gained access to medicines through MEA initiatives—are countries who can least afford novel, high-cost medicines receiving the largest discounts (Ferrario et al., 2017)?

Another drawback of MEAs is that key stakeholders may attempt to “game the system” when they are used in countries that utilize HTA for decisions about coverage (Kanavos et al., 2017; Towse, 2010). If MEAs become the norm in these countries, pharmaceutical companies may have an incentive to offer high initial prices in their first submission for drug approval that they know will be refused, as this will be viewed as the opening bid. Equally, payers are more likely to turn down an initial price offered by pharmaceutical companies, aware that a lower price will be offered and negotiated through a MEA. This process can result in significant transaction costs for both payers and pharmaceutical companies (Kanavos et al., 2017; Towse, 2010).

MEAs have additional limitations that are specific to certain stakeholder groups. For payers who use ERP to inform price levels, they will not benefit from confidential, negotiated prices as part of MEAs elsewhere (Kanavos et al., 2017). For pharmaceutical companies, MEAs require concessions such as refunds for particular outcomes, discounts, or the collection of real world evidence (Kanavos et al., 2017, p. 89). MEAs may introduce additional uncertainty in regards to their expected returns, and this could disincentivize the further collection of data, (Kanavos et al., 2017). Finally, pharmaceutical companies may feel that the more commonly used financial-based MEAs do not represent the value of their innovations (Faulkner, et al., 2016).

### **3.3.5 In which LMIC settings are MEAs a potentially effective strategy?**

Bearing in mind the limitations and challenges of MEAs discussed in Section 3.5, in those LMICs where an enabling set of factors exist, or can be built, MEAs can be considered as a potential policy tool for increasing sustainable access to innovative NCD medicines. This is particularly the case in upper middle-income countries that have greater negotiation and institutional capacity, as well as data infrastructure (see, for example, the context in Colombia in Box 3, Section 2). There is thus a greater opportunity to use MEAs (with a wider range of instruments) in these countries, particularly in those contexts with political stability, commitment to UHC, an enabling legal framework, HTA initiatives, and less fragmented health systems. MEAs are particularly suitable where there is one predominant purchaser (such as a social health insurance scheme) or in countries where resources are pooled in order to better negotiate prices and aggregate demand.

MEAs as a strategy to improve access to innovative NCD medicines are more challenging in countries that have the following characteristics (found in many low-income and lower middle-income countries):

- Competing priorities for government health budgets due to a “dual burden” of infectious diseases and NCDs.
- Limited health system capacity to regulate, negotiate, collect, monitor, and evaluate data.
- Fragmented health systems (the process of reaching an agreement on a MEA is more effective in those contexts which have centralized decision making and a “single payer” to conduct negotiations (Coulton et al., 2012));

There are, however, some instances in which simple MEA instruments may be an effective access strategy for innovative NCD medicines in these countries. First, financial-based MEAs are a potential strategy when there are centralized, single government payers for negotiations (see, for example, Table 6 about Rwanda and the HPV vaccine). Second, in those low-income and lower middle-income countries where donors are engaging in pooled purchasing for pharmaceuticals, financial-based MEAs negotiated by donors with pharmaceutical companies are an effective strategy for improving access to innovative NCD medicines. Given the limited health information infrastructure in these countries, performance-based agreements have minimal feasibility in these settings until sufficient capacity is built for processes such as HTA, health information systems, and implementation structures.

Commentators have pointed out that one of the main barriers to utilizing MEAs in LMICs is that many countries lack the administrative capacity and bargaining power to undertake price negotiations with pharmaceutical companies (Morgan et al., 2013). LMICs have navigated these issues before with respect to accessing antiretroviral medicines for HIV/AIDS, using a number of strategies to strengthen their position vis-a-vis pharmaceutical companies and achieving fair prices (Waning et al., 2009). In many instances, external, non-profit institutions—such as WHO or the Clinton Health Access Initiative—have helped support LMICs at the negotiating table, building capacity, establishing transparency with respect to price information, and providing technical expertise (Morgan et al., 2013). Good practice requires that a similar role be carved out for international agencies if MEAs are to be considered viable access strategies for LMIC.

In sum, countries can approach MEAs incrementally in which they begin with financial schemes while they strengthen systems for the selection, adoption, and monitoring and evaluation of innovative NCD medicines. This incremental approach recognizes that time and resources may have to be put into supporting governments to establish the requisite enabling environments related to policy, legal, and health systems. This includes identifying existing legal and policy frameworks and how these might constrain or facilitate MEAs (Morgan et al., 2013) and building implementation structures from the ground up if they don't already exist or, alternately, identifying existing institutions that might host such structures and targeting them for significant capacity building.

In Tables 10 and 11, we present an analytical framework to identify opportunities for MEAs in LMICs, including those with multiple payers, using two of our case study countries, Kenya and Colombia:

**Table 10: Kenya: Growing market with steadily increasing buying/negotiating power, shifting away from donor funding**

Contextual Factors	Situational Analysis	Implications for MEAs
<b>International and regional level policies</b>	TRIPS compliant, leverages TRIPS flexibilities for import of infectious disease drugs; growing local manufacturing. Fast growing economy with significant interest from foreign investors	Changes to the national procurement policy, limited use of CL, NEML update, plus a largely unregulated pharmaceutical pricing system provides significant opportunity for piloting MEAs for NCD medicines in the country. Decentralization indicates potential for designing innovative MEAs based on regional context and capacity. However, pharmaceutical companies wishing to engage will need to provide or partner with other organizations which can provide technical assistance and capacity-building support. Public, private, and faith based/non-profit could be separate market segments to target for MEAs and may have variable capacities for implementation. Starting with small pilots within various segments would provide an evidence base for expansion.
<b>National multi - Sectoral policies</b>	National Procurement Policy modified in 2015 to allow for competitive negotiations, framework contracts, direct procurement, and other flexible arrangements. No VAT on finished pharmaceuticals, though impacts raw material.	
<b>Health financing</b>	30% out of pocket spending a significant % of which is in the private sector, health sector reforms underway focused on UHC, though coverage for the NHIF is still limited (18%). Shifting away from donor funding as economy develops. Purchasing of services is mixed – 49% public and 48% private including faith based and non-profit providers.	
<b>Pharmaceutical policy</b>	NEML updated in 2016 based on latest 2015 WHO Model List and includes significant number of NCD medicines. NEML review process recommended HTA institutionalization in the country for context specific and evidence based decision making. NEML process also reflected capacity and funding gaps within the system to implement new initiative such as HTA.	
<b>Procurement and distribution processes and policies</b>	Public sector purchasing has become decentralized (unless donor funded commodities) leading to challenges in managing prices and quality of medicines. Procurement processes still focus on competitive tenders and price based bidding.	
<b>Pharmaceutical pricing policies</b>	Prices are not controlled – high and variable mark-ups across the value chain.	

**Table 11: Colombia: Upper middle-income country with UHC, high burden of NCDs, and significant capacity for health sector reforms**

Contextual Factors	Situational Analysis	Implications for MEAs
<b>International and regional level policies</b>	TRIPS compliant, increasing interest in using TRIPS flexibilities for CL and price reduction; strong local manufacturing and laboratories. Also has data exclusivity decree which provides protection for first entrants for products into the market.	With one of the largest populations in Latin America and increased burden of NCDs, and high <i>judicialization</i> rates Colombia is an ideal target market for MEAs. Changes to the national procurement policy, pressure of increasing OOP expenditure and
<b>National multi - Sectoral policies</b>	Has flexibilities for framework contracts and potentially other innovative methods. Health is a fundamental right within the constitution and	

	<p>influences issues on import and pricing of medicines. Colombia is one of the countries one of the highest number of judicial cases filed from patient groups and other stakeholders demanding access to various medicines, including innovative products after the right to health was enshrined within the constitution.</p>	<p>increased prices of pharmaceuticals, and continued focus on capacity building and health sector reform provide significant opportunities for pharmaceutical manufacturers to approach various health insurance organizations and providers (public/private) to collaborate on MEAs. Additionally, as the government shifts to evaluating value based pricing, working collaboratively with them as collective, the pharmaceutical sector can create win-win opportunities on both sides.</p>
<b>Health financing</b>	<p>70% total spending on health is by the government through its national health insurance programs (mandatory contributions from formal sector and subsidized/tax based for informal sector). The OOP expenditure has gone up in recent years to 18% in 2015 from 6.8% in 2000, still considered to be low compared to the LMIC average. Purchasing for services through both private and public health providers is done by various health insurance schemes. 48% of the population is covered by the subsidized scheme and almost 47% is covered by the contributory scheme. There are differences in the services provided between the two schemes beyond a basic package of services. However, with the shift towards universal access for all services as a part of health as a fundamental right, the government is focusing on reforms to provide a uniform package.</p>	
<b>Pharmaceutical policy</b>	<p>Colombia has one of the strongest National Regulatory Authorities in the region and associated systems for monitoring product quality and pharmacovigilance. Reimbursement of pharmaceuticals is based on the benefits packages for the respective schemes. Prescription by INN and of generics is mandatory in the public sector but patients can pay out of pocket for branded medicines in the private sector.</p>	
<b>Procurement and distribution processes and policies</b>	<p>Drug distribution for the public sector is through private health system distribution to the facilities. For the private sector manufacturers supply to pharmacies, supermarkets, and other supply stores. Tenders, negotiation, and a shift towards value based procurement are processes used to procure medicines. High markup levels on distribution channels.</p>	
<b>Pharmaceutical pricing policies</b>	<p>Prices of drugs are regulated by various means including focusing on use of generics, reference pricing, HTA, leveraging pooled procurement mechanisms such as ones managed by PAHO. With an aging population and increasing burden of NCDs in addition to demand for equitable access to medicines via the health as a legal right policy, Colombia faces continued pressure to manage budget impact and reduce product pricing</p>	

### **3.3.6 Decision making on whether to proceed with an MEA strategy**

Ultimately, deciding whether to pursue an MEA in a particular context requires a comprehensive process to support decision making toward adoption. This process begins with horizon-scanning (e.g. what similar products might be expected to enter the market? What might be the cost implications of these? What future funding challenges might be expected? Does an MEA make sense in this context?) and continuing all the way through post-marketing data collection and surveillance (e.g. Will evidence actually serve to reduce uncertainty? Will the MEA have truly resulted in increased access?) (Drummond, 2015). The decision-making process also should take into account whether timelines for implementation and evidence collection are realistic and whether the overall negotiation, administrative, implementation, evidence collection, and dissemination costs are affordable and sustainable (Garrison et al., 2013; Drummond, 2015; Pauwels et al., 2017). Additionally, decision making toward adoption should consider the process that will determine when and how agreements should be re-evaluated (Pauwels et al., 2017).

Importantly, decision-making about whether to move forward with an MEA should include a detailed and in-depth risk assessment of the arrangement, including any potential unintended consequences. This risk assessment should assess potential challenges—specifically risks and costs—of exiting the MEA if it does not turn out to be a favorable arrangement. Moreover, risks associated with potential power differentials between LMIC payers and pharmaceutical companies should be addressed. As mentioned earlier, external, non-profit institutions have helped support LMICs at the negotiating table before but this third party involvement could be difficult in negotiations requiring confidentiality. Finally, the risks associated with the requirement of confidentiality must be assessed in terms of potential long-term, negative impact on the accountability of institutions.

In those LMICs where decision makers have conducted these decision-making and risk assessment processes and have decided to explore the potential use of MEAs for a specific product, a key step is bringing payers and pharmaceutical companies together for dialogue. As we have seen in the compendium’s three LMIC case studies, despite a shared goal to improve access to innovative NCD medicines, there are challenges and sometimes a lack of willingness between payers and companies to advance dialogue. Decision analytic models are tools that can guide communication between payers and pharmaceutical companies by allowing stakeholders, prior to negotiations, to familiarize themselves with the terms and concepts, options for various instruments, and tradeoffs.

Three such decision analytic models, developed by RTI International in joint cooperation with MSH, are presented in Figures 8-10 and can be used for this purpose. These models are:

1. A Decision Tree Model (Figures 8a and 8b)
2. A Continuum or “Bridge” Model (Figure 9)
3. A Quantitative Spreadsheet Model (Figures 10a-10e)

These models offer progressively more specific approaches to facilitate the decision-making process in considering the form of agreement between companies and payers. The goal is to demonstrate what form of agreement would be most cost-effective and beneficial to both parties. Appendix II provides more information about how to use these models.

The first two models are qualitative and built around two key variables: 1) the amount of public, generalizable information regarding the medicine and 2) the institutional capacity of the health system and payer. The Decision Tree Model maps these variables to the optimal form of a MEA in a very simple framework as shown in Figure 8a, or in matrix form in Figure 8b. This model offers a discrete categorization of the two key determinants, but may be too simplistic or inflexible for real-life settings. Therefore, the second model—the Continuum Model—extends this representation to allow the amount of public information and the institutional capacity of the health system to vary along a continuum in a manner more consistent with reality (see Figure 9). In some cases, the simplicity of the first model may make it the best tool for some stakeholders. In other cases, stakeholders may find it more useful to study the continuum model for the additional insights it provides.

These two models guide decision makers to a determination of whether an agreement is feasible and lead stakeholders to one of three potential options. The first option is that the payer decides to adopt and cover the medicine without an MEA. As a second option, the payer declines to cover the drug. In this instance, the pharmaceutical company may choose to try again with more evidence, or apply to conduct a clinical trial in the country. The third option is that the payer and pharmaceutical company negotiate a financial, performance-based, or hybrid MEA.

When the outcome from the first two models is positive, the third model—the Quantitative Spreadsheet Model, accessible in an excel file [\[provide link to Model\]](#)—may be used to calculate expected values and confidence intervals for key metrics (such as overall budget impact and cost-effectiveness) under different price and coverage scenarios. The purpose of this model is to help payers decide on next steps toward specific terms of a likely MEA agreement, and to help stakeholders understand the impact on key outcomes of pricing and coverage decisions, taking into account uncertainty around factors like efficacy and safety, the size of the eligible patient population, physicians' prescribing behavior, and patients' adherence to prescribed treatment. The spreadsheet model contains five sections:

- A. Payer Budget – Baseline: Provides the baseline scenario (see Figure 10a).
- B. New Drug Impact – Payer Adopts: Represents the scenario of the payer adopting the new drug without implementing an MEA (see Figure 10b).
- C. New Drug Impact – Financial Agreement: Allows for MEA scenarios, specific to financial agreements, whereby a number of additional patients are treated at an agreed price (see Figure 10c).
- D. New Drug Impact – Performance-Based Agreement: Allows for MEA scenarios, specific to outcomes guarantees (see Figure 10d).

- E. New Drug Impact – Performance-Based Agreement: Allows for MEA scenarios, specific to coverage with evidence development agreements (see Figure 10e).

Figures 10a – 10e illustrate scenarios that may be implemented to introduce a new high-cost prescription drug (HCPD). Appendix II provides a guide to help payers navigate the spreadsheet model to effectively use it for the decision-making process.

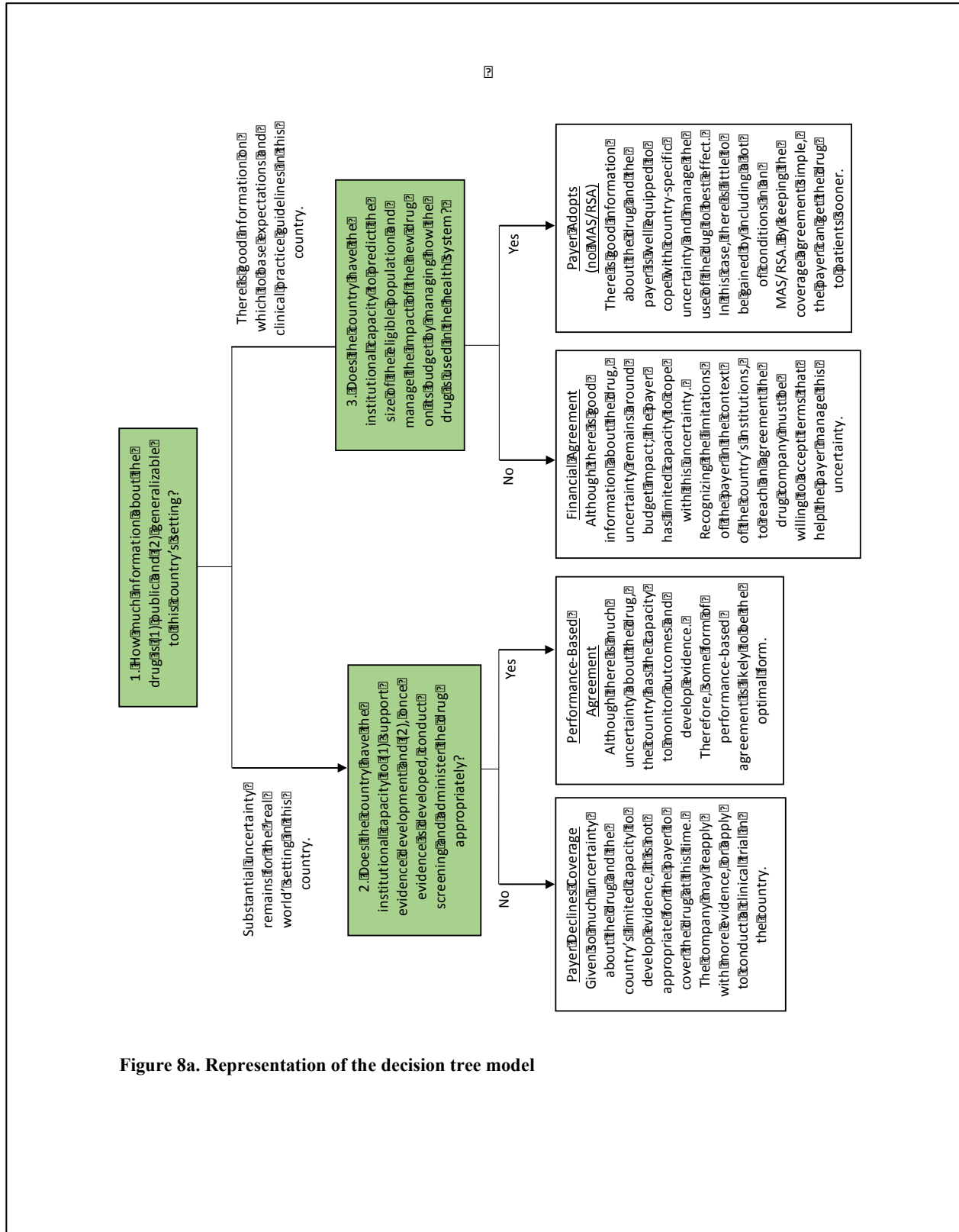
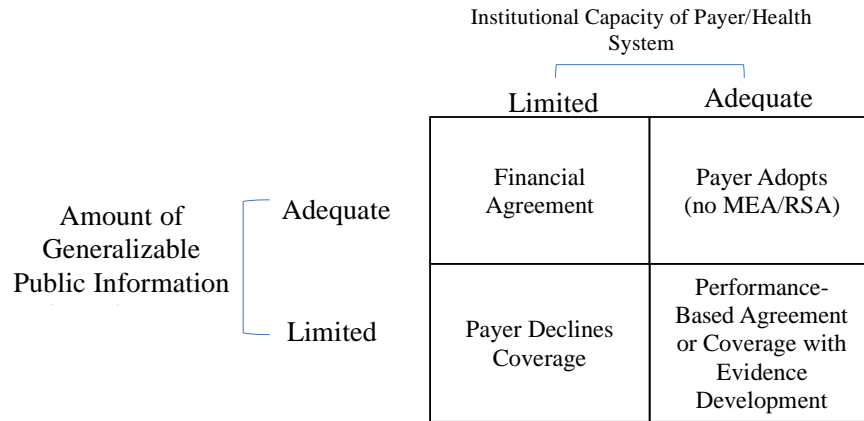
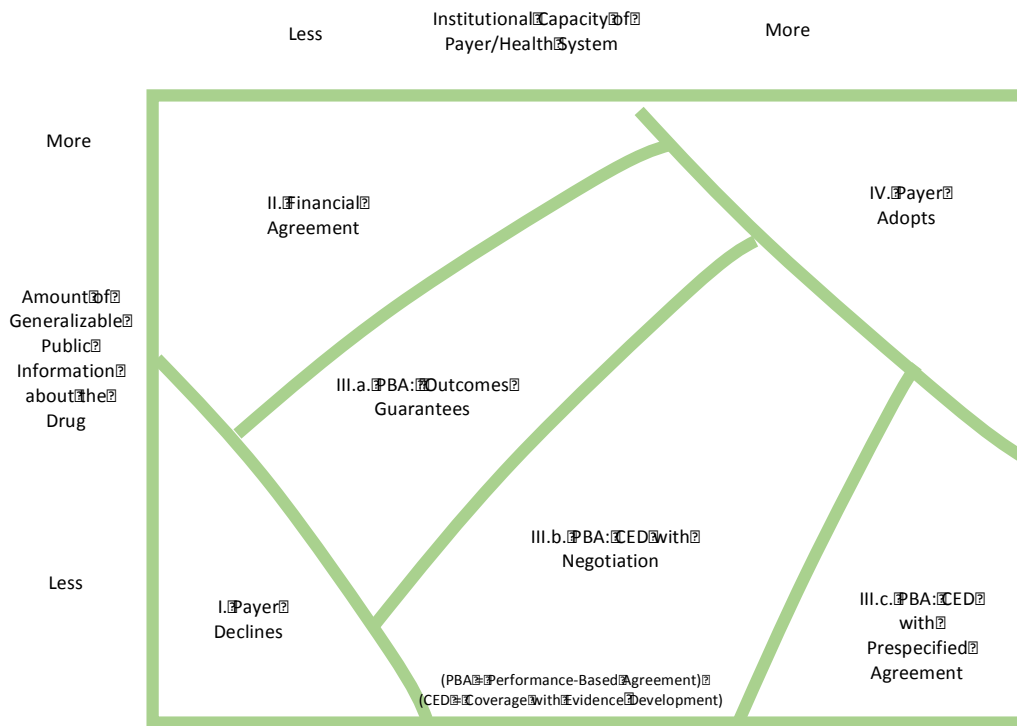


Figure 8a. Representation of the decision tree model



**Figure 8b. A representation of the decision tree model in matrix form**



**Figure 9. A representation of the continuum model**

**Figure 10a: Quantitative Spreadsheet Model (Part A)**

<b>Key:</b>	Input	Edit only orange cells. Click on other cells to view formulas, then 'Esc' out.																									
<b>Temporal assumptions:</b>		Assuming that plan potential is reached in the time unit and time horizon specified by the user in Section B																									
<b>A. Payer Budget — Baseline</b>																											
In table on right, please choose only <b>two</b> of the three variables: total budget, total number of patients, and average cost per patient. Then, enter the numbers in their respective boxes below																											
1. Total budget for high-cost prescription drugs (HCPD):		2,500,000		USD	per year	— Input values															<div style="border: 1px solid black; padding: 5px;"> <p style="text-align: center;"><u>Table of variable inputs</u></p> <input checked="" type="checkbox"/> Total Budget for HCPD  <input type="checkbox"/> Total number of patients receiving  <input checked="" type="checkbox"/> Average cost per patient         </div>						
2. Total number of patients receiving these drugs:		5,000		patients																							
3. Average cost per patient		285		USD	per year																						
<b>Calculated value:</b>		Total number of patients		8772		— Implied average cost per patient															285					USD	per year

Figure 10b: Quantitative Spreadsheet Model (Part B)

B. New Drug Impact — Payer Adopts																								
1. Treatable patient population:																								
10,000 patients who <u>could</u> benefit																								
2. Proposed number of patients to treat:																								
Choose <u>only one</u> type of calculation:																								
A.	20%	<input checked="" type="checkbox"/>	Per year	for	3	year	—E.g.: 20% per year for 3 years																	
B.	20%	<input type="checkbox"/>	By	year	3		—E.g.: 20% by year 3																	
<table border="0" style="width: 100%;"> <tr> <td style="width: 15%;"></td> <td style="width: 15%; text-align: center;">2,000</td> <td style="width: 15%;">first</td> <td style="width: 15%;">year</td> <td style="width: 15%;"></td> <td rowspan="2" style="font-size: 2em; vertical-align: middle;">}</td> <td rowspan="2" style="vertical-align: middle;">patients who <u>will</u> receive treatment</td> <td colspan="3" rowspan="2">—implies the following outcomes:</td> </tr> <tr> <td></td> <td style="text-align: center;">6,000</td> <td>year</td> <td>3</td> <td></td> </tr> </table>											2,000	first	year		}	patients who <u>will</u> receive treatment	—implies the following outcomes:				6,000	year	3	
	2,000	first	year		}	patients who <u>will</u> receive treatment	—implies the following outcomes:																	
	6,000	year	3																					
Budget Impact:							669,981	USD	first	year														
							( 27%	increase)																
							2,009,943	USD	year	3														
							( 80%	increase)																
3. Treatment expansion:																								
Of the patients to be treated, how many are <u>not</u> already receiving HCPD?																								
33% % of patients not already receiving HCPD																								
<table border="0" style="width: 100%;"> <tr> <td style="width: 15%;"></td> <td style="width: 15%; text-align: center;">667</td> <td style="width: 15%;">first</td> <td style="width: 15%;">year</td> <td style="width: 15%;"></td> <td rowspan="2" style="font-size: 2em; vertical-align: middle;">}</td> <td rowspan="2" style="vertical-align: middle;">new HCPD patients</td> <td colspan="3" rowspan="2">New average cost per HCPD patient per year:</td> </tr> <tr> <td></td> <td style="text-align: center;">2,000</td> <td>year</td> <td>3</td> <td></td> </tr> </table>											667	first	year		}	new HCPD patients	New average cost per HCPD patient per year:				2,000	year	3	
	667	first	year		}	new HCPD patients	New average cost per HCPD patient per year:																	
	2,000	year	3																					
							559	USD	first	year														
							( 96%	increase)																
							644	USD	year	3														
							( 126%	increase)																
4. Treatment replacement:																								
what is the average cost per patient of drugs this																								
285 USD per year																								
5. Price of new drug per patient treated:																								
500																								
-- In the case of <b>differential pricing</b> based on country income levels, please choose an option below and the corresponding price will be pulled from the table on the right. If choosing an income level, <b>only choose one</b>																								
<input type="checkbox"/> Low <input type="checkbox"/> Low-middle <input type="checkbox"/> Upper-middle																								
Price of new drug: 500							<table border="1" style="width: 100%;"> <thead> <tr> <th colspan="2">Price of HCPD based on country income level</th> </tr> </thead> <tbody> <tr> <td>Low-income (LI)</td> <td style="text-align: right;">100</td> </tr> <tr> <td>Lower-middle-income (LMI)</td> <td style="text-align: right;">250</td> </tr> <tr> <td>Upper-middle-income (UMI)</td> <td style="text-align: right;">350</td> </tr> </tbody> </table>			Price of HCPD based on country income level		Low-income (LI)	100	Lower-middle-income (LMI)	250	Upper-middle-income (UMI)	350							
Price of HCPD based on country income level																								
Low-income (LI)	100																							
Lower-middle-income (LMI)	250																							
Upper-middle-income (UMI)	350																							
NOTE: If one of the income levels is chosen, it will supercede the value in the orange input cell above																								
6. Markup imposed by intermediaries in the supply chain:																								
25 <i>Please include type of markup here</i>																								
* Price markup represents a divergence between what the drug company charges and what the payer pays and is caused by taxes or customs duties, wholesale or retail mark-ups...etc.																								
7. Final price to buyer of new drug per patient treated:*																								
525 USD per year																								
NOTE: If treatment duration is less than one year, this is simply the price for treating one patient.																								

Figure 10c: Quantitative Spreadsheet Model (Part C)

C. New Drug Impact — Financial Agreement							
Still assuming:		—implies the following outcomes:					
10,000 patients could benefit, and		Budget Impact:		694,981	USD	first	year
6,000 patients will receive treatment by the last time unit				(	28%	increase)	
at an average price per patient of				2,084,943	USD	year	3
525 USD per year				(	83%	increase)	
1. Effectively reduced price for additional patients:							
25 USD per year		New average cost per HCPD patient per time unit					
(to be achieved by caps, rebates, or other means)							
2. Percentage of additional patients treated at reduced price				510	USD	first	year
(Note: this will follow the same time units and time horizon as in Section B above)				(	79%	increase)	
10%				521	USD	year	3
				(	83%	increase)	
3. Number of additional patients treated at reduced price:							
1000	first	year	} patients treated at reduced price	Based on the following treatment assumptions for last time unit:			
3000	year	3		9,000	total patients treated with new drug		
				Of these, . . .			
4. Treatment expansion:							
Of these additional patients, what percentage were <u>not</u> already receiving HCPD?							
60%							
600	first	year	} new HCPD patients				
1800	year	3					
5. Treatment replacement: <b>not applicable*</b>							
*Assumption: New treatment at reduced cost will not be used to replace other HCPD usage; patients for whom the new treatment will replace HCPD will be covered at the negotiated price; coverage at the reduced price will be restricted to patients not already receiving HCPD for this condition .							
— Savings from implementation of the financial agreement (moving from section B to section C)							
-- Change in total budget between section B to section C in last time unit and beyond:							
		75,000	USD	per year			
		(	-19%	decrease)			
-- Change in average cost per HCPD patient from section B to section C in last time unit and beyond:							
		-123	USD	per year			
		(	-19%	decrease)			
Difference in cost-effectiveness	73%	positive response rate		-266.7			
with							
Difference in cost-effectiveness	0.85	DALY per year of treatment for positive responders		-221.0			
with							
( Cost effectiveness is defined as USD/DALY )							
( Difference = cost effectiveness with a financial agreement - cost effectiveness with payer adopts )							
* A negative difference value indicates that the cost of a DALY is lower with a financial agreement compared to payer adopts							
** Please refer to Sheet1 for the possible values for the positive response rate and the DALY per year of treatment							

Figure 10d: Quantitative Spreadsheet Model (Part D)

D. New Drug Impact — Performance-Based Agreement									
<b>Outcomes Guarantees</b>									
1. Percentage of treated patients expected to respond:					<i>—implies the following outcomes starting the last time unit and beyond:</i>				
55% expected positive response rate					Budget Impact: 1,458,693 USD per year				
2. Average health impact per responding patient					( 58% increase)				
0.85 DALY per year of treatment					New average cost per HCPD patient per year:				
					450 USD per year				
					( 58% increase)				
<b>Assumptions:</b>					Expected cost effectiveness:				
Rebates will be given for any non-responding patients. Rebates will be given at the reduced price as long as the total number of responding patients is greater than the number paying the negotiated price. If the number of responding patients falls short of the number paying the negotiated price, the difference between the number responding and the number paying the negotiated price will be rebated at the negotiated price.					347 USD per DALY				

**Figure 10e: Quantitative Spreadsheet Model (Part E)**

<p>In Part E, Coverage with Evidence Development, we model two things: (1) the negotiated price increases if the percentage of positive responders exceeds a target and decreases if the percentage of positive responders falls short of the target; (2) the magnitude of the price bonus or discount depends on the number of patients monitored to determine the percentage of positive responders: more patients are equated with stronger evidence and hence greater impacts on the negotiated price.</p>			
<b>E. New Drug Impact — Performance-Base Agreement</b>			
<b>Coverage with Evidence Development</b>			
Still assuming:			
<p>0.85 DALY per year of treatment          6,000 patients will receive treatment          at an average price per patient of          525 USD per year          55% expected positive response rate</p>			
<b>For this <u>example</u> of a CED agreement, expected positive response rate is taken as the performance measure</b>			
1. Minimum number of patients from whom complete data must be collected to <b>fully</b> implement price discounts/bonuses:			
1,000 patients monitored			
2. Minimum number of patients from whom complete data must be collected to implement <b>any</b> price discounts/bonuses:			
500 patients monitored			
3. Percentage bonus if positive response rate is greater than the target/benchmark (discount if it is less than the target/benchmark):			
10% bonus or discount			
<p><b>Assumptions:</b>          Between the high and low numbers of patients monitored, the price discounts/bonuses are assumed to phase out linearly: fully implemented for anything at or above the higher number of patients, nothing if less than the lower number of patients. For anything in between, the discount/bonus is pro-rated. For example, if we are to monitor at least 500 patients to have any price effect and at least 1,000 patients to have the full price effect, then if we end up monitoring 750 patients the discount/bonus will be half the full amount.</p>			

## SECTION 4: CONCLUSIONS AND CONSIDERATIONS FOR THE FUTURE

UHC is a tridimensional policy challenge that considers the population to be covered (breadth), the services to be included (depth), and the level of cost sharing to be faced by the population (height). For many LMICs, achieving UHC represents a substantial endeavor. As noted in Section 2, although LMICs are often grouped together under a single conceptual heading, in practice many structural characteristics vary dramatically across countries. Reaching more comprehensive and sustainable UHC and ensuring expanded access to innovative NCD medicines requires the implementation of a ‘potpourri’ of policy actions that go beyond MEA implementation. This concluding section present some considerations for LMICs that are transitioning from National Essential Medicines Lists (NEMs) to more dynamic benefits packages, discusses pricing strategies (including MEAs) and other access strategies to promote equitable access to innovative NCD medicines, and offers some preliminary recommendations for MEA implementation and research agendas in LMICs.

### **4.1 The challenge of transitioning from National Essential Medicines Lists (NEMs) to benefit packages in LMICs**

The need for building a multi-pronged, capacity-building strategy places significant additional challenges on already resource-constrained health systems in LMICs. In September 2015, UN member states reiterated their commitment to sustainable UHC by adopting the Sustainable Development Goals (SDG), with SDG 3.8 specifically focused on UHC. As countries gear up to meet these targets, both policy makers and the populations they serve want to maximize the quality of care they receive for the money invested. However, priority-setting and resource-allocation decision making in many LMICs remains inconsistent and unstructured. NEMs are often utilized as a means of rationing and, as described in Section 2, most LMICs do not update their NEMs regularly and systematically due to limited technical capacity and funding.

In a study of decision making in 25 LMICs implementing health coverage schemes, evidence used to inform coverage decisions focused on medical literature, regional and global guidance, and coverage policies of other coverage schemes (Hornberger et al., 2014), while coverage restrictions were based mostly on limitations in funding (Hornberger et al., 2014). These findings emphasize that important factors such as cost-effectiveness, budget impact, and equity are not always taken into consideration. If those instances where they have, it has often been done in an ad-hoc manner with limited acknowledgement as to how these factors have impacted a final decision (Baltussen et al., 2006).

Implicit and covert rationing through waiting lines, low quality, and inequities is not infrequent in LMICs (Glassman et al., 2012). As noted, many LMICs struggle at the same time with a dual burden of infectious diseases and NCDs, but most attention and resources are still given to vertical medical interventions and technologies for infectious diseases. Therefore, in the context of UHC, there is an opportunity for assisting LMICs to transition from NEMs to more dynamic benefits packages able to expand coverage, taking into consideration the above mentioned dual burden of disease.

As a result, explicit priority setting that uses HTA has become an issue of great interest, not only for countries but also for donors, because it helps promote efficiency of resource allocation. HTA processes examine the consequences of the application of health technologies and is closely related to evidence-based medicine (EBM). Both HTA and EBM are aimed at better informing decision makers. HTA mechanisms have gained space in taxation-based and social health insurance systems, and most high-income countries utilize some form of HTA process to facilitate their decision making for pricing, coverage, and reimbursement (Castro, 2017). More recently, LMICs, including Philippines, Brazil, Thailand, Colombia, Tunisia, South Africa, and Ukraine have advanced the use of HTA to discriminate among a list of competing priorities and determine those healthcare interventions that are “worth doing” and at what prices should be reimbursed to effectively proceed toward sustainable UHC.

Adoption of explicit priority-setting mechanisms such as HTA have varied across different types of markets. In upper middle-income countries such as Colombia and Brazil, the health as a human right policies enshrined in the countries’ constitutions has resulted in significant political and financial support at high levels of the government to institutionalize HTA. In lower middle-income countries such as Ghana, Tanzania, and Ukraine, HTA capacity building has been supported by donor-funded initiatives such as the International Decision Support Initiative and USAID-funded SAFEMED projects (IDSI, MSH, 2018). For example, in Vietnam, ministerial-level commitment led to the MOH commissioning Thailand’s HTA agency, HITAP, to provide support for revising Vietnam’s benefits package for high cost medicines and medical devices (Tantivess et al 2017).

## **4.2 Promoting equitable access to innovative NCD medicines**

NCDs are emerging on the global health agenda, and there is an increasing understanding of the social, economic, political, and health systems burden of these diseases for countries around the world. Both the 25x25 framework, established in 2013 and seeking a 25% reduction in premature death from NCDs by 2025, and Sustainable Development Goal 3.4, targeting an additional 5% (or 30% overall) reduction by 2030, highlight the critical importance of promoting equitable access to NCD medicines for achieving national and global goals.

Improving access to NCD medicines requires a combination of access strategies at different levels of the health system, and an architecture of individuals and organizations who partner in the design and implementation of these strategies (Frost and Reich, 2009). For new, breakthrough innovations for NCDs, pricing strategies (such as MEAs, voluntary licensing, differential pricing, and the use of TRIPS flexibilities) can help address high prices that are unaffordable for most LMIC payers. These pricing strategies, however, are alone insufficient for access in most settings and attention must also be given to rational selection of medicines; development and use of evidence-based clinical practice guidelines; capacity building amongst health professionals to manage NCDs; establishment of systems for collecting, monitoring, and using data on NCDs; strengthening of procurement and distribution systems; and a range of other policies and strategies at different levels of the health system (NCD Alliance, n.d.b.) (See Table 1, Section 1).

What can governments, pharmaceutical companies, and development partners do to support the design and implementation of these policies and strategies for improving access to innovative NCD medicines? One consideration relates to policy coherence and the UHC reforms being prioritized and undertaken by many countries. It is vital that national and global stakeholders seeking to improve access to NCD medicines, and those undertaking health systems strengthening and UHC efforts, work in cooperation to ensure policy coherence rather than vertically within silos (Bigdeli et al., 2014). This point was emphasized by the WHO Independent High-Level Commission on NCDs through its recommendation that governments include NCD and mental health services in UHC public benefit packages, including essential medicines and technologies (WHO, 2018).

Another consideration is how to improve collaboration and build trust between stakeholders. Dialogue across stakeholder groups on “unifying principles” for research and development and access is ongoing, but disagreements and mistrust between stakeholder groups remain. Efforts to build trust and understanding should continue, and could include the development of an NCD stakeholder framework—modelled on the framework created by HIV/AIDS stakeholders—to establish ground rules for involvement in the provision of access to NCD medicines.

Finally, future research and analysis should focus on innovative, synergistic access strategies for ensuring that NCD medicines get to patients in all market segments of LMIC with multiple payers, such as countries with high OOP spending and/or fragmented health systems. Chapter 4 offers initial ideas for how to utilize MEAs in different market segments and to harness the private sector and innovative technology platforms in LMICs, but more research and development of case studies is needed.

### **4.3 MASs as an access strategy for innovative NCD medicines**

In those settings in which the budget impact, effectiveness, and cost-effectiveness of innovative NCD treatments are not yet fully established, negotiated solutions in the form of managed access strategies (MASs) are potential mechanisms for further consideration by payers and pharmaceutical companies. MASs provide an alternative to policy solutions allowed by TRIPS flexibilities, such as compulsory licensing, an approach advocated by many international health activists. The benefit of compulsory licensing is that it can provide quick access to needed medicines in the short-term. However, as discussed in Section 2, this strategy has, in some settings, also led to challenges, such as conflict in trade agreements. MASs such as managed entry agreements (MEAs) could provide an alternative approach and can encourage the building of capacities and institutional arrangements for sustainable decision-making about NCD medicines.

MEAs have many advantages for stakeholders, but also come with a number of challenges. Critics of MEAs consider them as means for conducting confidential negotiations and agreeing on non-transparent portfolio discounts in order to create additional fiscal space for new products’ market access. Few LMICs have sufficient human resources and information systems capacity to collect and analyze real world data

on their own. Even if they will, they may be reluctant to commit since these resources may be more efficiently employed elsewhere given other pressing tasks. Therefore, it is worth considering whether piloting MEAs in a LMIC could be a shared activity between pharmaceutical companies and public payers. The collateral positive effects of joint cooperation through public and private partnerships would mean that both parties will be incentivized to promote rational prescribing, and development and use of clinical guidelines. Otherwise, under severe budget constraints and limited capacities to collect real world data, MEA arrangements may turn out to be financial schemes only rather than performance-based agreements.

From a clinical standpoint, performance-based agreements require the ex-ante agreement of surrogate and clinical measurable endpoints to guarantee the fulfilment of the promise of value. However, response rate will depend on many other factors that go beyond the therapeutic effect of a new drug, including how it is used (choosing the right patients and timing, complementary treatment, adherence, and follow-up). Therefore, without checks and balances and case or disease management tools in place, manufacturers and marketing authorization holders may object to being the only ones taking all the risk.

This compendium recommends strategies for those stakeholders considering MEAs and offers recommendations for further research and practical guidance.

***Recommendations for countries with limited previous experience and capacity for implementing MEAs:***

- Learn from the experiences of other countries—particularly other LMICs—in negotiating and implementing MEAs.
- Collaborate with organizations providing technical assistance related to pharmaceutical policy and pricing in order to access support and existing knowledge on MEA arrangements.
- Assess the potential for an MEA pilot for an innovative NCD medicine.
- Build individual and organizational capacities required for understanding MEA arrangements.
- Work with pharmaceutical companies to initiate policy dialogue. For low-income countries with limited fiscal space, support from external funders would be required.
- Prioritize one or two disease areas that could be part of an implementation pilot on MEAs.
- Consider financial schemes as the potential best MEA arrangement, dependent on the setting.
- Ensure sufficient resources for pilot implementation.
- Implement the pilot and assess the experience to identify capacity-building requirements for potential future use of MEA schemes.
- Publish and disseminate results of the pilot as a case study.
- Consider the initiation of other MEA pilots.

***Recommendations for countries with limited previous experience but higher capacity for MEAs (enabling environment, infrastructure, political will):***

- Learn from the experiences of other countries—particularly other similar LMICs—in negotiating and implementing MEAs.
- Collaborate with organizations providing technical assistance related to pharmaceutical policy and pricing in order to access support and existing knowledge on MEA arrangements.
- Consider strategy of starting small with MEA arrangements and incrementally expanding.
- Prioritize a small set of disease areas that could be part of an implementation pilot.
- Identify and choose the best MEA instrument according to the setting.
- Work with pharmaceutical companies to implement pilot(s) and assess implications for future MEAs.
- Assess the experience from the MEA pilot to identify regulatory and capacity-building requirements (both individual and organizational) for potential MEA scale up.
- Strengthen additional resources for MEA implementation (HTA, PBMs, and other tools)
- Publish and disseminate results of the pilot as a case study.
- Review policies within the health sector and across other relevant sectors to identify potential barriers to long-term implementation of MEA arrangements.
- Leverage reform processes in health and other relevant sectors, drawing from the experiences of the MEA pilots, to institutionalize legal and policy reforms supportive of MEAs.

***Recommendations for additional research and practice guidance on MEAs in LMICs:***

- Research and publish case studies on MEAs that have been negotiated and implemented in LMICs to build evidence on processes, facilitators and barriers, outcomes, and lessons learned.
- Examine the findings from the compendium’s case study countries in other LMIC settings, involving focus groups and workshops with targeted audiences in order to better identify potential uses of MEAs.
- Test and refine the compendium’s decision models and analytical framework in a set of LMICs to further explore how to reach certain market segments, assess barriers and facilitators, and identify synergistic access strategies that can work with MEAs to reach more patients.
- Develop practical guidance for LMIC governments, as well as development partners, regarding the steps required to build an enabling policy and legal environment, capacity in negotiation and implementation of MEAs, and rational decision-making on NCD medicines more generally.

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## APPENDIX I: Methodology

This compendium was informed by three research activities: 1) literature review of published and grey literature on MEAs; 2) semi-structured interviews with key informants in three LMIC (Colombia, Kenya, and Ukraine); and 3) development and testing of three models.

### 1. Literature review

A systematic search of published literature was undertaken by Management Sciences for Health (MSH) between December 2017 and February 2018 to identify MEA initiatives. Search terms were in three categories—risk-sharing agreements, patented medicines, and improved access—and were translated into French and Spanish in order to include non-English publications. The following databases were searched for publications between January 1, 2007 and December 31, 2017: Biomedical Reference Collection, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Embase, Medline, and Pubmed. A purposeful review of the grey literature was undertaken simultaneously to complement the systematic review.

Publications that were included in the review include original data, literature reviews, editorials, and author commentaries. Eligibility criteria were: 1) the paper must describe financial or performance-based schemes for granting access to innovative patented medicines and generics globally; 2) the paper must describe lessons learned and previous experiences with MEAs. Excluded papers included conference abstracts (because they had insufficient details on MEAs) and studies of other market access mechanisms (since they were not the focus of the literature review).

Papers were screened in two phases: first, titles and abstracts were reviewed, and all studies were removed that did not meet the inclusion criteria or were duplicates; second, the remaining full-text articles were screened by two reviewers who agreed on a final selection of studies, based on the eligibility criteria. The literature search retrieved 330 records and after screening, a total of 34 publications were ultimately considered for qualitative analysis. More information about search terms and eligibility criteria, the 34 publications identified, and literature review findings can be found in MSH (2018).

### 2. Semi-structured interviews

Interviews with key informants in three LMIC were conducted by MSH to identify contextual factors that could influence the implementation of MEAs. Three case study countries—Colombia, Kenya, and Ukraine—were chosen purposively to represent different geographical settings, levels of income, socio-political contexts, and healthcare systems. All three countries have demonstrated a political will for Universal Health Coverage (UHC) for their citizens.

Stakeholder mapping was undertaken to identify high-level decision makers in the three countries in the following institutions: the Ministry of Health, national drug regulatory authorities, public health insurance agencies, private payers and insurers, NCD patient associations, and pharmaceutical industry associations. A total of 32 stakeholders in the three countries were identified for semi-structured interviews. Each stakeholder was given an information sheet about the study and consent form for participation in the interview.

Interviews were conducted in person by two data collectors utilizing an interview guide that covered the following topics: the individual's knowledge and/or perception of current access challenges for NCDs, their level of awareness of MEAs and ongoing initiatives within their setting, and their views on potential barriers to and facilitators for the implementation of MEAs in their country. Interviews were conducted in English and Spanish (and with an interpreter as needed in Ukraine), lasted between 30-40 minutes, and were recorded when given consent.

Each interview was transcribed and then coded, using a deductive and inductive approach. Informal interviews in March 2018 were conducted with four subject matter experts in MEAs to validate the findings from both the literature review and the case studies. More information about the semi-structured interview methods and findings can be found in MSH (2018).

### **3. Modelling**

Three models were developed by RTI International to help improve access to innovative medicines in LMIC (Appendix II). The first two models provide a framework for dialogue between pharmaceutical companies and payers in LMIC. The purpose of these models is to inform discussions around whether an agreement can be reached that provides patients access to a patented medicine and, if an agreement can be reached, what it might look like. By presenting options—various types of contractual arrangements, managed access, or risk-sharing agreements—and describing circumstances where different options are most appropriate, the models are intended to expand opportunities for stakeholders to reach mutually beneficial agreements.

The third model is a working spreadsheet intended to support quantitative planning with scenario and sensitivity analyses, helping stakeholders—especially payers—understand the impact of pricing and coverage decisions. To help payers see how different contractual arrangements might assist them to manage various sources of uncertainty, the spreadsheet model shows graphically the effect of variation in uncertain factors (e.g. efficacy and safety of the new drug, the size of the eligible population, physicians prescribing behavior, and patients' adherence to prescribed treatment) on cost, cost-effectiveness, and other outcomes of interest. Ideally the spreadsheet model will serve as a set of examples on which payers can build to tailor analyses to suit their needs.

The models were discussed with representatives from pharmaceutical companies, the World Bank, and other stakeholders in two workshops: 1) Washington DC (6 June 2018); and 2) Ukraine (5 July 2018). Following these two rounds of feedback, the models were further revised.

## APPENDIX II: User Guide to Three-model Scenarios for Increasing Access to Innovative Medicines for Non-Communicable Diseases<sup>7</sup>

### The Three-Model Framework

#### I. Introduction

This section provides a description of three decision analytic models developed by RTI International to guide communication between payers<sup>8</sup> in developing countries and drug companies with the aim of increased access to new NCD medications. The models offer progressively more specific approaches to facilitate the decision-making process in considering the form of agreement between companies and payers. The goal is to demonstrate what form of agreement would be most cost-effective and beneficial to both parties. The three models are:

1. A Decision Tree Model
2. A Continuum or “Bridge” Model
3. A Quantitative Spreadsheet Model

Models 1 and 2 depict a decision process with two key variables: the amount of public, generalizable information about the drug and the institutional capacity of the health system and payer. Whereas the decision tree model offers a discrete categorization of the two key determinants, the continuum model extends this representation to allow the amount of public information and the institutional capacity of the health system to vary along a continuum in a manner more consistent with reality. These first two models guide decision makers to a determination of whether an agreement is feasible. When the outcome is positive, the quantitative spreadsheet model may be used to calculate expected values and confidence intervals for key metrics—like overall budget impact and cost-effectiveness—under different price and coverage scenarios.

#### II. The Models

The three models assume that increasing access to a new drug in a given population will typically be governed by some form of **Managed Entry Agreement (MEA)** or **Risk-Sharing Agreement (RSA)**, specifying pricing and coverage conditions.<sup>9</sup> Before delving more deeply into model details, it is worth noting that the options available to the players in any situation can be summarized in the following:

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<sup>7</sup> Nugent R, Scott T, Salem M (2018). *User Guide to Three-model Scenarios for Increasing Access to Innovative Medicines for Non-Communicable Diseases*. Prepared by RTI International and submitted to MSH for inclusion in “A Compendium of Good Practices for Sustainable Access.”

<sup>8</sup> A payer may be a government single payer or a private insurer. The payer is assumed to have some degree of ability to perform health technology assessment (HTA), either internally or by leveraging the capability of another group, like a national HTA organization.

<sup>9</sup> We intend the terms MEA and RSA to be very broad, encompassing any form of conditional coverage agreement.

**1. Payer adopts/covers the drug – No MEA/RSA.**

This option is appropriate if the payer intends to manage increased access without help from the drug company, so that the cost and time required to negotiate an MEA/RSA is not worthwhile.

**2. Payer declines to cover the drug –** This option is appropriate if/when it is apparent that negotiation will not conclude with an agreement. In such cases, the drug company may reapply for entry with more evidence, or apply to conduct a clinical trial in the country.

**3. Payer and drug company negotiate some form of MEA/RSA**

**a. The decision tree model**

This model maps the aforementioned determinants (public information about the drug and institutional capacity of the payer and country's health system) to the optimal form of MEA/RSA in a very simple framework, depicted by Fig. A1. To avoid redundancy, a matrix might be used to organize this information more effectively, as represented by Fig. A2.

It is reasonable to observe that the matrix model is inflexible: (1) it forces the two key determinants into discrete categories, when they are better described on a continuum; and (2) it forces the boundaries between regions to be vertical and horizontal. There are situations where an improvement in the amount of generalizable public information about the drug could move us from "Payer Declines Coverage" to a CED, holding institutional capacity constant. The continuum model provides an extension to the simple matrix representation of the decision tree model. In some cases, the simplicity of the decision-tree and simple matrix models may make them the best tools for some stakeholders to use. In some cases, stakeholders may find it useful to study the continuum model for the additional insight it provides, but still use the decision-tree or simple matrix models for easy reference to focus main ideas.

**b. The continuum "bridge" model**

Figure 3 shows the continuum model with the same four regions as the simple matrix model described in the previous section. This representation, however, introduces two innovations:

1. The two key considerations – amount of generalizable information and institutional capacity – are variable. Where a drug-country pairing would be located in this space would depend on different indicators for each determinant.<sup>10</sup>

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<sup>10</sup> For the amount of generalizable public information, indicators of where a drug-country pairing would be located could include, e.g., whether the company had made clinical trial results available in a public registry, like [clinicaltrials.gov](https://clinicaltrials.gov/) (<https://clinicaltrials.gov/>) or the WHO International Clinical Trials Registry Platform (<http://www.who.int/ictrp/en/>), whether the results of any post-marketing surveillance in other countries had been made public, and if so some characterization of the similarities and differences between these other countries and the one in question. For the institutional capacity of the health system, broad indicators like health-system spending, per-capita and as a percentage of GNP, could help benchmark against other countries. More practice-oriented indicators are the capacity for monitoring specific health outcomes (specific to a disease/drug in question) or the readiness with which that capacity could be provisioned; the capacity for developing evidence – gathering and assessing data (again, considering what is in place and the readiness with which capacity could be added in a specific

2. The boundaries between regions are sloping, showing the more realistic situation that a difference in *either* key consideration could change the optimal design of MEA/RSA.

*Note:* An MEA/RSA could have *both* financial and performance based features.

We describe the decision-making process in a stepwise fashion that spans the range from the region where the payer declines coverage completely to the region where no MEA/RSA is made because the payer adopts the drug with a simple coverage agreement. In between there are several MEA/RSA forms of agreement that can be reached depending on the location of the drug-country pairing on the plane.

*Payer Declines:* Too much uncertainty about the drug combined with the country's limited capacity to monitor outcomes and develop evidence may make it not appropriate for the payer to cover the drug at this time. The company may reapply with more evidence, or apply to conduct a clinical trial in the country. As information improves or institutional capacity increases, making the payer better able to cope with a given level of uncertainty, possibilities for agreements open up.

*Financial Agreement:* Budget cap, discounts, and other simple mechanisms can help the payer manage uncertainty around budget impact. Even though better information about the drug is available, payers may be limited in their ability to estimate the size of the eligible population and predict physicians' prescribing behavior and patients' adherence. Recognizing these limitations of the country's institutional capacity, to get coverage the drug company may need to accept terms that help the payer manage their uncertainty around budget impact. This will typically involve the company taking on some additional risk therefore reaching a financial agreement will depend on the company's willingness to take on this risk to obtain coverage for their drug.

*Performance-Based Agreements (PBA)* can take several forms:

- a. Outcomes Guarantees:

Capacity for monitoring exists or can be developed, making outcomes guarantees feasible. Some degree of uncertainty about how well the drug will work in this setting combined with limited capacity to manage that risk in other ways justifies outcome guarantees as part of MEA/RSA.

- b. Coverage with Evidence Development (CED) with negotiation:

For the feasibility of this type of agreement, the presence of capacity for developing evidence either exists or can be developed along with the capacity for negotiating pricing and coverage terms based on new evidence. A justification for this type of agreement is the higher degree of uncertainty about how well the drug will work in this setting or in general, or the likelihood of substance updates to clinical practice guidelines based on evidence developed.

- c. CED with pre-specified agreement:

In region III.c. in Fig.3, the country's institutional capacity makes it practical to develop evidence on which binding medium-term and longer-term contracts are written—and where the dearth of public information about the drug justifies the cost of doing so.

Writing a binding agreement with provisions based on the collection and assessment of clinical outcomes

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area); the capacity to negotiate pricing and coverage terms with drug companies on the basis of evidence; the capacity to write binding long-term contracts based on evidence to be developed.

data is not trivial. The country must have the institutional capacity to (1) collect and assess data on, e.g., survival, disease progression, disease recovery, significant events, symptoms scores, and (2) craft legally binding agreements that base future pricing and coverage on those assessments.

To be worth the cost of this approach, there must be very little relevant public information already available on the drug, implying a real potential to add value by developing new evidence. In this situation, with very little prior information to go on, it would be reasonable for the drug company to accept as a starting point low prices and limited coverage. For the company to be willing to accept such terms as part of a long-term contract (long enough to allow for the development of clinical evidence), the company will need to be convinced that the evaluation approach to be implemented will be adequately powered—that good performance by the drug will be recognized, triggering higher prices and expanded coverage. Similarly, the payer will need to be convinced that the evaluation will not bind it to higher prices and expanded coverage unless the drug truly does perform well.

Stronger institutional capacity enables payers to control costs and promote cost effectiveness through the health system (by means of, e.g., evidence-providing registries; limiting prescribing to special treatment centers; requiring physicians to certify patients' eligibility, backed up by monitoring and verification systems). This approach may be especially attractive if the drug is complicated to administer or very expensive.

*Payer Adopts:*

Evidence gathered through the health system could always be used to negotiate prices or adjust coverage, so the line between Region IV and Region III.b is somewhat soft. The idea is that in Region IV public information about the drug itself is already so good that renegotiation with the drug company is unlikely.

Likewise, the measures payers use in Region IV to control costs and promote cost effectiveness (e.g., evidence-providing registries; limiting prescribing to special treatment centers; requiring physicians to certify patients' eligibility, backed up by monitoring and verification systems) could also be used in the upper-rightmost parts of Regions II and III, as long as public information about the drug is good enough to inform best practices and institutional capacity is adequate to support these measures.

### c. The quantitative spreadsheet model

The purpose of the spreadsheet model is to help payers decide on next steps toward specific terms of a likely MEA/RSA agreement. The model can be used to calculate expected values and confidence intervals for key metrics – like overall budget impact and cost-effectiveness – under different price and coverage scenarios. The purpose is to help stakeholders understand the impact on key outcomes of pricing and coverage decisions, taking into account uncertainty around factors like efficacy and safety, the size of the eligible patient population, physicians prescribing behavior, and patients' adherence to prescribed treatment. What follows is a guide to help payers navigate the spreadsheet model to effectively use it for the decision-making process.

### How to use the spreadsheet model:

The spreadsheet model is contained in an excel file [\[add link to model\]](#), which is comprised of two sheets: Budget Impact and Calculations. The user should only interact with the former, the Budget Impact sheet. There are two types of cells that the user can edit:

1. Orange cells: these are “Input” cells that provide the numbers used in further calculations
2. Yellow cells: these are “Note” cells. There are three instances of them in the spreadsheet (cells L44, L45 and L46). They are to be populated when differential pricing based on country income levels is planned.

In addition to these cells, there are grey “Calculation” cells that are automatically updated as the input cells are edited. The user can click on a grey cell to view the formula and then press “Esc” to exit the cell.

The model assumes that the full impacts of the plan are reached in year 3, whereby one third of the impacts are achieved in year 1, two thirds in year 2 and full impacts in year 3. This applies to the following variables, which build on one another sequentially:

- The proposed number of patients to treat
- The total budget impacts
- The average cost of treatment per HCPD patient

The file illustrates scenarios of MEA/RSAs that may be implemented to introduce a new high-cost prescription drug (HCPD). The spreadsheet contains five sections, A through E, and what follows is a description of each section:

#### *Section A: Payer Budget – Baseline*

This section provides the baseline scenario. There are five input boxes in this section:

- Cell D11, in which a user would input the relevant currency
- Cell E11, which contains the temporal unit in use within the model
- Cell C11: the total baseline budget of HCPD
- Cell C13: the total number of patients receiving the HCPD drugs
- Cell C15: the average cost per patient

To construct the baseline scenario, a user would only need to input two of the three variables: total budget, total number of patients and average cost per patient. The third would be calculated accordingly.

**Important:** There is a table located on the right with three checkboxes, each representing one of the three variables. Please check only two of the three checkboxes and input the corresponding numbers into their respective boxes.

#### *Section B: New Drug Impact – Payer Adopts*

This section represents the scenario of the payer adopting the new drug without implementing a MEA/RSA. There are several sub-sections here:

1. The treatable number of patients: the total population of patients whom this drug could treat, which the user should input

2. The proposed number of patients to treat: this is a subset of the above population and the user should input the total number they expect to treat annually by year 3 in the orange cell (C27).
3. Treatment expansion: this section shows the number of patients being treated with the new drug who had not been already receiving HCPD. As with sub-section 2, the user should input the total number of new patients in the orange box (C33) for year 3 and the corresponding numbers of years 1 and 2 will be calculated.
4. Treatment replacement: The average cost per patient of the drugs this new drug will replace. This is also an input by the user.
5. Price of the new drug per patient treated:  
In the absence of differential pricing, the user should input the price of the new drug in cell C40. If, however, there exists differential pricing based on country income level (in which case the yellow cells L44, L45, and L46, will be populated with a pricing guide), the user should check one of the checkboxes in line 44 indicating the appropriate income level.  
**Important:** Only one of the checkboxes should be checked at any one time. If more than one is chosen, an alert will be given to the user. Further, if any one of the checkboxes is chosen, the differential price will override the number the user may have put in cell C40.
6. Markup imposed by intermediaries in the supply chain: If there a markup applied to the price imposed by the pharmaceutical company (taxes, customs duties, etc.), the user should input that number in cell C51.
7. Final price to buyer of new drug per patient treated in cell C56. This cell adds up the price imposed by the drug company to the markup price if the latter is not zero.

When all the input cells are populated on the left, the grey calculation cells to the right of them (cells L23 – L36) will update to the calculated total budget and average cost per patient in each year. These calculations also display the difference between this scenario and the baseline (Section A) in terms of total budget and average cost per patient.

### *Section C: New Drug Impact - Financial Agreement*

This section allows for MEA/RSA scenarios, whereby a number of additional patients are treated at an agreed price. This represents an expansion to section B and includes the following sub-sections:

1. Effectively reduced price for additional patients: this should be entered into cell C66.
2. Number of additional patients treated at the reduced price. As with section B above, the user should enter the total number of additional expected patients to the year 3 cell (C71) and the corresponding numbers for years 1 and 2 will be populated automatically.
3. Treatment expansion: similar to the corresponding sub-section in section B.
4. Treatment replacement: Not applicable. The assumption is that new treatment at reduced cost will not be used to replace other HCPD usage; patients for whom the new treatment will replace HCPD will be covered at the negotiated price; coverage at the reduced price will be restricted to patients not already receiving HCPD for this condition.

As with section B, the total budget impact, the effect on average cost and the total number of patients treated under the new plan will be calculated by year on the right (cells L70 – L80).

Below the aforementioned sub-sections is a box that will display the total budget impact of the expansion from section B to section C as well as the difference in average cost per patient. Furthermore, in cells D92 and D94, the user could input a percentage positive response rate and DALY per year of treatment for positive responders, respectively and the calculation boxes (cells I92 and I94) will populate with the difference in cost-effectiveness in going from scenario B to C.

#### *Section D: New Drug Impact – Performance-Based Agreement (PBA)*

In the case of the implementation of a PBA, a user should input the expected positive response rate in cell C106 and the DALY per year of treatment in cell C108. On the right, the average cost per patient, total budget impact and the expected cost-effectiveness will be calculated.

The assumption in this scenario is that rebates will be given for any non-responding patients. Rebates will be given at the reduced price as long as the total number of responding patients is greater than the number paying the negotiated price. If the number of responding patients falls short of the number paying the negotiated price, the difference between the number responding and the number paying the negotiated price will be rebated at the negotiated price.

#### *Section E: New Drug Impact – PBA: Coverage with Evidence Development (CED)*

In Part E, Coverage with Evidence Development, we model two things: (1) the negotiated price increases if the percentage of positive responders exceeds a target and decreases if the percentage of positive responders falls short of the target; (2) the magnitude of the price bonus or discount depends on the number of patients monitored to determine the percentage of positive responders: more patients are equated with stronger evidence and hence greater impacts on the negotiated price. The user inputs the following:

1. Minimum number of patients from whom complete data must be collected to fully implement price discounts/bonuses
2. Maximum number of patients from whom complete data must be collected to implement any price discounts/bonuses
3. Percentage bonus if positive response rate is greater than the target/benchmark (discount if it is less than the target/benchmark)

The assumption in this scenario is that between the high and low numbers of patients monitored, the price discounts/bonuses are assumed to phase out linearly: fully implemented for anything at or above the higher number of patients, nothing if less than the lower number of patients. For anything in between, the discount/bonus is pro-rated. For example, if we are to monitor at least 500 patients to have any price effect and at least 1,000 patients to have the full price effect, then if we end up monitoring 750 patients the discount/bonus will be half the full amount.

On the right of the all the aforementioned sections are graphs that plot the impacts on total budgets, average cost per patient and cost-effectiveness for the aforementioned scenarios to facilitate visual comparison.

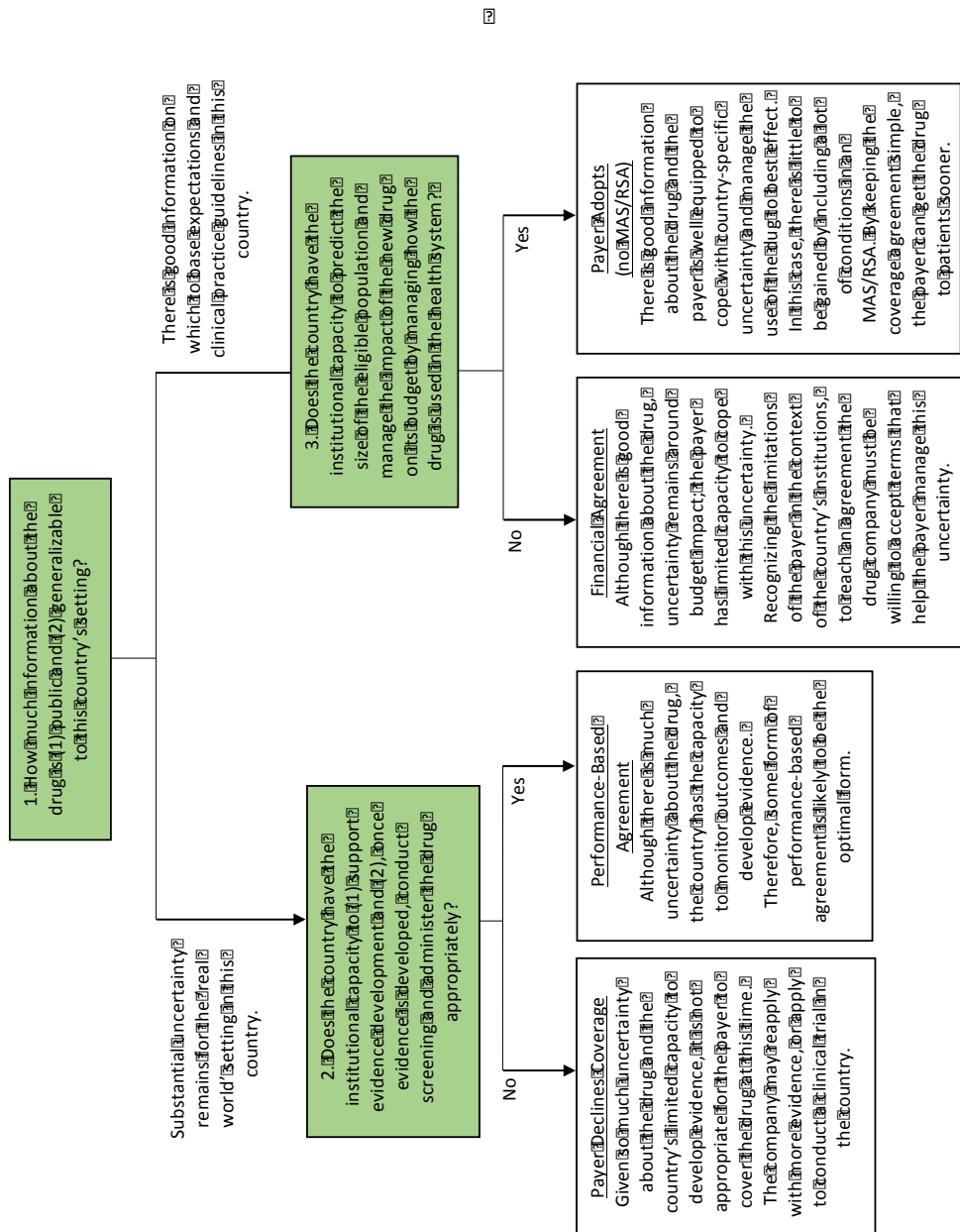
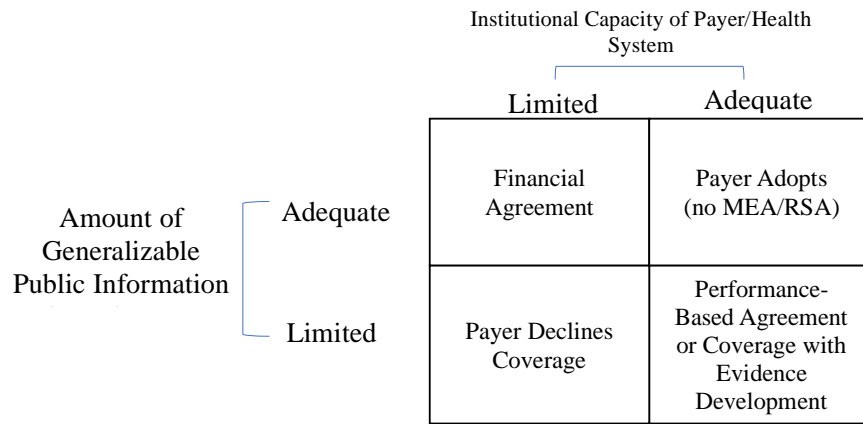
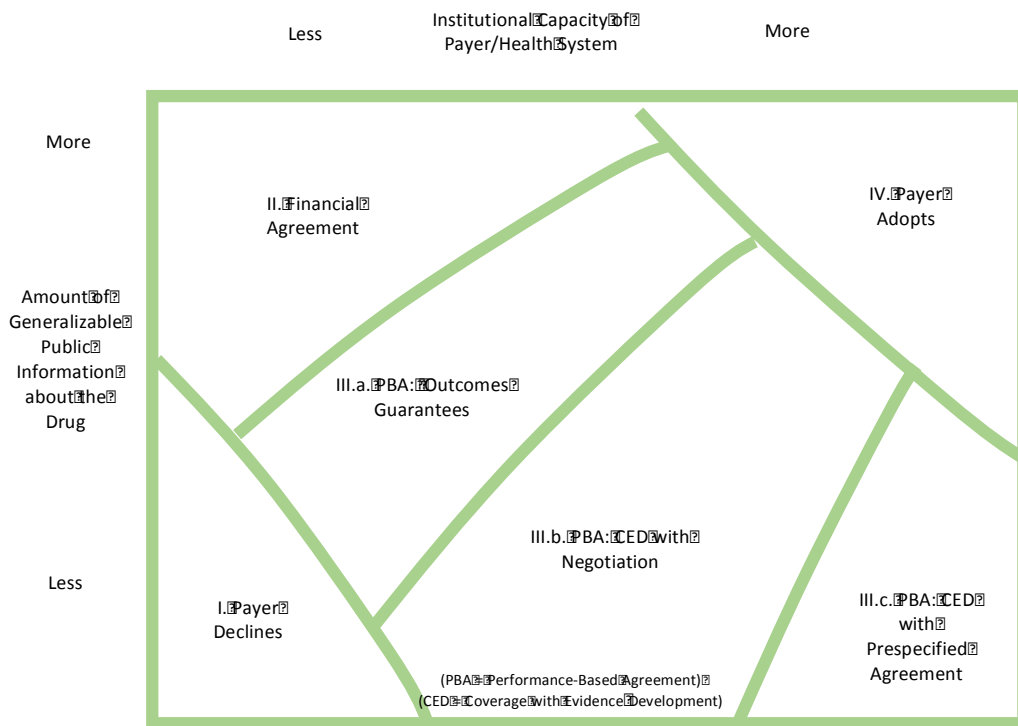


Figure A1. Representation of the decision tree model



**Figure A2. A representation of the decision tree model in matrix form**



**Figure A3. A representation of the continuum model**