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Strengthening Global Knowledge on Access Solutions for Innovative Medicines

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Activity 1:

Lessons learned from existing medicines access programs—the international experience on the implementation of MEAs

CONTENTS

EXECUTIVE SUMMARY

All health systems face the challenge of managing finite resources to address an unlimited demand for services. According to the World Health Organization (WHO), 70% of the 56.4 million deaths globally in 2015 were due to non-communicable diseases (NCDs). More than 30 million of these deaths occurred in low- and middle-income countries (LMICs). Cardiovascular disease (CVD), cancer, diabetes, and chronic lung diseases are the four leading causes of NCD deaths.

In recent decades, research and development for diagnostics and treatment for NCDs has proven to be effective and cost effective in many cases. However, a lack of information on effectiveness and concerns about the cost of new, patented therapies leads to uncertainty and may delay reimbursement decisions and patient access, particularly in LMICs. Various access strategies, such as community- and systems-based, production and price approaches, have been implemented in different settings to enable access to innovation and promote better resource allocation. Of special interest is the case of "managed entry agreements" (MEAs)—a type of formal institutional arrangement between manufacturers and payers aimed at sharing the financial risk surrounding the introduction of new pharmaceutical technologies.

A literature review to identify publicly available relevant sources of data describing financial medicines access initiatives in both LMICs and high-income country (HIC) settings was performed; this was followed by semi-structured interviews with key participants in three countries of interest and informal interviews with global experts in the field of market access and risk sharing agreements. Finally, triangulation from all three sources served to identify recurring, divergent, and converging findings. This report presents the methods and findings and delivers some key messages for future policy action in LMICs on MEAs (namely, financial schemes and performance-based agreements).

Colombia, Kenya, and Ukraine were selected to represent variation in geographical setting, level of income, sociopolitical contexts, and health care systems, as well as because of their commonly demonstrated political will to advance toward Universal Health Care (UHC) for their citizens. All three countries also had financial constraints or fragmented purchasing/procurement mechanisms common to LMICs.

The systematic literature search retrieved 330 records, and 34 publications were considered for qualitative analysis. The number of publications on MEAs has increased by 38% in the past five years. We identified 285 agreements through our search, with most of those taking place in HICs. A total of 23 European countries have implemented one or more types of MEA, followed by Asian countries, North America, and Oceania. No records of ongoing MEAs for NCDs in Latin America or Africa were retrieved from our search (except for the case of Rwanda and Human Papilloma Virus (HPV) vaccines).

According to our findings, financial schemes were slightly more frequent than outcome-based schemes. Financial-based schemes were more prominent in Europe, Asia, and Oceania; by contrast, performance-based agreements were more prevalent in North America. Among the financial schemes, price/volume and discounts were predominant. In the case of performance-

based agreements, coverage with evidence development was the most frequent type of scheme. Most of the financial or outcome-based agreements retrieved through our search covered a wide range of NCDs, predominantly different types of cancer (e.g., breast cancer, chronic myelogenous leukemia, colon and rectal cancer). Other NCDs included multiple sclerosis, osteoporosis, diabetes, CVD, and Alzheimer's.

Most of the targeted grey literature is focused on licensing agreements and how to navigate Trade-Related Aspects of Intellectual Property Rights (TRIPS) flexibilities. Worth mentioning is the WHO tool box on NCDs, which contains a range of policy statements and technical documents, including those related to pricing, financing, and intellectual property issues. A total of 36 initiatives were also retrieved from the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) Health Partnership Directory and Access Accelerated Initiative (AAI). Of these 36 programs, all but one included the use of differential pricing solely or paired with supplemental efforts such as capacity building activities, general financial support, product donations, and technology transfer. The geographical reach of medicines access programs initiated by pharmaceutical companies is substantial and quasi-global.

In February 2018, 31 participants (21 male; 10 female) were interviewed in Bogota (Colombia), Nairobi (Kenya), and Kiev (Ukraine). All were experts and familiar with their local health systems and included senior policy and decision makers from the Ministry of Health (MoH), national regulatory authorities (NRAs), payers, procurement agencies, and pharmaceutical companies and patient associations. The average interview lasted 22 minutes (range, 15–35 minutes). In all three case studies, the challenges regarding access to innovative medicines for NCDs, the level of awareness on the use of MEAs and ongoing initiatives, and the potential emergence of barriers to and facilitators for MEAs were explored during the interviews.

Although there were limitations, this work adds to the global knowledge on the use of MEAs as potential policy options for promoting sustainable access to on-patent drugs for NCDs. It appears that the growing burden of NCDs in these LMICs, especially of orphan conditions, cancer (breast, lung, colon), and CVD; the concept of health as a fundamental right; and competing priorities under UHC commitments, limited financial resources, and a growing social-urban middle class that is pressuring for coverage emerged as the most prominent challenges. Lack of capacity, data, and standardized health care were also cited, as were concerns about the high cost of innovative medicines and their long-term affordability.

The level of awareness of and experience with MEAs in the case study countries was very limited. That said, Kenya has a longer tradition of centralized procurement and pooled purchasing for both infectious diseases and NCDs. In Ukraine and Colombia, there are limited initiatives in place for infectious diseases, the most salient one being the case of purchasing agreements for drugs to treat Hepatitis C. Although health as a human right is envisioned as an opportunity to advance UHC in all three countries, the *judicialization* for health care was a prominent finding only in Colombia.

Government officials are considering TRIPS flexibilities as possible solutions but are fully aware of their complexities. Price regulation using international reference pricing (IRP) and health

technology assessment (HTA) is seen as a means to assist priority setting and better allocate constrained budgets. In all three countries, the interest in using MEAs is growing and the position of both payers and pharmaceutical companies is converging through a need to establish early dialogues and trust-based negotiations.

Limited awareness of and familiarity with MEAs; competing interests of stakeholders; limited flexibility of budget allocation; an overall lack of institutional capacity (i.e., patient registry, electronic health records, standard treatment protocols); lack of trust among key players; limited availability of quality data to inform risk sharing agreements; and the need for a well-planned implementation plan emerged as potential barriers. Cultural aspects such as lack of transparency and trust, inherent resistance to change, and corruption are also potential barriers worth considering in these settings.

Ongoing health sector policy initiatives, including reforms in Ukraine and Colombia and the future establishment of central procurement bodies or value-based approaches, could become platforms to incorporate MEAs in the near future. Building on existing HTAs and pricing practices, using more systematic priority setting, and learning from previous experience in granting access to innovative medicines for infectious diseases were perceived as potential facilitators for MEAs.

After further analysis, the term "drivers" for implementing MEAs was coined to encompass barriers and facilitators. Ten drivers emerged with the potential capacity to help or hinder the inception of MEAs in these LMICs. They were coded as *capacity, existence of clear rules, political support, local context, perception, cultural factors, evidence related, risk bearing attitudes, uncertainty issues,* and *transparency requirements*. However, our preliminary findings should be tested and refined in light of further research in this field.

It appears from our preliminary findings that there is insufficient knowledge on the use of MEAs as policy options for granting access to on-patent medicines for NCDs in LMICs. Beyond China, India, and Thailand, it seems that the level of awareness on MEAs might be very limited, and there is an opportunity through the initiative for Strengthening Global Knowledge on Access Solutions for Innovative Medicines, supported by the World Bank (WB), to disseminate our findings and provide technical assistance in other LMICs to strengthen their capacities for MEAs.

Financial-based schemes were slightly more frequent than performance-based mechanisms. Arguably, this could mean it is more straightforward and feasible to negotiate prices and volumes and ex-ante agree on the level of risk to be borne by payers and manufacturers than to pursue more complex and data requiring mechanisms. Therefore, if there is interest in implementing MEAs in countries with limited capacity, financial-based agreements could potentially be more feasible than performance-based mechanisms in the short run. The fact that performance-based schemes seemed to be more predominant in North America may reflect the importance of structural, contextual, and cultural factors that may be worth considering when thinking about deferring to MEAs as policy options.

The track record of success stories for granting access to drugs for infectious diseases may pave the road for incrementally introducing MEAs for NCDs in LMICs. A significant number of international nongovernmental organizations (NGOs) and global advocacy groups are working on raising

awareness on TRIPS flexibilities to promote access to on-patent medicines for NCDs, despite the complex political implications of doing so. Also, the level of involvement from international organizations and donors in the case of MEAs still seems limited. All of these findings may represent an opportunity for the WB, AAI, and manufacturers to seize global attention regarding the use of MEAs as potential solutions for sustainable access to on-patent medicines for NCDs.

Because the level of awareness of and experience with MEAs in LMICs seems very limited and the overall geographical reach of medicines access programs initiated by pharmaceutical companies is quasi-global, the importance of market-driven approaches should be considered. Reshaping the balance of top-down vs. bottom-up policy initiatives in LMICs could be a pathway to explore in the case of access for on-patent medicines for NCDs.

Subject matter experts (SMEs) highlighted that performance-based agreements were more complex in nature and therefore less likely to be implemented in LMICs. In such cases, performance-based agreements could simply be based on information from HICs that had a well-established and reliable data collection and analysis infrastructure. Further, the SMEs acknowledged that although the terminology "managed entry agreements" and "risk-sharing schemes" was relatively new, some of the simpler financial instruments, such as discounts and price-volume agreements, have already been implemented in LMICs.

Among the benefits of MEAs are that they serve as frameworks to provide guidance in decision making processes and provide an opportunity to standardize dosing requirements; they could also potentially help mitigate the impact of increasing costs and create incentives for all involved parties. However, they also come with caveats. The high cost of medicines could prevail even if MEAs are implemented, and there is the perception that a lack of strong incentives for producers to reduce prices lessens the attractiveness of tiered pricing. MEAs may also delay competition and once a financial agreement has been reached, MEAs could potentially lead to losses of revenue in the global marketplace due to the growing trend of using external reference pricing.

Arguably, MEAs are also perceived as quick fixes to access barriers, and there is criticism about fairness for those patients with diseases that do not receive special sources of funding. In the case of price capping, if local competition arises, it may undercut prices and if patients require longer courses of treatment, they may challenge the pre-agreed prices. Finally, the lack of compliance with clinical protocols or an inability to monitor and evaluate prescribed dosages once patients are granted access may lead to supplier-induced demand and higher drug expenditures, jeopardizing trust among payers and manufacturers.

Taking into consideration the identified drivers as well as building up health systems' capacities and developing a well-established roadmap of processes, rules, and regulations to help the inception of MEAs in these LMICs, there is a need to work on the political economy of the policy process as a whole—the political landscape, context, perception, and cultural factors should be examined. It also seems relevant and somewhat complementary to improve the quality and availability of data to improve evidence and mitigate risk and uncertainty regarding the real value of innovation. It seems that the systematic use of HTAs may improve transparency and trust among all stakeholders.

According to key informants, the desirability and willingness for payers and pharmaceutical companies to engage with MEAs has increased over time, but there is still resistance from both sides. The issue of growing public scrutiny with regard to national budgets for research and development, as well as medicines pricing and value-price trade-offs, are worth considering for market access strategies as a whole. Some important questions remain and should be addressed by future global initiatives, such as the question of how MEAs could address equity in access to medicines (horizontal vs. vertical) and the real impact or effectiveness of MEAs in relation to other types of medicines access approaches.

1 INTRODUCTION

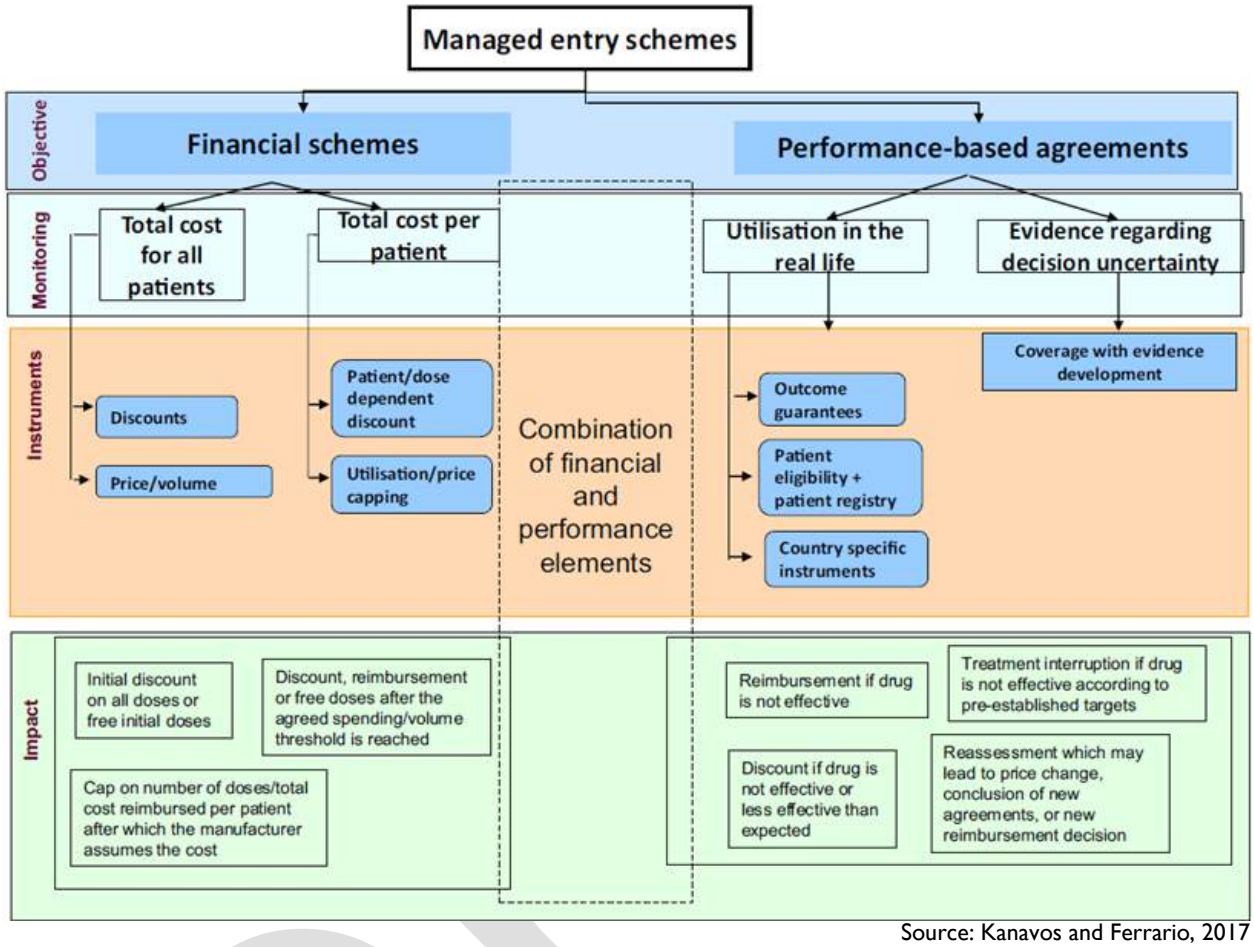
All health systems face the challenge of managing finite resources to address an unlimited demand for services. According to WHO, 70% of the 56.4 million deaths globally in 2015 were due to NCDs. More than 30 million of these deaths occurred in LMICs. CVD, cancer, diabetes, and chronic lung diseases are the four leading causes of NCDs deaths (World Health Organization, 2018).

In recent decades, research and development for diagnostics and treatment for NCDs has proven to be effective and cost effective in many cases. However, a lack of information on effectiveness and concerns about the cost of new, patented therapies leads to uncertainty and may delay reimbursement decisions and patient access, particularly in LMICs (Sherman et al 2016). Various access strategies, such as community-based, systems, production, and price approaches, have been implemented in different settings to enable access to innovation and promote better resource allocation. Of special interest is the case of MEAs—a type of formal institutional arrangement between manufacturers and payers aimed at sharing the financial risk surrounding the introduction of new pharmaceutical technologies in both LMICs and HICs (Kanavos et al 2017). In recent years, increasing pressure to find alternative access solutions for NCDs in LMICs has led manufacturers and governments or insurers to start considering MEAs; thus, there is a need to document lessons learned from their implementation.

Different frameworks have been developed for defining and classifying MEAs and measuring their impact. However, for the purpose of our analysis, we used the MEA taxonomy defined by Kanavos and Ferrario (2017) because their work presents a thorough review of a variety of terms used in the literature and provides a general taxonomy to enable harmonized and common understanding of these types of arrangements in different country contexts. The framework defines two main categories of MEAs—financial schemes and performance-based agreements. The former includes the subcategories of discounts, price/volume, and utilization price capping agreements. Performance-based agreements were subcategorized as outcome guarantees, patient eligibility/patient registry, and coverage with evidence development (see figure 1 for a detailed description of MEAs).

Through an initiative for Strengthening Global Knowledge on Access Solutions for Innovative Medicines, supported by the WB, there is an opportunity to document international experiences and understand contexts in which MEAs might be useful to promote early and affordable access to on-patent innovative medicines in LMICs. The body of work entails two related activities. Activity 1 sought to document international experiences on the implementation of MEAs and identify potential barriers to and facilitators for their successful implementation. Activity 2 set out to promote better informed decisions by developing a decision model that will bridge the gap between payers and manufacturers when facing uncertainty, budget constraints, and limited capacity to achieve sustainable access to innovative medicines for NCDs. Findings from both activities will be used to develop a compendium of good practices for access solutions to innovative medicines for NCDs.

Figure 1. Taxonomy for MEAs



Source: Kanavos and Ferrario, 2017

The purpose of this report is to present the results of activity 1 on the lessons learned from existing medicines access programs, with a particular emphasis on MEAs, and key success factors for their potential implementation. It is worth mentioning that broader information on existing medicines access programs was commissioned by the WB and AAI for the Boston University School of Public Health; that information is not included in this document.

This report presents the methods and findings and delivers some key messages for future policy action in LMICs on MEAs, namely financial schemes and performance-based agreements for prompting sustainable access to on-patent medicines for NCDs.

2 METHODS

As mentioned previously, activity 1 sought to document international experiences on the implementation of MEAs and identify potential barriers to and facilitators for their successful implementation. The work for this activity was based on a literature review of peer-reviewed publications and grey literature sources aimed at identifying existing international financial medicines access initiatives. To inform contextual factors that could influence the implementation of MEAs, semi-structured interviews with key participants in three LMICs of interest were conducted. This was complemented by informal interviews with global experts in the field of market access and risk sharing agreements. Finally, triangulation from all three sources served to identify recurring, divergent, and converging findings.

2.1 Systematic and grey literature review

Between December 2017 and February 2018, we conducted a systematic search of published literature to identify studies discussing relevant information and presenting data on MEAs. We searched the Biomedical Reference Collection, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Embase, Medline, and PubMed for peer-reviewed literature published within a 10-year time frame (January 1, 2007–December 31, 2017).

The list of keywords was categorized into three groups—risk-sharing agreements, patented medicines, and improved access. The following keywords and MeSH terms (including variations) were used: financing mechanism, risk sharing, managed entry agreement, performance-based agreement, patient assistance program, patient access program, patent, patented medicines, on patent medicines, patent drug, generics, generic medicines, off patent, improved access, market access, improved outcome, and improved results. Search terms were translated into French and Spanish to capture non-English publications (Appendix 1).

2.1.1 Eligibility criteria

We included primary studies using original data, literature reviews, editorials, and author commentaries. Studies meeting the following criteria were included: 1) articles describing financial or performance-based mechanisms for granting access to innovative patented medicines and generics globally and 2) articles generally describing lessons learned and previous experiences with MEAs. We excluded conference abstracts because of insufficient detailed accounts on MEAs and studies that described other market access mechanisms, namely community based, management strengthening, health care delivery, therapeutic substitution (e.g., introduction of generics), supply chain or production related (manufacturing or research and development), and licensing agreements or TRIPS flexibilities because these were not the focus of this review.

2.1.2 Systematic review data extraction, synthesis, and analysis

We undertook a two-phase screening approach: 1) we controlled for duplicates, screened all titles and abstracts, and removed studies that did not meet the inclusion criteria and 2) two reviewers screened the remaining full-text articles and made final selection of studies based on inclusion criteria. For each article that passed both levels of screening, one reviewer extracted authors; title; type of article

(primary/published original data, literature review, editorial/commentary); country implementing the MEA; MEA main category (financial scheme vs. performance-based agreement); detailed mechanism used to achieve type of agreement (e.g., discounts, utilization/price cap, coverage with evidence development); disease; and medications covered under the agreement. Two reviewers extracted information on factors facilitating or hindering the implementation of the MEA from all publications that met the inclusion criteria. In a second step, two reviewers synthesized the facilitators for and barriers to implementing MEAs. This coding system formed the basis for a series of iterative discussions with the broader project team during the qualitative analysis.

Those schemes that did not fit into the Kanavos and Ferrario (2017) MEA taxonomy were categorized as other. There were also different approaches or hybrid models that combined two or more of the above components, such as a combination of a financial scheme (i.e., a discount) and a program linking patients to care or subjected to real-world data collection.

2.1.3 Grey literature review methods

A review of the grey literature from targeted sources recently involved in access solutions for innovative medicines for NCDs was simultaneously carried out to complement the systematic review findings. The review entailed gathering relevant information from the following sources:

(i) Consultation with WB SMEs
(ii) World Health Assembly meetings that took place between 2007 and 2017
(iii) WHO toolbox on NCDs
(iv) Targeted websites that present medicines access programs led by pharmaceutical companies, namely AAI and the International Federation of Pharmaceutical Manufacturers & Associations
(v) Independent tools in the Medicines Law and Policy website whose purpose is to provide analysis, policy recommendations, and tools to aid practitioners on universal access to medicines
(vi) European Commission Expert Panel on Effective Ways of Investing in Health website
(vii) Organisation for Economic Cooperation and Development (OECD) website
(viii) Websites of NGOs working to increase access to medicines or vaccines; namely, Medicins Sans Frontieres (MSF), Medicins du Monde, Initiative for Medicines, Access & Knowledge, Drugs for Neglected Diseases initiative (DNDi), Bioventures for Global Health, and the Union for International Cancer Control (UICC)

2.2 Semi-structured interviews

2.2.1 Country selection rationale and characteristics

Purposive sampling was used in the selection of countries and participants to be included in the case studies. Three countries (Colombia, Kenya, and Ukraine) were selected to represent variation in geographical setting, level of income, socio-political contexts, and health care systems as well as because of their commonly demonstrated political will toward UHC for their citizens. All three

countries had financial constraints or fragmented purchasing/procurement mechanisms common to LMICs. Table 1 presents a summary of relevant country characteristics.

Table 1.Summarized case study country characteristics

Country name	Colombia	Kenya	Ukraine
Classification by income level	UMIC	LMIC	LMIC
Population	49,702,869 (National Administrative Department of Statistics (DANE), 2018)	49,699,862 (UN DESA, 2017)	45,004,645 (World Bank, 2016)
Percent total deaths due to NCDs	71% (WHO 2014)	27% (WHO 2014)	90% (WHO 2014)
GDP	GDP p.c US$5,806/p.p.p CI$14,154 (World Bank 2016)	GDP p.c US$1,455/p.p.p CI$3,155 (World Bank 2016)	GDP p.c US$2,185/p.p.p CI$8,270 (World Bank 2016)
% GDP allocated to health care	7.2% (WHO 2014)	5.7% (WHO 2014)	7.1% (WHO, 2014)
Per capita health expenditure	US$569 (World Bank 2016)	US$78 (World Bank 2016)	US$203 (World Bank 2016)
Health system characteristics	Mostly public funding; public-private mix provision; centralized	Public-private mix financing and provision; decentralized; highly fragmented	Mostly public financing and provision; decentralized
Health financing	Two major public insurance regimes with around 97% coverage (OECD 2016) are the Contributory Regime (employed and pensioners) and the Subsidized Regime (low-income population).	National Health Insurance Fund (NHIF) has 18% coverage; private, community-based and microfinance insurance companies have 2% coverage. Out-of-pocket (OOP) expenditure is 24%. (Kenya Ministry of Health, 2014)	Health financing is raised through taxation. Voluntary Health Insurance (VHI) covers services not financed by the state health system. OOP expenditure was 39.6% in 2012. (Lekhan et al, 2015)
Key distinguishing feature relevant to implementation of MEAs	Decentralized public-sector procurement and substantial judicialization of access to innovative medicines. Low OOP sources.	Centralized public procurement system that runs parallel to a progressive commercialized medicines market. High OOP sources.	Decentralized public-sector procurement system and prohibited negotiations between government and developers. High OOP sources.

Two countries (Kenya and Colombia) are part of the AAI—a global initiative involving more than 20 biopharmaceutical companies and associations that includes partners such as the WB and the UICC to help address the full spectrum of access barriers to NCD medicines in LMICs. Ukraine recently passed a major health sector reform that aims to establish a centralized procurement body expected to negotiate on-patent innovative medicines.

2.2.2 Stakeholder mapping and semi-structured interviews

Stakeholder mapping was conducted to identify high-level decision makers in the three countries of interest. The targeted institutions included the MoH, National Drug Regulatory Agency, National Health Insurance Fund, private payers and insurers, NCD patient associations, and pharmaceutical industry associations. Individuals with similar characteristics from these institutions were considered eligible (e.g., local stakeholders, decision and policy makers familiar with ongoing strategies for market access to medicines for NCDs).

A total of 32 stakeholders in the three countries were identified as potential target participants. All key informants were validated with the technical lead team for Strengthening Global Knowledge on

Access Solutions for Innovative Medicines with input from the WB Washington DC, WB Kenya, and WB Ukraine.

Each semi-structured interview was scheduled to last between 30 and 40 minutes, which was considered enough time to capture the salient findings. An interview guide was developed to follow a predetermined set of topics that included the individual's knowledge and/or perception of current access challenges for NCDs, level of awareness of MEAs and ongoing initiatives within their setting, and potential barriers to and facilitators for the implementation of MEAs in their country context.

To ensure uniformity, key informant interviews were conducted in person by two data collectors using the semi-structured interview guide. The project technical director (HC) and the project senior medicines access advisor (NK), both Management Sciences for Health (MSH) staff, personally conducted the interviews in all three countries. All individuals received an information sheet and consent form in English (Kenya and Colombia) or Ukrainian (Ukraine) that explained the objectives of the study and stressed that participation was completely voluntary.

Participants were asked to agree to be audio-recorded during the interviews. Participants were assured that only the MSH team would retain the audio files to enable transcription of the interview and that in the final aggregated report, no name would be attributed to any individual. All participants gave consent to participate in the study and all but one agreed to be recorded. Interviews were open ended to allow the participants to guide the discussion as much as possible and to diverge if necessary to address ideas and concepts not anticipated by the data collectors.

Interviews in Colombia were conducted in Spanish and translated into English. Interviews in Kenya were conducted in English. Interviews in Ukraine were conducted with the assistance of an interpreter or in English if the respondent was comfortable with this language. Interviews took place in quiet, private environments. During the interviews, data collectors summarized major themes from each participant and highlighted those considered potential barriers to or facilitators for the implementation of MEAs.

2.2.3 Analysis

Once completed, each interview was transcribed verbatim by an independent transcriber. Each interview was then coded and entered into an Excel spreadsheet for thematic content analysis. Before starting the analysis, the project technical director predetermined emerging codes to facilitate analysis. This labelling scheme was informed by the interview guide and preliminary barriers to and facilitators for the inception of MEAs emergent from the literature review and interviews.

To enhance the rigor of the findings, analyze emerging data and decide on and refine a potential taxonomy of codes a panel meeting was held by MSH team members in early March 2018. No preliminary hypothesis was considered, and the team aimed to interpret data instead of simply describing it. The term "drivers" for implementing MEAs was coined to encompass barriers and facilitators. Coding was open and looked at previously depurated quotations, and reviewers looked for emergent drivers. The findings section presents a detailed description of the context, participants' profiles, and the emergence of drivers.

2.3 Triangulation

As a first step, findings from the literature review were triangulated with those from the key informant interviews. The project team then conducted two iterative discussions to categorize and define the extracted drivers (facilitators and barriers) of implementing MEAs. Finally, informal interviews were conducted during early March 2018 with four global SMEs in the field of MEA to validate the findings and further enrich project team discussions. Interviewees were global experts/leaders in advancing financial/outcomes-based access strategies for medicines around the world; previous peer-reviewed publications in the field of market access/managed entry agreements/risk sharing mechanisms were desirable, as was previous experience in the implementation of MEAs in LMICs. The project team then conducted a final iterative discussion to refine the categories and definitions of the emerged drivers for implementing MEAs.

3 FINDINGS

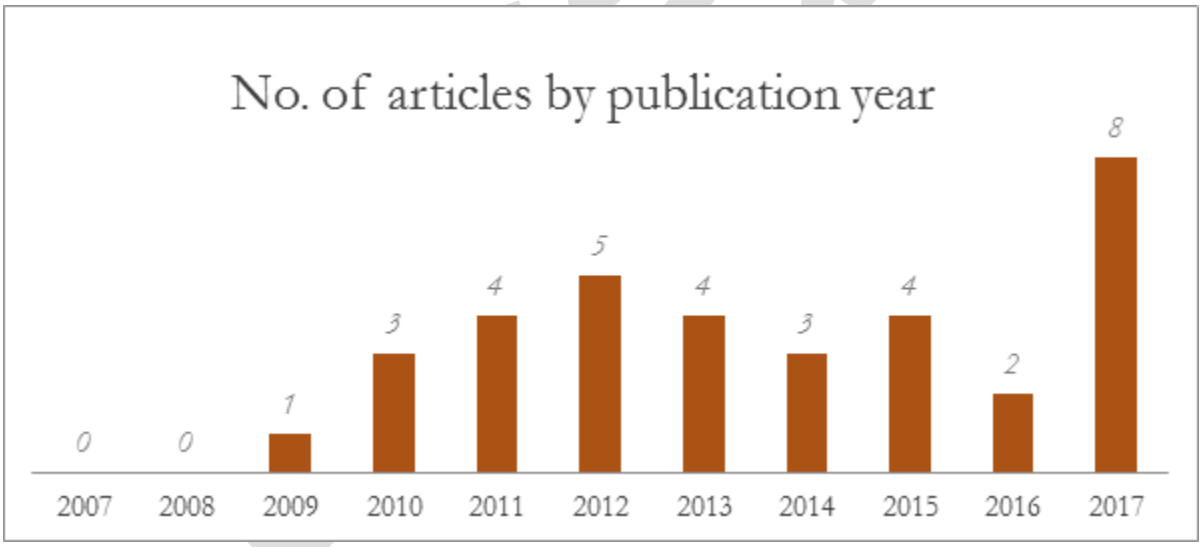
3.1 Literature review

3.1.1 MEAs: publications and trends

The systematic literature search retrieved 330 records; 296 records were identified through database searching and 34 were added through other sources (project technical experts and previous publications gathered by MSH). After controlling for duplicates, 253 records remained and were screened for titles and abstracts. At this stage, 186 records were excluded after screening, and 67 full-text articles were assessed for eligibility. A total of 33 articles were excluded with reasons and 34 publications were ultimately considered for qualitative analysis—18 primary publications (using original data), 12 literature reviews, and 4 editorial or author's commentaries. See Appendix 2 for a detailed graphic description of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) diagram and Appendix 3 for the list of 34 publications considered for qualitative analysis.

Out of the 34 selected publications, 13 (38%) were published between 2007 and 2012 and 21 (62%) were published between 2013 and 2017. This shows a 38% increase over the last five years in the number of publications regarding the use of MEAs in different settings (see Figure 2 for a pictographic representation of this trend).

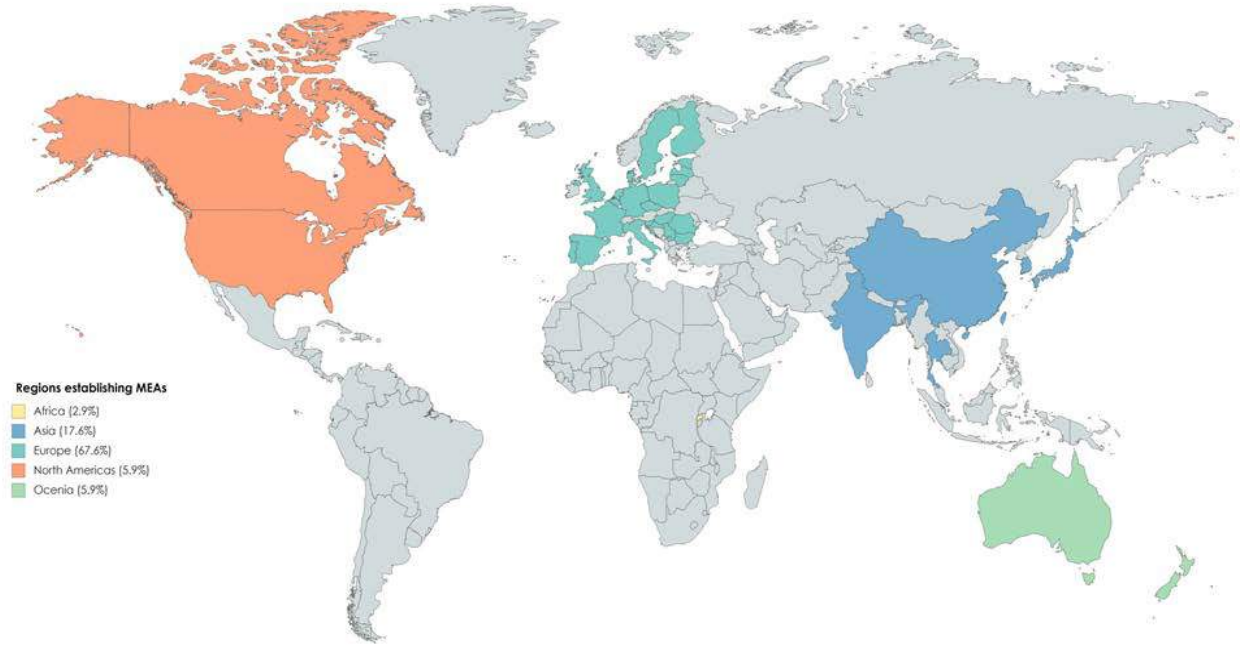
Figure 2. Evolving stock of knowledge



3.1.2 Diversity of MEAs

We identified 285 MEAs through our search; most took place in HICs. A total of 23 European countries (67.6%) have implemented one or more types of MEAs, followed by six Asian countries (17.6%), two countries in North America, and two countries in Oceania (Figure 3). Beyond China, India, and Thailand, it seems that the level of documentation on MEAs in LMICs might be very limited. No records of ongoing MEAs for NCDs in Latin America or Africa were retrieved from our search (except for the case of Rwanda and HPV vaccines).

Figure 3. Implementation of MEAs by region



According to our findings, financial schemes were slightly more prominent than outcome-based schemes, at 50.2% vs. 44.9%, respectively. The remaining 4.9% of the agreements covered hybrid schemes that included elements from both financial and performance-based schemes, such as a combination of a financial scheme (i.e., price and volume) and patient eligibility and registry requirements. Generally, financial-based schemes were more prominent in Europe, Asia, and Oceania, while performance-based agreements were more prominent in North America.

Among financial schemes, price/volume and discounts were the most predominant at 18.9% and 17.5%, respectively. Utilization and price capping schemes accounted for 7.7% of the financial schemes, and 56% of the remaining schemes were either not specified in the literature or had a mix of financing components.

Among performance-based agreements, coverage with evidence development was the most frequent type of scheme (39.1%), followed by outcome guarantees (32.8%), and patient eligibility based on patient registry (5.5%). The remaining schemes (22.7% of performance-based agreements) were either not specified or contained more than one performance-based component (Figure 4).

Most of the financial or outcome-based agreements retrieved through our search covered a wide range of NCDs and their treatment, predominantly different types of cancer (e.g., breast cancer, chronic myelogenous leukemia, colon and rectal cancer). Other NCDs covered included multiple sclerosis, osteoporosis, diabetes, CVD, and Alzheimer's. It is worth noting that fewer schemes retrieved through our search focused on communicable conditions, such as HIV/AIDS, cervical cancer, malaria, tuberculosis, and pneumococcal disease.

Figure 4. Participation (%) of sub-scheme by type of agreement (financial and performance-based)

3.1.3 Enabling and hindering factors for MEAs

The published data indicated that having good quality administrative and information systems was key to tracking the implementation of coverage with evidence schemes. The implementation of MEAs seemed to be labor and resource intensive, according to the literature. The existence of legal requirements supporting patient enrollment; clear contract terms and definitions; evaluations of performance metrics and goals linked to specific pricing and reimbursement decisions; and clear, measureable, realistic, objective outcome measures seemed to reduce the administrative burden and promote the implementation of MEAs.

It appears that MEAs are culturally more accepted in HICs, and in some of these countries there was a preference for certain types of agreements (financial vs. performance-based). The lack of trust among payers, manufacturers, and health care providers could potentially hinder the implementation of MEAs. Countries may even move away from performance-based agreements due to a lack of transparency, the complex nature of the agreements, and language barriers that make it difficult to track the impact.

Aspects related to the quality of data and evidence were also reported in the literature. For example, the need for data on pricing and real-world evidence on clinical outcomes should be considered when pursuing MEAs. On the one hand, the evidence of positive performance on clinical outcomes and the availability of patient information in administrative claims databases seems to facilitate these types of agreements. On the other, limited evidence of effectiveness of a new drug makes it difficult to choose the right schemes, and there is very little evidence to support claims made, which may discourage payers from investing in diseases that are not strongly “evidence based".

Issues about uncertainty regarding data, financial impact, or other patient and institutional factors that may affect patient outcomes could affect the perception of MEAs as potential policy options for improving access. Small treatment populations may lead to delays in data collection and ultimately delay the inception of MEAs. The use of HTAs or comparative safety and effectiveness and cooperation among institutions, their governments, NGOs, and manufacturers of diagnostic and research teams seem to enable MEAs. All enabling and hindering factors retrieved from the literature review were coded and analyzed as potential barriers and facilitators that served to inform the qualitative analysis of our work (Appendix 4).

3.1.4 Grey literature

Based on the inclusion and exclusion criteria and after screening, it became clear that some of the targeted grey literature sources were not relevant for the purpose of this review. The WHO tool box on NCDs contains a range of policy statements and technical documents, including those related to pricing, financing, and intellectual property issues. The independent tools on the Medicines Law and Policy website focused on licensing agreements and how to navigate TRIPS flexibilities. Likewise, the WHA meetings (2011–2017) discussed five main mechanisms to improve access to medicines: TRIPS flexibilities and the Doha agreement, voluntary pooled funding and procurement, sin taxes (alcohol and tobacco) to boost government revenue, public-private partnerships (shared risk), and grant schemes. All but one of the NGOs that we identified focused on patent opposition to lower drug prices and were therefore excluded from the narrative report.

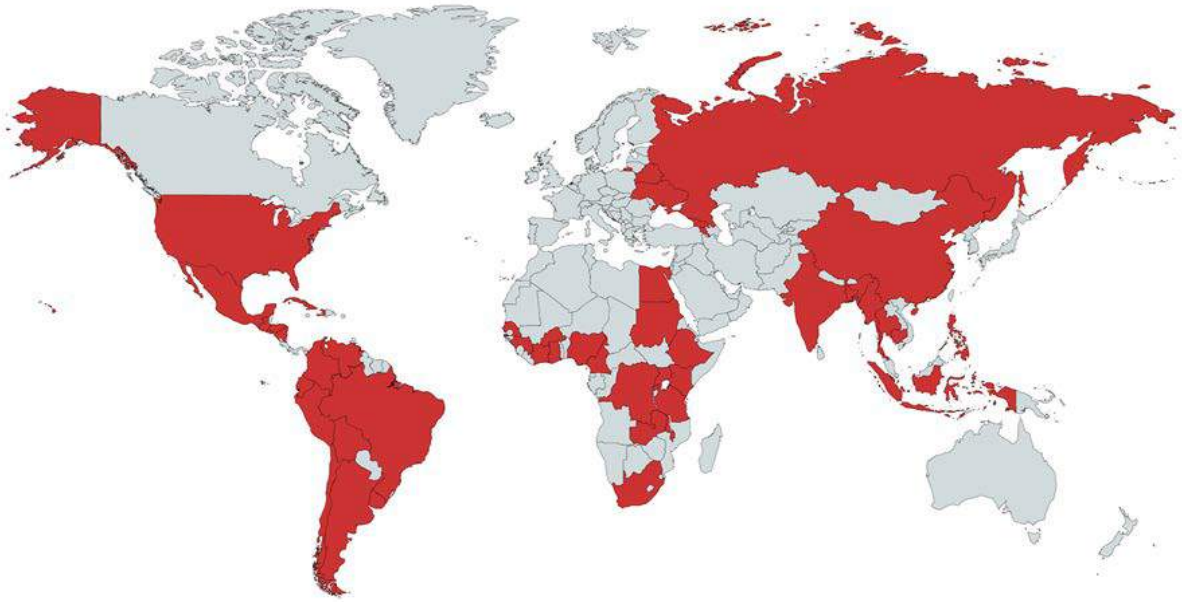
The work presented in the OECD (2017) and European Commission reports (Ferrario and Kanavos 2013 and European Union 2018) essentially provided reviews of peer-reviewed publications that were included in the systematic review of the literature, and no additional distilling of information from these sources was necessary. The findings reflect initiatives undertaken by organizations whose focus is to increase access to medicines and health technologies for specific NCDs.

A total of 36 access initiates for NCDs were identified and examined from the IFPMA Health Partnership Directory and AAI, none of which were considered within the narrowly defined categories of MEAs. The NCDs that the access programs are targeting include chronic conditions such as epilepsy and hypertension; cancers; and some conditions that go beyond NCDs (i.e., infectious diseases, including vaccine-preventable conditions; neglected tropical diseases; and maternal, newborn, and child health concerns, including contraceptives and pediatric medicines for a broad range of conditions).

Of the 36 programs reviewed from these sources, all but one included the use of differential pricing. Of the 35 programs that did include differential pricing, 10 focused exclusively on it and 25 paired differential pricing with supplemental efforts such as capacity building activities, general financial support, product donations, and technology transfer, all of which we classified as other. The geographical reach of medicines access programs initiated by pharmaceutical companies is significant (Figure 5).

In addition the reach of access programs for NCDs, the DNDi's multipronged 2009 strategy was to ensure consistent and affordable access to medicines that treat neglected diseases. This was of interest because it was a comprehensive approach to access to medicines. DNDi's approach includes 1) entering into agreements with manufacturers to secure long-term treatment and/or active pharmaceutical ingredient production; 2) accelerating regulatory approvals and/or updating WHO and in-country guidelines by working closely with stakeholders (e.g., WHO, NRA, MoH); 3) getting accurate demand forecasts to ensure realistic supply planning by working closely with stakeholders (manufacturing and program); 4) in partnership with manufacturers and users, facilitating the extension of medicine shelf lives and improving the product profile and packaging so it is relevant for targeted health systems; and 5) simplifying procurement and supply chain in cooperation with national control programs, WHO, distributors, and other partners.

Figure 5. Geographical reach of medicines access programs initiated by pharmaceutical companies



Bio-ventures for Global Health's AAI is a partnership of pharmaceutical companies, governments, health care providers, and NGOs that focuses on access to cancer medicines and technologies. A recently launched platform by AAI provides information about access agreements between pharmaceutical companies and African hospitals and facilitates knowledge exchange among companies, NGOs, and African oncologists and researchers.

3.2 Semi-structured interviews

In February 2018, 31 participants (21 male; 10 female) were interviewed in Bogota (Colombia), Nairobi (Kenya), and Kiev (Ukraine). All were experts and familiar with their local health systems and included senior policy and decision makers from the MoH, NRAs, payers, procurement agencies, and pharmaceutical companies and patient associations. The average interview lasted 22 minutes (range, 15–35 minutes). In all three case studies, the challenges regarding access to innovative medicines for NCDs, the level of awareness on the use of MEAs and ongoing initiatives, and the potential emergence of barriers to and facilitators for MEAs were explored during the interviews. Table 2 presents the number of interviewees by setting.

Table 2. Response rate by country

Country	No. of interviews	Response rate
Colombia	8/8	100%
Kenya	11/12	92%
Ukraine	12/12	100%

3.2.1 Country case studies

Colombia

Since 1991, access to health services in Colombia has been considered a right. The country is currently an upper-middle income country and one of the largest economies in South America. Colombia allocated 7.2% of its GDP to health care in 2014 (WHO). Access to a comprehensive package of services is granted through health insurers (public, mixed, and private), known as health promoting entities (EPS). These entities are responsible for ensuring the provision of and collecting funds to pay for health services. Colombians are entitled to enroll in one of the EPS through two major insurance regimes: the Contributory Regime (CR) and the Subsidized Regime (SR). Both SR and CR members are entitled to a benefits package. Those who are employed and pensioners are mandated to affiliate to the CR and contribute a percentage of their income to health care, whereas SR affiliates are low-income individuals funded by the national government, local governments, and the CR. According to the WB, the 2014 per capita health expenditure in Colombia was US$569. Colombia currently has health care coverage for approximately 95% of its population.

Respondents considered, the main challenges to granting sustainable access to on-patent medicines for NCDs are related to sustainability issues and budget constraints; price discrimination in LMICs; the uncertainty of the real value of innovation; and technological pressure (meaning social demand and financial strain from health care innovation) under a very protective environment toward intellectual property (IP) rights. The high cost of medicines for orphan diseases, cancer, and CVD is the most pressing challenge. The concept of health as a fundamental right has led to substantial *judicialization* of health care coverage, especially among the social-urban middle class. According to recent figures from the Peoples Advocates Office (*Defensoria del Pueblo*), every 3.5 minutes a Colombian citizen challenges the health system's coverage through judicial claims (*accion de tutela*), and nearly 120,000 *tutelas* were ruled in 2015 (Ombudsman's Office Colombia). Health care coverage is still perceived to be fragmented, and priority setting for health care remains nonsystematic and lacks transparency.

In 2013, the MoH re-established price regulation using IRP, while in 2012 the establishment of the local HTA institute improved the use of evidence to inform price and reimbursement decision making. Among the current initiatives for access to costly medicines was a recent pilot of centralized negotiation/purchasing for Hepatitis C medicines.

In recent years, Colombia has become very active in making use of TRIPS flexibilities for cancer drugs (Resolution 2475/2015) and more recently received a request from civil society organizations for medicines for Hepatitis C. In March 2018, Decree 433 was passed by the MoH to strengthen its capacity to assess the value of innovative medicines and regulate prices of new drugs based on value. Fast track approval for bio-competitors began in August 2017, and the recent health sector reform (Law 1751/2015 (statutory law), which entitles the population to more generous coverage, is being implemented. There are quite a few pilots of MEAs, and early dialogues (for PCSK9s) are currently taking place with pharma companies in Colombia, especially for orphan diseases (i.e., hemophilia, Morquio's syndrome).

Limited awareness and familiarity with MEAs, competing interests of stakeholders, limited availability of quality data to inform risk sharing agreements, and a lack of trust among key players and their limited local experience on MEAs as policy options were identified as barriers to the implementation of MEAs. The recent use of HTA, the increasing awareness of the limitations of other policies (i.e., IRP), and the growing interest in MEAs and their usefulness could be seen as potential facilitators.

Other potential barriers include the fragmentation of funding sources for health care, which prevents the aggregation of demand; regulatory uncertainty and instability (unpredictability); a lack of clear roles and responsibilities and the need for a well-established roadmap for MEAs; and limited capacities (managerial, institutional, government, manufacturing) and high turnover of policy makers in many LMICs. Cultural aspects such as a lack of transparency and trust, limited willingness to share data and risks among stakeholders, and corruption also emerged as potential barriers in Colombia.

Kenya

Kenya is considered a lower-middle income country; its 2010 constitution recognized health as a human right. Despite Kenya being the most advanced economy in Central and Eastern Africa, only approximately 5.7% its GDP is allocated to health care (WHO 2014). Further adding to this challenge, the NHIF covers approximately 18% of the population; private, community faith-based, and microfinance insurance companies provide coverage to an additional 2%. The health sector is predominantly financed by private sources with an OOP expenditure of 24% for health care services. Additional funds for health care come from the government (29%) and contributions from donors (35%). The per capita health expenditure in Kenya was US$78 in 2014.

According to the respondents, the main challenges for granting sustainable access to on-patent medicines for NCDs are related to their high cost, which limits their long-term affordability due in large part to the chronicity of health care needs for NCDs. Like many LMICs, Kenya faces competing priorities now that the health system is aimed at reaching UHC. The lack of standardized health care and limited patient education/awareness and self-care translate into delays in access to health care.

In Kenya, certain types of cancer (e.g., breast, lung, colon) and chronic renal failure contribute most to NCD burden-related challenges. Financial efforts are still focused on infectious diseases, and a lack of trust in the quality of generic drugs and falsified, substandard, and counterfeit medicines are unresolved challenges within the market. In Kenya, there is willingness among patients to choose branded medicines instead of generics, and high OOP spending translates to both unfulfilled needs and a means for choice. Geographical barriers to medicines and supply chain limitations also negatively affect the availability of drugs for NCDs.

Fragmented health care coverage and sources of funding; uncertainty about the real value of innovation vs. short-term investment; technological pressure (especially for biological medicines); long registration processes; and the concept of health as a fundamental right all emerged as ongoing challenges for NCDs in this setting.

Kenya's commercial sector has been very active regarding the implementation of public and private partnerships (PPP) for medicines within the marketplace. Among the current initiatives for access to costly medicines, the programs for breast cancer medicines (tamoxifen and trastuzumab, led by Novartis and Roche, respectively) and discounts and subsidies were most commonly mentioned by interviewees. Healthy Heart Africa by AstraZeneca, which focused on CVD and cancer (aimed at improving screening and providing subsidies), and the asthma and diabetes mellitus programs led by GSK and Novo, respectively, were also mentioned.

In Kenya, previous large-scale initiatives for infectious diseases such as malaria, TB, and HIV have been taking place for years. The country also has experience in pooled procurement and discounts based on price/volume agreements being undertaken by the Kenyan Medical Supplies Authority and the Mission for Essential Drugs and Supplies. Retailers have also expressed interest in being part of MedSource Inc., a recently launched group purchasing organization in Kenya that is a wholly owned subsidiary of MSH. All of these efforts were considered by participants to be small-scale initiatives.

International donor support has resulted in health systems strengthening (i.e., supply chain and centralized quantification) through the Health Commodities and Supply Chain program, implemented by MSH and funded by the US Agency for International Development (USAID). There is growing interest and investment in advocacy groups, patient awareness rising, and patient-supported groups for NCDs. TRIPS flexibilities awareness has increased, and although it is envisioned as a policy option by government officials, they are also aware of the political complexities of enforcing TRIPS flexibilities. It also emerged that the NHIF recently earmarked funding for NCDs. Within Africa, there are ongoing efforts for expedited pathways for registration and NRA harmonization.

Limited awareness of and familiarity with MEAs; competing interests of stakeholders; a lack of trust among key players and mistrust regarding previous government decisions; and limited availability of quality data to inform risk sharing agreements emerged as potential barriers to the implementation of MEAs. The ongoing PPP working in supply chain and the country's interest in pooled procurement; the growing pressure and willingness to achieve UHC and the fact that the NHIF has been compelled to expand coverage; increasing interest from payers (insurers) and pharmaceutical companies; and previous experience promoting access to drugs for infectious diseases on a large scale were identified as potential facilitators.

Other potential barriers include the fragmentation of funding sources for health care, which prevents the aggregation of demand; limited capacity of HTAs; a lack of clear roles and responsibilities and the need for a well-established roadmap for MEAs; inflexibility of the annual funding allocation for health care; limited capacities (managerial, institutional, government, manufacturing); and regulatory limitations (i.e., timelines for registration, generic substitution or price/capping). Cultural aspects such as a lack of transparency and trust, limited willingness to share data and risks among stakeholders, resistance to change, and corruption also emerged as potential barriers in Kenya.

Ukraine

Ukraine is a lower-middle income country according to the Soviet Semashko model. The Ukrainian health system provides universal access to a guaranteed basic package of health services at no cost to all citizens and to registered long-term residents in public facilities. Although no major reform had taken place since the system's inception, a series of changes was introduced in 2010 to reduce fragmentation and prioritize primary care. Ukraine is currently undergoing a major health sector reform aimed at strengthening the financing function of the system.

According to WHO, Ukraine allocated 6.1% of its GDP to health care in 2015. Although most health financing comes from general government revenues raised through national and local taxation, the system has suffered a major financial crisis since the 1990s, and the government has made several attempts to limit the package of services provided at no cost. An essential medicines list (EML) was introduced in 2017 and is expected to be updated periodically.

Private health care is available and is financed mostly through OOP payments, which amounted to 39.6% of the health care expenditure in 2012 and 46.2% in 2014 (Knoema). This covers payments for services and treatments not financed by the state health system and allows members to choose their providers and treatments in exclusive public and private facilities, where access to diagnostics and treatments is normally faster.

According to the respondents, the main challenges for granting sustainable access to on-patent medicines for NCDs are related to their high cost and the fact that 80% to 90% of medicine costs are paid by patients, which limits their long-term affordability and exposes citizens to impoverishment. As in many LMICs, Ukraine's EML does not include adequate numbers of innovative medicines. According to the respondents, patients are being treated with old medicines based on outdated treatment protocols. There are competing priorities and inadequate state funding to procure sufficient innovative medicines for orphan diseases and other conditions now that the health system is aimed at reaching UHC. The lack of standardized health care and limited patient education/awareness and self-care translate in delayed access to health care. Participants perceived the lack of financial protection from health insurance as another challenge for sustainable access to medicines for patients affected by NCDs.

The country's current health sector reform effort creates an opportunity for policy action. For example, the draft National Drug Policy document mentions access to innovative medicine initiatives but needs more work, and HTA initiatives and an external reference pricing approach for reimbursement programs covering generic medicines are under way. After recent corruption scandals, international procurement agencies engaged in direct negotiation with manufacturers, which has increased patient access to innovative medicines. However, there is little engagement of the state in these direct negotiations with the exception of treatment for Hepatitis C (sofosbuvir), which led to negotiations between the State and Gilead in 2017 that significantly reduced the price of the medicine.

Among the current initiatives for access to costly medicines, new products are sometimes accessed through clinical trials; medicine donations by manufacturers occur on a case-by-case basis; patient associations typically access innovative medicines through third parties (e.g., donor funds,

international mechanisms); and individual patients work with manufacturers for humanitarian aid and may purchase three packs for the price of one, which does not affect the state budget. Patient associations have pressured the government for innovative NCD medicines in the past (e.g., the partially successful "right to life" program where the state covered 35% of medicine needs while the rest was covered by the manufacturer as humanitarian need—one such case involved nilotinib for the treatment of leukemia, which was funded by the state for three months and by Novartis for the remaining nine months).

Another success story is the reimbursement program for the treatment of CVD, diabetes, and bronchial asthma, which led to an 85% increase in daily defined dose consumption of medicines. The MoH is amending legislation on medicinal products to include long-term agreements with manufacturers through a planned central procurement body. There is limited awareness of the existence of MEAs, but they are being considered for orphan diseases, certain types of cancer, and Hepatitis C. The Association of Pharmaceutical Research and Development advocated for MEAs at the end of 2014, as reflected in the Vision 2020 document, and manufacturers have apparently supported the establishment of a patient registry.

Limited awareness of and familiarity with MEAs; competing interests of stakeholders; limited state funding; an overall lack of institutional capacity (i.e., patient registry, electronic health records, standard treatment protocols); a lack of trust among key players and mistrust regarding previous government decisions; limited availability of quality data to inform risk sharing agreements; and the need for a well-planned implementation plan emerged as potential barriers to the inception of MEAs. The ongoing health sector reform; the future establishment of a central procurement body that could become a platform to incorporate MEAs; building on existing HTA initiatives and using multicriteria decision analysis for priority setting; previous experience in granting access to innovative medicines through clinical trials; interest in adopting European Union and other international practices; and the opportunity for international cooperation are perceived as potential facilitators for MEAs in Ukraine.

Other potential barriers include political instability; the fact that currently MEAs may not be high on the political agenda; and the time needed to develop appropriate legislation, which could delay access to innovative medicines. In Ukraine, there is limited flexibility in budgeting and no common stakeholder platform for open communication and transparency. The pharmaceutical market is perceived as small, fragile, over-regulated, and very corrupt. Cultural aspects such as a lack of transparency and trust, inherent resistance to change, and corruption also emerged as potential barriers in Ukraine.

3.2.2 Common findings

(i) Access challenges

After the thematic content analysis, the common challenges of access to medicines in Colombia, Kenya, and Ukraine, according to interviewees, could be classified as health system, financial, patient, regulatory, or innovation/trade associated (Table 3).

Table 3. The perception of challenges for sustainable access to innovative medicines for NCDs

Health system challenges	Growing NCD burden, with orphan diseases; cancer (breast, lung, colon); chronic renal failure; and CVD being the most prominent
	The concept of health as a fundamental right; yet there are competing priorities under UHC, including nonsystematic priority setting and limited/fragmented coverage
	Unlimited needs/social-urban middle-class pressure
	Lack of data – inability to understand disease burden and by extension the market
	Lack of standardized health care (no CPGs or protocols, barriers to diagnosis)
Financial challenges	Cost, affordability, and chronicity of health care for NCDs
	Sustainability, budget constraints, and price discrimination
	Inadequate and inflexible state budget to procure sufficient innovative medicines
	Financial efforts still focused on infectious diseases
	Lack of health insurance; not affordable to payer
	High risks and high costs of doing business contribute to the high cost of medicines
Innovation, manufacturing and trade challenges	Uncertainty of real value of innovation vs short-term investment
	Protective legislation toward IP; judicial system takes a long time (up to three years) when IP infringements are taken to court
	Limited local willingness to innovate
	National EML does not include adequate innovative medicines; patients are being treated with old medicines based on outdated treatment protocols
	Technological pressure (biologicals)
	Manufacturers game the system of price registration by listing very high prices. Typically, some split distributing products into two, with the cost in the first invoice and no cost in the second.
	Limited PPP initiatives in place
	Limited local manufacturing capacity
Regulatory challenges	Lack of trust in generics; falsified, substandard, and counterfeit medicines on the market
	Regulatory barriers to competition and price regulation
	Long registration process
Patient-related issues	Limited patient education/awareness/self-care
	High OOP/limited insurance coverage

(ii) Level of awareness of MEAs and ongoing initiatives

The level of awareness of and experience with MEAs (financial or performance-based mechanisms) in the case study countries was very limited. That said, Kenya has a longer tradition of centralized procurement and pooled purchasing for both infectious diseases and NCDs. Various pharma companies have worked in PPP to advance access to medicines for NCDs such as cancer, asthma, diabetes, and CVD (mainly discounts and price and volume agreements).

Notably, global PPPs have also negotiated price and volume agreements on behalf of the Kenyan government, such as GAVI for access to vaccines. In Ukraine and Colombia, there are initiatives in place for infectious diseases, the most salient one being the case of a purchasing agreement for drugs to treat Hepatitis C. Although procurements predominantly occur through a tender process in Ukraine, discount schemes and external reference pricing for reimbursement programs exist for both generic and innovative patented medicines. A few pharma companies have also entered into PPPs directly with providers to increase access to medicines. The growing interest in MEAs in Colombia has been evidenced by pilots for high-cost medicines that treat chronic diseases that have been initiated by insurers in the last two years.

Although health as a human right is envisioned as an opportunity to advance UHC in all three countries, the *judicialization* for health care was a prominent finding only in Colombia. Government officials are considering TRIPS flexibilities as options but are fully aware of the complexities of such

mechanisms; they consider them very "politically contested" and the whole process to be "tedious"[1]. Only Colombia in recent years has been very active in declaring its public interest in cancer and Hepatitis C drugs without pursuing compulsory licensing. Price regulation using IRP is in place in both Ukraine and Colombia, as it is HTA as a means to assist priority setting. Ukraine is undergoing a major health sector reform that envisions the establishment of a local HTA, and Colombia established its own agency in 2012.

While none of the three countries seem to be fully familiar with the MEA taxonomy, the interest in using MEAs seems to be growing, and the position of both payers and pharmaceutical companies seems to be shifting from "innovation is problematic" [2] to "looking at previous international experiences"[3] and having "open arms"[4] to sitting down and negotiating through early dialogues and trust-based negotiations.

3.3 Emergence of drivers

We identified some aspects that may help or hinder the implementation of MEAs based on findings from the literature review and interviews. After further analysis of these potential barriers and facilitators, we determined that these aspects could be influential enough to promote or prevent the implementation of MEAs. The term "drivers" for implementing MEAs was coined to encompass these barriers and facilitators; a "driver" in this case was a metaphor for a wheel or other part in a mechanism that receives power directly and transmits motion to other parts. This motion could have induced or prevented the implementation of MEAs. In some circumstances there may be overlaps or interconnections among those aspects. For example, an aspect that was missing (e.g., capacity) could be considered as a hindrance but if it were present it could be considered a booster. These barriers and facilitators are referred to as drivers.

After conducting semi-structured interviews in Colombia, Kenya, and Ukraine and triangulating information with global experts, 10 drivers with the potential of helping or hindering the inception of MEAs in these three LMICs were identified:

1. *Capacity*: the institutional or individual capacity of the health system to regulate, collect, monitor, and evaluate data for estimating volumes in the case of financial schemes and to assess evidence in the case of performance-based agreements as well as regulatory capacity to aggregate demand, homogenize clinical care, determine level of knowledge or awareness on the use of MEAs, etc.
2. *Existence of clear rules*: the need to have clear rules, roles, and responsibilities within the health sector, especially in terms of payers and manufacturers, and also the need for a well-planned implementation plan, binding power of decisions made, standard operation procedures, pre-established goals and outcomes, and ex-ante and ex-post negotiation adjustment rules.

[1] Participant # 2 from Kenya
[2] Participant # 1 from Colombia
[3] Participant # 4 from Colombia
[4] Participant # 3 from Kenya

3. *Political support:* goes beyond support from governments or politicians and refers to social acceptance and acceptability from different stakeholders of MEAs as a policy solution (including MEAs on the policy agenda, formulation, and implementation); also considers the policy process, coalitions and networks, financial support, and policy champions.
4. *Local context:* intrinsic characteristics at the country level, such as level of income, market size, market ability to aggregate or negotiate, political stability, level of fragmentation, previous local successes, international cooperation, and level of coordination.
5. *Perception:* MEAs are not magic bullets, but rather are a disposable policy tool to payers and manufacturers. Perception includes usefulness perception, perception of complexity of MEA implementation, market attractiveness perception from payers and manufacturers, perception of feasibility (successful experiences from other similar countries), and perception of limitations of MEAs.
6. *Cultural factors:* local characteristics that may promote or prevent MEA implementation, such as resistance/willingness to change or innovate, levels of corruption, culture and tradition of transparency/accountability, level of trust among key stakeholders, attitudes toward big pharma, and attitudes toward the public and private sectors.
7. *Evidence related:* the sufficiency and quality of available evidence regarding a new drug, real-world evidence, and evidence on cost-effectiveness and patient eligibility criteria.
8. *Risk bearing attitudes:* take into consideration risk attitudes from payers or manufacturers (neutral, averters, and seekers); the need for assurance that heavy losses would be compensated; risk attitudes toward noncompliance with agreement; potential risk of affecting international or portfolio revenues; and risk attitudes toward uncertainty.
9. *Uncertainty issues:* take into consideration the possibility of generalizability/extrapolation of clinical results into local population, uncertainty of real efficacy/effectiveness, safety, value of innovation, other structural factors that may influence performance/outcomes, eligibility, and long-term performance and financial impacts.
10. *Transparency requirements:* take into consideration how transparency requirements (e.g., data disclosure on quality, safety, efficacy, price agreements) by law or cultural may affect negotiations; issues about transparency of pricing or confidential agreements; competition; publicly released information; and information on rebates and discounts.

Table 4 presents the operational definition of each driver and responses from participants.

Table 4. The drivers for the implementation of MEAs

Driver	Characteristics/factors that facilitate or hinder implementation of MEAs	Stakeholder quotes
Capacity	Regulatory, availability and quality of data, patient registry, ability to monitor and evaluate performance/outcomes, availability of local CPGs, HTAs or priority setting in place, centralized or pooled procurement, level of awareness on MEAs	**Capacity: lack of ability to monitor and evaluate** "*We have a big weakness in our information systems that do not allow us to a strict follow-up to see health outcomes after incorporating any technology. This limits us because we have risk agents that could be weak or strong but are not under just one negotiation instance and there is also a lack of information systems or experience to implement risk agreements that are more specific and need to have feedback in time*" - Colombia Medicines Regulatory Authority **Capacity: regulatory system limitations** "*The registration/regulatory processes required for new innovative patented medicines may be tedious though right now in our country we have adopted what we call the Expedited Registration Pathway...which may take a maximum of 3 months*" -Kenya Medicines Regulatory Authority **Capacity: lack of patient registry** "*If I understand you right, I think first of all we need to have a patient registry; we have electronic systems in order to calculate what amount of patients we have in reality for which we are buying such high cost treatment*" -Ukraine Ministry of Health
Existence of clear rules	Legislation, roles and responsibilities, sources of funding, SOPs, roadmap for implementation, timelines, enforceability, pre-established goals and outcomes, price adjusting rules	**Existence of clear rules: roles and responsibilities** "*If you are negotiating and managing risk and you have a technology, it is easy to do that transfer from the technology. Discount for purchasing that technology or free goods, but if this is a collectable technology, to whom do you transfer that to? The Nation? Do you keep it? That is not too clear… there must be a better rule in that regard.*" -Colombia, market access expert **Existence of clear rules: legislation** "*On Price capping, it is not possible in this country because it is a liberalized economy....We tried to come up with principles for medicines pricing policy but our Constitution does not allow it*" -Kenya, National Medicines Regulatory Authority **Existence of clear rules: roles and responsibilities** "*And the legislation framework for this process must be clearly defined how the manage entry agreements need to be done, both for manufacturer and decision maker/payer; without the legislation framework, it cannot be established.*" -Ukraine, National Medical University
Political support	Policy agenda; political will; support from payers, manufacturers, or government; coalitions and networks; financial support; policy champions	**Political support: political will** "*The problem in Colombia is that our health system is very decentralized, decisions about purchase or acquisition of medications is not a decision directly from the central government but from liaisons, some kind of HMO that we have in the country, and that has been a difficulty at the time of implementing MEAs*" -Colombia, Ministry of Health **Political support: buy in for NCDs and UHC** "*The Ministry of Health having realized that NCDs in Kenya are an important issue… has already established a department … and there are those initiatives especially Access initiatives [with] Novartis and Roche. I think the biggest is the President's directive for universal health coverage*" -Kenya, National Medicines Regulatory Authority

Driver	Characteristics/factors that facilitate or hinder implementation of MEAs	Stakeholder quotes
Local context	Level of income, market size, ability to aggregate or negotiate, political stability, fragmentation, previous local successes, international cooperation, coordination	**Local context: coordination** "*We have bureaucratic ways of doing things especially in third world countries. Sometimes we have things on order and have difficulty in having them cleared on time and all that. That also brings problems sometimes in the supply chain.*" -Kenya, Faith-based Medicines Supply Agency **Local context: inability to negotiate** "*We have not done any negotiations; as a civil service, we have no influence on that; it's an international experience that exists, but in Ukraine it's not really practiced*" -Ukraine, Health Department **Local context: limited budget** "*Another thing, any pharmaceutical company wants to have programs for like 3 years; usually these programs are implemented for 3 years, so the state, the Ministry of Health, has to have guaranteed funds for these 3 years, so there is a guaranteed security platform that for 3 years we will have the money for this very disease or medicine; this budget has to be guaranteed for 3 years, not 1 year*" -Ukraine, Patient Association
Perception	Usefulness perception, perception of complexity, market attractiveness from both sides (payers and developers), successful experiences from similar countries, perception of limitations on MEAs	**Perception: potential limitations of MEAs** "*Erroneously managed entry agreements are considered as a delay in the payment from payers, better said, "I don't pay you until I know that this works" and this is a misunderstanding.*" -Colombia, Market Access **Perception: market attractiveness from both sides (payers and developers)** "*Obviously for Pharma, they have commercial interests; and anything that doesn't make business sense will not fly. For government, I mean I have sat in many task forces and committees with government. For government, anything that smells expensive will also not fly. If it sounds too expensive for our economy to support, then the government will start dragging its feet. Again it's the same thing with the insurers, whether it's public or private insurance, it's the same thing. If it smells expensive they will not buy into it very easily.*" -Kenya, Cancer Patient Association
Cultural factors	Resistance to change, corruption, culture of transparency, lack of trust among key stakeholders, attitudes toward big pharma, attitudes toward the public and private sectors	**Cultural factors: lack of trust among stakeholders** "*As the health system has some kind of problem of lack of public legitimacy and there is always a reform going on, or people in congress saying that they want to change everything and that could be a barrier, in my opinion.*" -Colombia, Ministry of Health **Cultural factors: lack of trust in government** "*The reality today in the country is that there is no trust between the government and the different agents, I am not going to talk about anyone in particular, but the level of trust is minimal, which doesn't allow to develop schemes that could be important around health outcomes for the population*" -Colombia, Medicines Access Expert **Cultural factors: corruption** "*In order to buy something from a multinational company, it's not only them that have to be compliant, it's also us (procurement agencies); we have to do due diligence, and we are also requested sometimes to pass through compliance and due diligence training….Due diligence is a huge risk, compliance is a huge risk, corruption is a huge risk; that all will top the price of the drugs* " -Ukraine, Medicines Supplier and Distributor

Driver	Characteristics/factors that facilitate or hinder implementation of MEAs	Stakeholder quotes
Evidence related	Sufficiency and quality of evidence, real-world evidence, evidence on cost effectiveness and patient eligibility	**Evidence related: lack of real-world evidence** "*All this, or any effort to have managed entry agreements implies to share information that is reliable, available, understandable, etc...*" -Colombia, National Pharmaceutical Industry Association **Evidence related: lack of evidence on patient eligibility** "*We don't have anything like that [MEAs], and if we do not know the real demand, and we don't know every patient that needs this medicine, it is very difficult to track the results, and we don't even have a chance if, for example, the efficacy is not proved, we cannot send/return back the lot*" -Ukraine, Health Department
Risk bearing attitudes	Risk attitudes from payers or manufacturers, assurance that heavy losses would be compensated, compliance with agreement, potential risk of affecting international or portfolio revenues, risk attitudes toward uncertainty	**Risk bearing attitudes: risk attitudes from payers and providers** "*it is true that people think that these packages are a lifesaver, first of all because the EPS could transfer part of the technical risk to the provider and second because the provider gains some resources in a package. But this has its own risks, the fact that when the provider sees at some point that the budget derived from that contract is constraining, they can offer less than what they committed to offer.*" -Colombia, National Pharmaceutical Industry Association **Risk bearing attitudes: limited local experience impacts risk attitudes from payers or manufacturers** "*[There is] limited experience in Kenya for such approaches and how might they work*" - Kenya, Insurer
Uncertainty issues	Uncertainty of real world (efficacy/ effectiveness), safety, value of innovation, other structural factors that may influence performance/outcomes, eligibility, long-term impact (performance and financial)	**Uncertainty: value of innovation** "*To really push the governors to understand the necessity of such a thing – first of all they should really evaluate and understand the value of innovation and these so called long term prospects of what will happen if we live without innovations here, innovative medicines*" - Kenya, Association of Innovative Pharmaceutical Producers **Uncertainty: high level of uncertainty of future performance** "*I have heard a little bit about MEAs, but I think that this is not the practice which we are using, and I think we have to introduce the practice when we have to, for instance, for high cost medicines, we have to put down when we will introduce these negotiations which we are talking about, then we will have to have some provisions that they will take risk in case, for instance, if the patient will die, for a period which was not stipulated, so they have to cover all the costs for such medicines*" -Ukraine, Ministry of Health
Transparency requirements	Issues about transparency of pricing or confidential agreements, competition, publicly released information, information on rebates and discounts	**Transparency requirements: competition** "*I would say competition is also playing a role in ensuring that some of these branded products are having their prices come down.*" -Kenya, Faith-based Medicines Supply Agency **Transparency requirements: lack of transparency in negotiation of agreements** "*Farmak and a few Ukrainian pharmaceutical companies had agreements on technology transfer with multinational companies for certain biosimilars, vaccines and specific diabetes medicines which were predominantly imported. After the joint manufacturing initiatives, the Ministry of Health (MOH) refused to buy medicines from domestic companies that produced these medicines under the technology transfer agreement...*" - Ukraine, Pharmaceutical Company

For a detailed list of findings from the peer-reviewed publications and their categories of analysis, see Appendix 4.

3.4 Convergence and divergence of findings

SMEs highlighted that performance-based agreements were more complex in nature and less likely to be implemented in LMICs. One SME remarked that performance-based agreements could simply be based on data from HICs that had a well-established and reliable data collection and analysis infrastructure. SMEs also acknowledged that although the terminology "managed entry agreements" and "risk-sharing schemes" was relatively new, some of the simpler financial instruments, such as discounts and price-volume agreements, have been implemented in LMICs.

SMEs concurred with the emergent drivers identified in this study. It was noted that there was overlap/interdependence between some of the categorization of drivers for the implementation of MEAs. With regard to transparency, SMEs cautioned that confidentially on price negotiations could be a barrier to the implementation of MEAs, as it was the nature of the confidentiality of agreements that facilitated reduced prices. That said, MEAs could be fully transparent in all other aspects of the agreement (e.g., where, when, what drug, what company), which provides an opportunity to learn from these experiences, especially when taking into consideration the lack of transparency that is tied to the perception of a lack of legitimacy/integrity or corruption.

4 DISCUSSION

Several limitations to our approach are worth considering. First, since this activity is exploratory in nature, we included articles publishing original data and literature reviews, which could result in overestimation of the number of existing agreements due to double counting. Nevertheless, the trends of our general findings concur with other published data (Kanavos et al 2017). Second, our study relied on publicly available and published data. Given confidentiality agreements between manufacturers and payers, it is likely that some schemes remain unpublished or are not in the public domain, and we may have missed those in our analysis. In addition, the terms surrounding MEAs have been gaining popularity within the past decade. We believe that some countries may have been using different taxonomies to describe such agreements; therefore, such studies may not have been included in this review.

Third, our findings suggest that there have been slightly more implemented financial schemes than performance-based schemes. SMEs agreed with this finding because performance-based agreements may require greater capacity because they tend to be more complex than financial agreements and require closer monitoring and evaluation In the case of performance-based agreements, coverage with evidence development seemed to be the most favored instrument for such agreements. We recognize the risk of publication bias that favors such agreements due to the higher number of retrieved publications in the US.

Despite its limitations, this work adds to the global knowledge on the use of MEAs as policy options for promoting sustainable access to on-patent drugs for NCDs. The literature review indicated that interest from policy makers and researchers in MEAs has increased in recent years, based on the increasing number of peer-reviewed publications. Most of these publications on MEAs report the experience of HICs, with European countries being the most prominent. Performance-based schemes were more predominant in North America. The majority of schemes reported in HICs covered treatments for NCDs, predominantly different types of cancer, and fewer focused on communicable conditions (i.e., ARVs for HIV/AIDS and the HPV vaccine).

It appears that a significant number of international NGOs and global advocacy groups have been working on diverse access strategies, some of which focus on raising awareness of TRIPS flexibilities to promote access to on-patent medicines for NCDs. It is worth noting that the level of involvement from international organizations and donors in MEAs still seems limited. More comprehensive approaches for NIDs have existed since 2009 and could be worth considering for NCDs. Overall, the geographical reach of medicines access programs (usually coupled with health worker capacity building and patient awareness initiatives) by pharmaceutical companies is quasi-global, reflecting the importance of market-driven approaches for policy action.

In the three case study LMICs, we observed a growing burden of NCDs, especially orphan conditions; cancer (breast, lung, colon); and CVD. In all three countries, health care is a fundamental right, but the countries are faced with competing priorities under well-intentioned but under-resourced UHC commitments. This challenge is compounded by nonsystematic priority setting and a growing middle class that demands expanded coverage. The lack of institutional capacity; a dearth of

accurate, meaningful data; a lack of standardized treatment protocols; and concerns about the high cost of innovative medicines and their long-term affordability were also mentioned as challenges for sustainable access to on-patent drugs for NCDs.

The level of awareness of and experience with MEAs in the case study countries was very limited. That said, Kenya has a longer tradition of centralized procurement and pooled purchasing for both infectious diseases and NCDs. In Ukraine and Colombia, there are existing but limited initiatives in place for infectious diseases, the most salient being the case of a purchasing agreement for drugs to treat Hepatitis C. Although health as human right is envisioned as an opportunity to advance UHC in all three countries, the *judicialization* for health care was a prominent finding only in Colombia.

While officials from the three countries are aware of the complexities of MEAs, a recent analysis found that they were frequently used primarily for HIV medications and to a lesser degree for cancer treatments, generally in middle-income countries (‘t Hoen et al 2018), but not for other NCDs. Price regulation using IRP and HTAs is seen as means to assist priority setting and better allocate constrained budgets, but it come with limitations. Therefore, there is an opportunity to explore those aspects that may promote or prevent the implementation of MEAs.

Limited awareness and familiarity with MEAs; competing interests of stakeholders; limited flexibility of budget allocation; the overall lack of institutional capacity (i.e., patient registries, electronic health records, standard treatment protocols); a lack of trust among key players; limited availability of quality data to inform risk sharing agreements; and the need for a well-planned implementation plan emerged as potential barriers. Cultural aspects such as a lack of transparency and trust, inherent resistance to change, and corruption are also potential barriers worth highlighting in these settings.

Ongoing health sector policy initiatives, including the reforms in Ukraine and Colombia, and the imminent establishment of central procurement bodies or value-based approaches may become platforms to incorporate MEAs in the near future. Building on existing HTAs and pricing practices, using more systematic priority setting, and learning from previous experiences that increased access to innovative medicines for infectious diseases were perceived as potential facilitators for MEAs.

Ten drivers emerged with the potential to help or hinder the inception of MEAs in these LMICs and were coded as *capacity, existence of clear rules, political support, local context, perception, cultural factors, evidence related, risk bearing attitudes, uncertainty issues,* and *transparency requirements*. However, our preliminary findings should be tested and refined in light of further research in this field.

5 IMPLICATIONS AND KEY MESSAGES FOR POLICY ACTION

Our preliminary findings indicate that interest in MEAs has increased exponentially in recent years, especially in HICs, based on the number of peer-reviewed publications retrieved. It is worth noting that there is little information on the use of MEAs as policy options for granting access to on-patent medicines for NCDs in LMICs. Beyond China, India, and Thailand, the level of documentation on MEAs appears to be very limited, and there is an opportunity through the Strengthening Global Knowledge on Access Solutions for Innovative Medicines initiative, supported by the WB and AAI, to disseminate our findings and provide technical assistance to other LMICs to strengthen their capacity for implementing MEAs in these settings.

Financial-based schemes were slightly more frequent than performance-based mechanisms. Arguably, this implies that it is more straightforward and feasible to negotiate prices and volumes and ex-ante agree on the level of risk to be borne by both parties (payers and manufacturers) than it is to pursue more complex, data-demanding mechanisms. Consequently, if there is interest in implementing MEAs in countries with limited capacity, financial-based agreements may be more feasible than performance-based agreements in the short run. The fact that performance-based schemes seemed to be more predominant in North America may point to structural, contextual, and cultural factors that should be considered, such as regulatory bans on price control in the US or the existing capacity to monitor and evaluate clinical outcomes within both the US and Canada.

The previous experience of many LMICs in granting access to drugs for infectious diseases may pave the way for incrementally embarking on MEAs for NCDs in these settings. It appears that a significant number of international NGOs and global advocacy groups are working on raising awareness of TRIPS flexibilities to promote access to on-patent medicines for NCDs, despite the complex political implications of doing so. The level of involvement in MEAs by international organizations and donors still seems limited. All of these findings may represent an opportunity for the WB, AAI, and manufacturers to seize global attention regarding the use of MEAs as potential solutions to sustainable access to on-patent medicines for NCDs and to promote further research to understand their perceptions/positions on MEAs as access solutions for NCDs.

More comprehensive approaches used in the past, such as those for NIDs, are worth considering for NCDs. Since the level of awareness of and experience with MEAs in LMICs seems very limited and the overall geographical reach of medicines access programs initiated by pharmaceutical companies is quasi-global, the importance of market-driven approaches could be considered; reshaping the balance of top-down (national regulations) vs. bottom-up (academic research) policy initiatives in LMICs could be a pathway to explore in the case of access for on-patent medicines for NCDs.

SMEs emphasized that performance-based agreements were more complex in nature and less likely to be implemented in LMICs. In such cases, performance-based agreements could simply be based on data from HICs that had a well-established and reliable data collection and analysis infrastructure. For example, data on clinical safety and effectiveness or real-world data on clinical effectiveness could be considered. SMEs also acknowledged that although the terminology “managed entry

agreements" and "risk-sharing schemes" was relatively new, some of the simpler financial instruments, such as discounts and price-volume agreements, have been implemented in LMICs.

Among the benefits of MEAs are that they serve as frameworks in decision making processes and provide an opportunity to standardize dosing requirements and minimize overuse of products, and they could potentially help mitigate the impact of increasing costs and create incentives for all involved parties (patients, payer, and manufacturer). However, as with any other intervention, they also come with caveats. MEAs may not address the high cost of medicines. There is a perception that tiered pricing is a disincentive for manufacturers to reduce prices. Once a financial agreement has been reached and a new negotiated price had been publicly released, this could lead to losses of revenue in the global marketplace due to the growing trend of using external reference pricing and the same countries of reference repeatedly.

Arguably, MEAs are also perceived as quick fixes to access barriers, and there is criticism about fairness for those patients with diseases that do not receive special sources of funding. In the case of price capping, if local competition arises it may undercut prices without of the need to implement resource- and labor-intensive mechanisms such as MEAs. If patients require longer courses of treatment, they may challenge the pre-agreed prices. Finally, the lack of compliance with clinical protocols and the inability to monitor and evaluate prescribed dosages once patients are granted access may lead to supplier-induced demand and higher drug expenditures, jeopardizing trust among payers and manufacturers.

The emergent drivers have implications for policy action in the three case study countries. There is a need to develop and establish a roadmap of processes, rules, and regulations to guide the inception of MEAs. This would be complemented by building health system capacity to implement and monitor the impact of MEAs by improving the quality and availability of data and evidence and mitigating risk. There is also a need to better understand the political economy of the policy making process as a whole by examining the political landscape, context, perception, and cultural factors and by addressing uncertainty regarding the real value of innovation. It is likely that the systematic use of HTAs may improve transparency and the trust of all stakeholders.

According to key informants, the desirability and willingness for payers and pharmaceutical companies to utilize MEAs has increased over time, but there is still resistance from both sides. The issue of growing public scrutiny with regard to national budgets for research and development and of medicine pricing and value-price trade-offs are worth considering for market access strategies as a whole. Some important questions remain and should be addressed by future global initiatives, such as how MEAs could address equity in access to medicines (horizontal vs. vertical) and the real impact or effectiveness of MEAs in relation to other types of medicines access approaches, such as community based, systems strengthening, and production.

6 REFERENCES

1. World Health Organization (2018). NCD Mortality and Morbidity. Last accessed January 25, 2018. www.who.int/gho/ncd/mortality_morbidity/en/.

2. Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, LaVange L, Marinac-Dabic D, Marks PW, Robb MA, Shuren J, Temple R, Woodcock J, Yue LQ, Califf RM. Real-World Evidence - What Is It and What Can It Tell Us? N Engl J Med. 2016 Dec 8;375(23):2293–2297.

3. Kanavos P, Ferrario A, Tafuri G, Siviero P. Managing Risk and Uncertainty in Health Technology Introduction: The Role of Managed Entry Agreements. Global policy. 2017 March; 8(S2):84–92.

4. Access Accelerated https://accessaccelerated.org/ (last accessed on April 13, 2018)

5. Drugs for Neglected Diseases initiative (DNDi). https://www.dndi.org/ (last accessed on April 13, 2018).

6. European Commission. Expert Panel on Effective Ways of Investing in Health. https://ec.europa.eu/health/expert_panel/home_en (last accessed on April 13, 2018).

7. European Union, 2018. Opinion on Innovative payment models for high-cost innovative medicines. Report of the Expert Panel on effective ways of investing in Health (EXPH). https://ec.europa.eu/health/expert_panel/sites/expertpanel/files/docsdir/opinion_innovative_medicines_en.pdf (last accessed on April 13, 2018).

8. Ferrario A and Kanavos P. April 2013. Managed entry agreements for pharmaceuticals: The European experience. EMiNet, Brussels, Belgium. http://eprints.lse.ac.uk/50513/ (last accessed on April 13, 2018).

9. Initiative for Medicines, Access & Knowledge. http://www.i-mak.org/ (last accessed on April 13, 2018).

10. International Federation of Pharmaceutical Manufacturers & Associations. https://www.ifpma.org/ (last accessed on April 13, 2018).

11. Kanavos P, Ferrario A, Tafuri G, Siviero P. Managing Risk and Uncertainty in Health Technology Introduction: The Role of Managed Entry Agreements. Global policy. 2017 March; 8(S2):84–92.

12. Knoema: Ukraine - Out of pocket expenditure as a share of total health expenditure. https://knoema.com/atlas/Ukraine/topics/Health/Health-Expenditure/Out-of-pocket-expenditure-as-a-share-of-total-health-expenditure (last accessed on April 18, 2018)

13. Medicins du Monde. http://www.medecinsdumonde.org/en (last accessed on April 13, 2018).

14. Medicins Sans Frontieres (MSF) http://www.msf.org/ (last accessed on April 13, 2018).

15. Medicines law and policy – tools. https://medicineslawandpolicy.org/tools/ (last accessed on April 13, 2018)

16. Ministry of Health 2014. Kenya Health Policy 2014–2030

17. Lekhan VN, Rudiy VM, Shevchenko MV, Nitzan Kaluski D, Richardson E. Ukraine: Health system review. Health Systems in Transition, 2015; 17(2): 1–153

18. National Administrative Department of Statistics (DANE), Colombia. http://www.dane.gov.co/reloj/ (last accessed on April 4, 2018)

19. Ombudsman's Office Colombia. http://www.defensoria.gov.co/es/nube/enlosmedios/5911/Cada-35-minutos-se-presenta-una-tutela-por-la-salud.htm (last accessed on April 13, 2018)

20. Organisation for Economic Co-operation and Development (OECD). http://www.oecd.org (last accessed on April 13, 2018).

21. Organisation for Economic Cooperation and Development (OECD), 2016. OECD Review of Health Systems: Colombia. https://read.oecd-ilibrary.org/social-issues-migration-health/oecd-reviews-of-health-systems-colombia-2015_9789264248908-en#page3 (last accessed on April 17, 2018)

22. Organisation for Economic Cooperation and Development (OECD), 2017. New Health Technologies. Managing Access, Value and Sustainability. DOI:http://dx.doi.org/10.1787/9789264266438-6-en. http://www.oecd.org/health/health-systems/managing-new-technologies-in-health-care-9789264266438-en.htm (last accessed April 2018)

23. 't Hoen EFM, Veraldi J, Toebesc B, Hogerzeila HV. Bull World Health Organ 2018;96:185–193. doi:http://dx.doi.org/10.2471/BLT.17.199364

24. Union for International Cancer Control (UICC). https://www.uicc.org/ (last accessed on April 13, 2018).

25. United Nations Department of Social and Economic Affairs (UN DESA). https://esa.un.org/unpd/wpp/Download/Standard/Population/ (last accessed on April 4, 2018)

26. Vitry A, Roughead E. Managed entry agreements for pharmaceuticals in Australia. Health Policy. 2014 Sep;117(3):345-52. doi: 10.1016/j.healthpol.2014.05.005. Epub 2014 Jun 2.

27. World Bank Open Data on Ukraine. https://data.worldbank.org/country/Ukraine (last accessed on April 4, 2018)

28. World Bank Open Data on GDP. https://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD (last accessed on April 13, 2018).

29. World Bank Open Data on Health Expenditure. https://data.worldbank.org/indicator/SH.XPD.TOTL.ZS (last accessed on April 13, 2018).

30. World Health Organization 2014. Noncommunicable diseases country profiles 2014. http://www.who.int/nmh/publications/ncd-profiles-2014/en/ (last accessed on April 13, 2018).

31. World Health Organization. Toolbox for access to essential medicines and health technologies for NCDs. http://www.who.int/nmh/ncd-tools/target-9/en/ (last accessed on April 13, 2018)

32. World Health Organization, 2014. Countries: Ukraine. http://www.who.int/countries/ukr/en/ (last accessed on April 17, 2018).

APPENDICES

Appendix 1: Search terms

Improved access:

(financing mechanism*) OR financial mechanism*) OR risk sharing) OR managed entry agreement*) OR performance based agreement*) OR patient assistance program*) OR patient access program*) OR mecanismo de financiacion) OR mecanismos de financiacion) OR mecanismo de financiamiento) OR mecanismos de financiamiento) OR distribucion de riesgo*) OR reparto de riesgo*) OR basados en el rendimiento) OR basado en el rendimiento) OR programa de asistencia al paciente) OR programa de asistencia para paciente*) OR programa de ayuda al paciente) OR programa de ayuda para paciente*) OR programa de accesibilidad para pacientes) OR mecanisme de financement) OR mecanisme financier) OR mecanismes de financement) OR mecanismes financiers) OR partage des risques) OR mieux geree) OR programme d'aide aux patients) OR programmes d'assistance aux patients) OR programme innovant acces des patients) OR d'acces destine aux patients

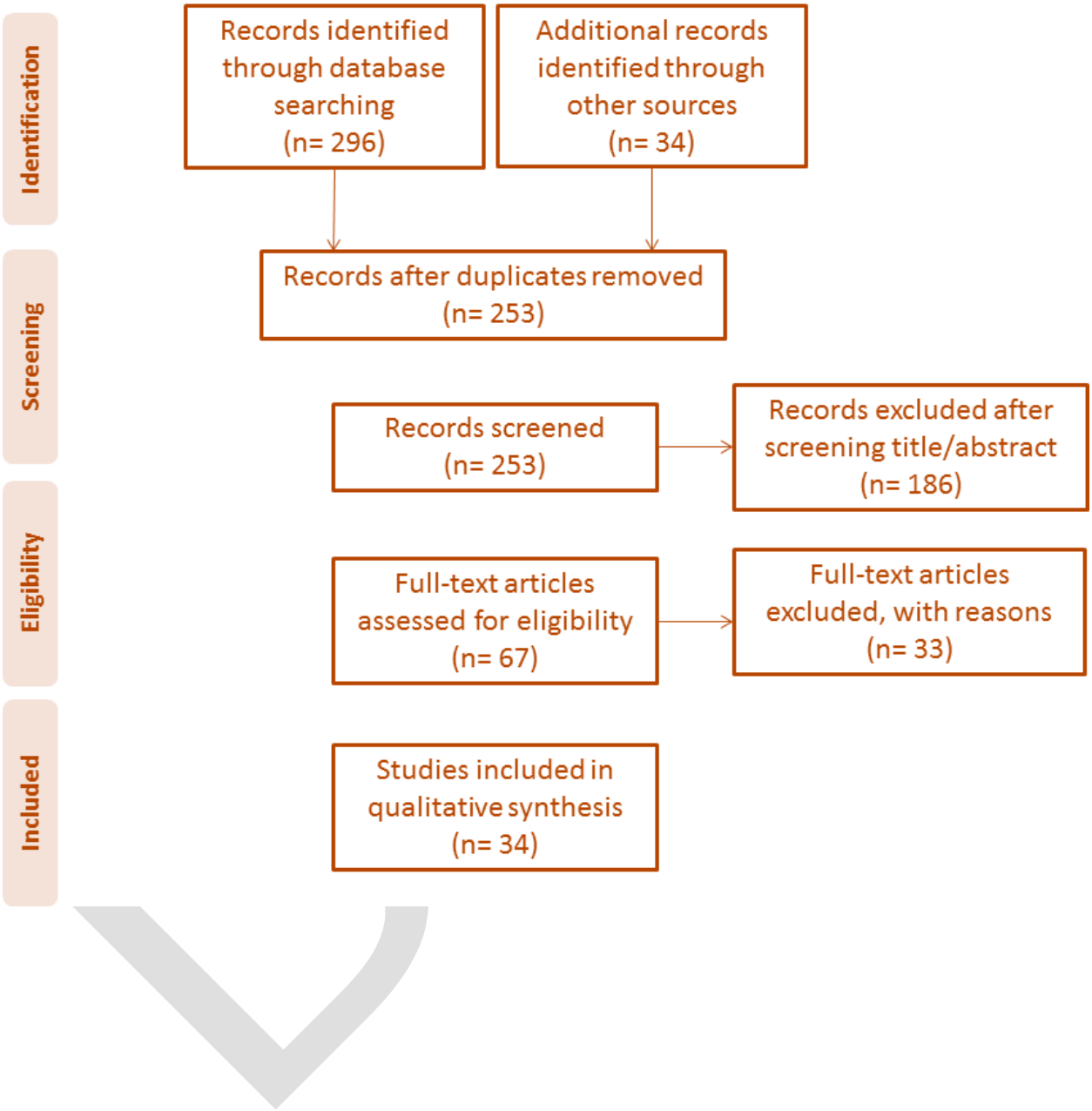
Risk-sharing agreements:

(patented medicines) OR on-patent) OR on patent) OR on-patent medicin*) OR on patent drug*) OR patented drug*) OR generic medicine*) OR generic drug*) OR off-patent) OR off patent) OR off-patent medicin*) OR off patent drug*) OR patent*) OR medicina de patent*) OR medicamentos protegidos por patente*) OR medicamento generic*) OR medicamentos generic*) OR medicaments brevet*) OR medicament brevet*) OR brevet*) OR drogues brevet*) OR medicament brevet*) OR generiques

Patented medicines:

(improve access) OR improving access) OR improved access) OR market access) OR improve outcome*) OR improved outcome*) OR improve result*) OR improved result*) OR mejor acceso) OR mejoramiento del acceso) OR acceso mejorado) OR acceso al mercado) OR acceso a los mercados) OR resultado mejorado) OR mejores resultados) OR resultados mejorados) OR meilleurs acces) OR meilleur acces) OR ameliorer l'acces) OR d'ameliorer l'acces) OR l'acces au marche) OR acces au marche) OR meilleurs resultats) OR resultats ameliores) OR ameliorer les resultats) OR meilleur resultat

Appendix 2: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) diagram of systematic literature search



Appendix 3: Systematic literature review: List of selected studies included in qualitative analysis

List of 34 selected studies

1. Acosta A, Ciapponi A, Aaserud M, Vietto V, Austvoll-Dahlgren A, Kösters JP, Vacca C, Machado M, Diaz Ayala DH, Oxman AD. Pharmaceutical policies: effects of reference pricing, other pricing, and purchasing policies. Cochrane Database Syst Rev. 2014 Oct 16;(10):CD005979. doi: 10.1002/14651858.CD005979.pub2.
2. Adamski J, Godman B, Ofierska-Sujkowska G, Osińska B, Herholz H, Wendykowska K, Laius O, Jan S, Sermet C, Zara C, Kalaba M, Gustafsson R, Garuolienè K, Haycox A, Garattini S, Gustafsson LL. Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers. BMC Health Serv Res. 2010 Jun 7;10:153. doi: 10.1186/1472-6963-10-153.
3. Binagwaho A, Wagner CM, Gatera M, Karema C, Nutt CT, Ngabo F. Achieving high coverage in Rwanda's national human papillomavirus vaccination programme. Bull World Health Organ. 2012 Aug 1;90(8):623-8. doi: 10.2471/BLT.11.097253. Epub 2012 May 23.
4. Carlson JJ, Garrison LP Jr, Sullivan SD. Paying for outcomes: innovative coverage and reimbursement schemes for pharmaceuticals. J Manag Care Pharm. 2009 Oct;15(8):683-7.
5. Carlson JJ, Gries KS, Yeung K, Sullivan SD, Garrison LP Jr. Current status and trends in performance-based risk-sharing arrangements between healthcare payers and medical product manufacturers. Appl Health Econ Health Policy. 2014 Jun;12(3):231-8. doi: 10.1007/s40258-014-0093-x.
6. Carlson JJ, Sullivan SD, Garrison LP, Neumann PJ, Veenstra DL. Linking payment to health outcomes: a taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers. Health Policy. 2010 Aug;96(3):179-90. doi: 10.1016/j.healthpol.2010.02.005. Epub 2010 Mar 11.
7. Cheema PK, Gavura S, Migus M, Godman B, Yeung L, Trudeau ME. International variability in the reimbursement of cancer drugs by publically funded drug programs. Curr Oncol. 2012 Jun;19(3):e165-76. doi: 10.3747/co.19.946.
8. Coulton L, Annemans L, Carter R, Baltazar Herrera M, Thabrany H, et al. Outcomes-based Risk-sharing Schemes: Is There a Potential Role in the Asia-Pacific Markets?. Health outcomes research in medicine. 2012 November; 3(4):e205-e219.
9. Drummond M. When do performance-based risk-sharing arrangements make sense? Eur J Health Econ. 2015 Jul;16(6):569-71. doi: 10.1007/s10198-015-0683-z.
10. Faulkner SD, Lee M, Qin D, Morrell L, Xoxi E, Sammarco A, Cammarata S, Russo P, Pani L, Barker R. Pricing and reimbursement experiences and insights in the European Union and the United States: Lessons learned to approach adaptive payer pathways. Clin Pharmacol Ther. 2016 Dec;100(6):730-742. doi: 10.1002/cpt.508. Epub 2016 Oct 22. Review.
11. Ferrario A, Arāja D, Bochenek T, Čatić T, Dankó D, Dimitrova M, Fürst J, Greičiūtė-Kuprijanov I, Hoxha I, Jakupi A, Laidmäe E, Löblová O, Mardare I, Markovic-Pekovic V, Meshkov D, Novakovic T, Petrova G, Pomorski M, Tomek D, Voncina L, Haycox A, Kanavos P, Vella Bonanno P, Godman B. The Implementation of Managed Entry Agreements in Central and

Eastern Europe: Findings and Implications. Pharmacoeconomics. 2017 Dec;35(12):1271-1285. doi: 10.1007/s40273-017-0559-4.
12. Ferrario A, Kanavos P. Dealing with uncertainty and high prices of new medicines: a comparative analysis of the use of managed entry agreements in Belgium, England, the Netherlands and Sweden. Soc Sci Med. 2015 Jan;124:39-47. doi: 10.1016/j.socscimed.2014.11.003. Epub 2014 Nov 5.
13. Garrison LP Jr, Towse A, Briggs A, de Pouvourville G, Grueger J, Mohr PE, Severens JL, Siviero P, Sleeper M. Performance-based risk-sharing arrangements-good practices for design, implementation, and evaluation: report of the ISPOR good practices for performance-based risk-sharing arrangements task force. Value Health. 2013 Jul-Aug;16(5):703-19. doi: 10.1016/j.jval.2013.04.011. Epub 2013 Jul 19.
14. Goble JA, Ung B, van Boemmel-Wegmann S, Navarro RP, Parece A. Performance-Based Risk-Sharing Arrangements: U.S. Payer Experience. J Manag Care Spec Pharm. 2017 Oct;23(10):1042-1052. doi: 10.18553/jmcp.2017.23.10.1042.
15. Kaló Z, Annemans L, Garrison LP. Differential pricing of new pharmaceuticals in lower income European countries. Expert Rev Pharmacoecon Outcomes Res. 2013 Dec;13(6):735-41. doi: 10.1586/14737167.2013.847367.
16. Kanavos P, Ferrario A, Tafuri G, Siviero P. Managing Risk and Uncertainty in Health Technology Introduction: The Role of Managed Entry Agreements. Global policy. 2017 March; 8(S2):84–92.
17. Kawalec P, Sagan A, Stawowczyk E, Kowalska-Bobko I, Mokrzycka A. Implementation of the 2011 Reimbursement Act in Poland: Desired and undesired effects of the changes in reimbursement policy. Health Policy. 2016 Apr;120(4):356-61. doi: 10.1016/j.healthpol.2016.02.010. Epub 2016 Mar 8.
18. Kibicho J, Pinkerton SD. Multiple drug cost containment policies in Michigan's Medicaid program saved money overall, although some increased costs. Health Aff (Millwood). 2012 Apr;31(4):816–26. doi: 10.1377/hlthaff.2011.0246.
19. Lineberry N, Snyder E, Gunda S. Market watch: pricing strategies for emerging markets. Nat Rev Drug Discov. 2011 Aug 1;10(8):567. doi: 10.1038/nrd3519.
20. Lu CY, Lupton C, Rakowsky S, Babar ZU, Ross-Degnan D, Wagner AK. Patient access schemes in Asia-pacific markets: current experience and future potential. J Pharm Policy Pract. 2015 Feb 16;8(1):6. doi: 10.1186/s40545-014-0019-x. eCollection 2015.
21. Moon S, Jambert E, Childs M, von Schoen-Angerer T. A win-win solution?: A critical analysis of tiered pricing to improve access to medicines in developing countries. Global Health. 2011 Oct 12;7:39. doi: 10.1186/1744-8603-7-39.
22. Morgan S, Daw J, Thomson P. International best practices for negotiating 'reimbursement contracts' with price rebates from pharmaceutical companies. Health Aff (Millwood). 2013 Apr;32(4):771-7. doi: 10.1377/hlthaff.2012.1268.
23. Nazareth T, Ko JJ, Sasane R, Frois C, Carpenter S, Demean S, Vegesna A, Wu E, Navarro RP. Outcomes-Based Contracting Experience: Research Findings from U.S. and European Stakeholders. J Manag Care Spec Pharm. 2017 Oct;23(10):1018–1026. doi: 10.18553/jmcp.2017.23.10.1018.

24. Neumann PJ, Chambers JD, Simon F, Meckley LM. Risk-sharing arrangements that link payment for drugs to health outcomes are proving hard to implement. Health Aff (Millwood). 2011 Dec;30(12):2329-37. doi: 10.1377/hlthaff.2010.1147.
25. Pauwels K, Huys I, Vogler S, Casteels M, Simoens S. Managed Entry Agreements for Oncology Drugs: Lessons from the European Experience to Inform the Future. Front Pharmacol. 2017 Apr 4;8:171. doi: 10.3389/fphar.2017.00171. eCollection 2017.
26. Piatkiewicz TJ, Traulsen JM, Holm-Larsen T. Risk-Sharing Agreements in the EU: A Systematic Review of Major Trends. PharmacoEconomics Open. 2017.
27. Sruamsiri R, Ross-Degnan D, Lu CY, Chaiyakunapruk N, Wagner AK. Policies and programs to facilitate access to targeted cancer therapies in Thailand. PLoS One. 2015 Mar 23;10(3):e0119945. doi: 10.1371/journal.pone.0119945. eCollection 2015.
28. Stéphenne J. Vaccines as a global imperative—a business perspective. Health Aff (Millwood). 2011 Jun;30(6):1042-8. doi: 10.1377/hlthaff.2011.0338.
29. Tekinturhan E, Audureau E, Tavolacci MP, Garcia-Gonzalez P, Ladner J, Saba J. Improving access to care in low and middle-income countries: institutional factors related to enrollment and patient outcome in a cancer drug access program. BMC Health Serv Res. 2013 Aug 10;13:304. doi: 10.1186/1472-6963-13-304.
30. Towse A. Value based pricing, research and development, and patient access schemes. Will the United Kingdom get it right or wrong? Br J Clin Pharmacol. 2010 Sep;70(3):360-6. doi: 10.1111/j.1365-2125.2010.03740.x.
31. Vitry A, Roughead E. Managed entry agreements for pharmaceuticals in Australia. Health Policy. 2014 Sep;117(3):345-52. doi: 10.1016/j.healthpol.2014.05.005. Epub 2014 Jun 2.
32. Wonder M, Backhouse ME, Sullivan SD. Australian managed entry scheme: a new manageable process for the reimbursement of new medicines? Value Health. 2012 May;15(3):586-90. doi: 10.1016/j.jval.2012.02.004. Epub 2012 Apr 11.
33. Yeung K, Li M, Carlson JJ. Using Performance-Based Risk-Sharing Arrangements to Address Uncertainty in Indication-Based Pricing. J Manag Care Spec Pharm. 2017 Oct;23(10):1010-1015. doi: 10.18553/jmcp.2017.23.10.1010.
34. Yu JS, Chin L, Oh J, Farias J. Performance-Based Risk-Sharing Arrangements for Pharmaceutical Products in the United States: A Systematic Review. J Manag Care Spec Pharm. 2017 Oct;23(10):1028-1040. doi: 10.18553/jmcp.2017.23.10.1028.

Appendix 4: Emergent drivers for implementation of MEAs (Systematic review findings)—summary

Category	Enabling Factors	Hindering factors
Capacity	Good administrative/information systems to track implementation of the coverage with evidence scheme	Lack of adequate systems to collect a wide range of data, reliable information systems, and databases
	Ability to evaluate results rapidly	Lack of operational expertise
	Available human and financial resources for monitoring financial transactions and patients outcomes	Administrative burden due to lack administrative capacity in hospitals to manage schemes
	Established bodies that address drug coverage, cost-effectiveness, etc.	Labor and resource intensive data collection practices
	Availability of health information systems to determine if P/V schemes are meeting expected outcomes	
	A system to monitor patients	
	Online patient registries allow for continuous monitoring	
	Reliable system that allows for data collection in real-life clinical settings to answer some of the questions contributing to uncertainty	
	Flexible databases with capacity to collect enough information to evaluate schemes	
	Negotiating power due to experience with technology assessment	
	Manufacturers' ability to measure outcomes in a short time frame, availability of multiyear clinical data, products with clinical advantages over low-cost competitors	
	Existence of pharmaceutical benefits program	
	Dedicated resources to improve program infrastructure	
Clear rules	Available mechanism for adjusting price or level of reimbursement when expected endpoints are not met	No framework or guidelines for implementation of MEA
	Existing legal requirements surrounding data protection at the patient level	Unclear scheme details (e.g., clinical endpoints, price negotiations)
	Processes that allow for rapid patient enrollment	Difficulty agreeing on specific details and intended outcomes of the scheme
	Having clear goals linked to specific pricing and reimbursement decisions	Poor/misalignment of data needs and expectations between partners
	Selecting clear, measureable, realistic, objective outcome measures	Unclear eligibility criteria for patients
	Compliance/enforceability: Companies fined if RSSs conditions are not met	Lack of standardized information on patient access schemes
	Early/sustained involvement of health economics and outcomes research in the scheme design and implementation stages	Hinder future implementation of MEA: Often prices are not renegotiated after data collection during MEA and clinical evidence is no longer assessed at the completion of the MEA
	Clear contract terms and definitions and evaluations of performance metrics	Risk (in risk-sharing) is not clearly defined
	Discipline when negotiating contracts–need to make sure they are fair, straightforward, and clearly determine who will be responsible for burden of proof	
	Informal agreement between manufacturer and payer indicating that the generated data will be used for future coverage decisions	
	High ethical standards for implementation and evaluation of schemes	

Category	Enabling Factors	Hindering factors
	For payers, clear payment method; unequivocal outcome measure Ability to address both financial and non-financial issues in same agreement	
Cultural	Schemes are culturally accepted Country preference for a specific type of agreement	Countries may move away from performance-based risk sharing agreements due to lack of transparency, complex nature of agreement, and language barriers that make it difficult to track impact Lack of trust among payers, manufacturers, and health care providers
Evidence	Increased reporting and available data on pricing and reimbursement Need for real-world evidence at the time of drug approval Evidence of positive outcome Patient information already available in administrative claims databases	Performance-based scheme: Limited evidence of effectiveness makes it difficult to analyze schemes Lack of data on patient and institutional factors that affect patient outcomes Performance-based agreements: • Lack of outcome data to use for further analysis to determine other populations where the drug might be useful • Very little evidence to support claims made may discourage payers from investing in diseases that are not strongly evidence based • Lack of availability, consistency, and reliability of patient data (including poor selection of appropriate conditioning outcomes) • Small treatment population may lead to delays in data collection Initial overpricing by drug companies in anticipation of drug cost lowering once evidence is collected
Perception	Low administrative burden Schemes are simple to monitor and evaluate Scheme provides opportunity to standardize dosing requirements and minimize overuse of products Existing evidence framework to provide guidance in decision making process Value in health care: Potential to address increasing costs Incentives for all the involved parties (patients, payer, manufacturer) Manufacturers motivated by potential access and reimbursement	Steps involved in risk sharing can be costly (e.g., administrative cost, operational cost) High cost of medicines even if MEA is implemented Tiered pricing: 1) lack of strong incentives for producers to reduce tiered prices; 2) absence of competition; 3) overly low prices leading to no competition Financial responsibility of payers to cover significant portion of drug's development cost Potential loss of revenue globally due to external reference pricing Sustainability: Many MEAs right now are designed as quick fixes Price caps: If local competition arises it may undercut prices. Also, if patients require longer courses of treatment they may challenge the price. Lack of compliance with prescribed dosages once patients receive access may lead to increased drug expenditure by payers Criticism about fairness for patients with diseases that don't receive special funding Lack of standard definition and perception of MEAs As MEAs become more popular, manufacturers may raise entry prices in anticipation Lengthy negotiations due to unwillingness to compromise

Category	Enabling Factors	Hindering factors
		Lack of standardization in implementation of MEAs in different countries, including different pricing and/or reimbursement arrangements for the different indications of a same medicine
Political	Champions leading the way Established small group or defined body/organization (decision makers) to agree on a scheme Political support/will to engage in these schemes Government offers incentives to pharmaceutical companies Multisectoral stakeholder engagement Stakeholder willingness to discuss schemes to improve patient access Power to adapt the product price depending on consumer's willingness/ability to pay Desire of stakeholders to assess or convey the value of a drug (as opposed to solely cost)	Potential change of administration (government) with whom agreement is made if follow-up is long
Risk bearing	Low risk for manufacturers: patients willing to pay due to no local competition in the market. Lower cumulative drug expenditure for insurers (reference drugs and cost sharing drugs) Payers motivated by potential improvements to health along with cost and financial risk reduction Assurance to payers that over-spend will be covered by the pharmaceutical company Incentives to payers if MEA is implemented to control costs without negatively impacting patients Scheme gives manufacturers reassurance on initial price and financial gains	Risk for the manufacturer if competitors take advantage of accumulated knowledge and data through MEA
Structural	Economic country context (e.g., UK economic crisis of 2008 helped catalyze the implementation of value-based pricing agreements) Competitive pressure for costly drugs Patient, physician, and pharmaceutical company pressure on governments to fund costly new treatments Large HICs have more power to achieve heavily discounted confidential agreement. Multicountry collaboration to procure larger batches of drugs at a discount Cooperation among institutions, their governments, NGOs, and manufacturers of diagnostic and research equipment No available treatments for existent clinical needs	Decentralized health and finance systems may make implementation difficult Limited budget For payers in the US, risk-sharing agreements are challenging due to market fragmentation.
Transparency	Improved price transparency of payers: country shares information on pricing/reimbursement policies and price levels	Confidential contracts are less appealing if HICs also achieve substantial confidential discounts Lack of transparency between manufacturers and health insurers Lack of transparency with rebates and discounts prevents physician associates from accurately monitoring drug budgets Lack of a transparent decision making process and on what is actually being implemented

Category	Enabling Factors	Hindering factors
		When countries keep agreements confidential: • There is little room for others to engage and improve • It may result in duplication of data collection efforts • There is limited information on technicalities and outcomes, which restricts cross-country learning • Price confidentiality doesn't allow the impact of financial agreements on price and budget to be assessed • It is difficult to analyze trends and the impact of programs and use those findings to inform future decisions • There is no standard definition of what is fair/normal price in low-income countries and it is difficult to assess the cost-effectiveness of pharmaceuticals without transparent information about the price of the comparator drug
Uncertainty	Uncertainty about medicines From payer point of view: Likelihood that the drug will be paid by the marketing authorization holder and not the public payer	Benefits for payers may be in distant future, no significant effect in the immediate future Uncertainty of budget impact for payers and use of economic modeling Uncertainty from a manufacturer's perspective about cost-effectiveness of drugs Outcomes guarantees could represent a high level of uncertainty in real-world effectiveness if expected and resulted outcomes are different Performance-based agreements: • Uncertainties surrounding which patients will be treated (i.e., eligibility) and what the impact will be • Lack of evidence on long term impact/ uncertainty about clinical benefits of medicine Scheme doesn't meet needs of manufacturer or payer Uncertainty about outcomes poses a high risk for the manufacturer Uncertainty from a manufacturer's perspective about the way the evidence is assessed