Project Title: Next Generation Health Technology Assessment to support patient-centered, societally oriented, real-time decision-making on access and reimbursement for health technologies throughout Europe

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Description of the deliverable	Representatives of healthcare payers and policymakers from EU-15 and non-EU-15 Member States will be invited to take part in a policy workshop. First a pre-conference survey will collect the participants' experience with the implementation and operation of existing payment models in their own jurisdiction. Survey findings and the results from task 4.4.2. will be presented at the workshop, followed by stakeholder group discussions on I) the rationale of introducing new payment models, ii) the transferability of models evaluated in task 4.4.2 and iii) the feasibility of harmonising these models with current national or regional models. Special emphasis will be paid to influence of payment models on equity in health, how these models can improve equal access to new technologies in lower income compared to higher income countries. A post-conference survey will explore stakeholder perspectives on innovative payment schemes and key facilitators and barriers in their local implementation. Pre-workshop survey, workshop conclusions and post workshop survey
Key words	Payment Models, Outcome-based Reimbursement,

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EXECUTIVE SUMMARY

This study aimed to gain a greater understanding of the current use, implementation barriers and future preferences for reimbursement and payment models in Central and Eastern Europe (CEE) and Middle East (ME) countries. Between May and July 2021, a survey was sent out to experts in pricing and reimbursement, most notably those with current or former payer experience from CEE and ME countries. The survey questioned the current use of and future preferences for reimbursement and payment models using Likert scales, and the perceived barriers through open questions. Results were analysed using descriptive statistics. In total, 27 healthcare payer experts completed the survey. Our inquiry shows that financial-based reimbursement models, specifically discounts, are currently applied most in CEE and ME countries. The respondents indicated to prefer using outcome-based reimbursement models more in the future, where particularly pay-for-outcome models were preferred. Upfront payments are currently the most frequently applied payment model in CEE and ME countries. However, delayed payment models are preferred to be applied more often. The respondents especially preferred payment at outcome-achieved models to be applied more often in the future.

Barriers hindering the implementation for outcome-based reimbursement models are mostly related to IT and data infrastructure, the transaction costs, and governance. Barriers perceived with delayed payments are mostly related to transaction costs, IT and data infrastructure and payments structures. This overview can provide healthcare payers from CEE and ME countries with future direction when implementing innovative reimbursement and payment models.

SECTION 1

REIMBURSEMENT AND PAYMENT MODELS IN CENTRAL AND EASTERN EUROPEAN AND MIDDLE EASTERN COUNTRIES: CURRENT USE AND FUTURE OUTLOOK

1. Introduction

Pharmaceutical innovations associated with high prices and large uncertainties are increasingly challenging the sustainability of healthcare reimbursement systems (1–6). Given that healthcare budgets are finite, competent authorities for pricing and reimbursement (CAPR), such as healthcare payers, governmental organizations, or health technology assessment (HTA) agencies, are challenged to find solutions for optimizing expenditure of, and access to, medicines (2–4,7). Consequently, innovative arrangements between CAPR and drug manufactures aiming to enable access to new medicines while sharing risks due to uncertainty are gaining relevance (4,7–12).

These arrangements can exist in a variety of forms and combinations and are often referred to as 'managed entry agreements' and/or 'risk-sharing arrangements' (2,12–14). They can be defined as "arrangements between drug manufacturers and CARP that ensure access to coverage or reimbursement of a drug under specified conditions" (2,12–14). Such agreements can be further divided into arrangements that relate to pricing and reimbursement status (reimbursement models) and the way payments are organized (payment models). Reimbursement models are usually broken down into two main categories: purely financial agreements (e.g., discounts) and outcome-based agreements (e.g., pay-for-performance) (2,15–17). Payment models can be structured such that the therapy is paid upfront –possibly with rebates when a result is not achieved– or with a delayed or spread-out payment –possibly only after certain (prespecified) results have been achieved (2,15,16).

To mitigate high upfront payments and to answer remaining uncertainties that often go hand in hand with the introduction of innovative therapies, outcome-based reimbursement models and delayed payment models have especially been seen as promising alternatives to the more commonly used financial-based and upfront agreements (2,17,18). However, there is considerable variation between countries in how payment and reimbursement systems are organized (19). Research shows that the applicability of these models therefore might differ between countries (3,17,19).

A lot of attention has been given to different models and their implementation feasibility in high-income countries (8,9,17,20). However, little is known on how transferable these models are to lower income countries such as Central and Eastern Europe (CEE) and Middle East (ME) countries which are facing the same challenges as high-income countries (1,21,22). The population health status in these countries is generally poorer compared to high-income countries and healthcare resources are more limited. Most

CEE and ME countries often do not have a clear roadmap for HTA implementation and have a much greater social opportunity cost of adopting inappropriate health technologies and introducing inappropriate decisions on pricing and reimbursement (1). Given that the way in which countries organize their healthcare system and funding and the way decisions are made have an impact on the success of the implementation of payment and reimbursement models, a greater understanding is required of the compatibility/transferability of these models to CEE and ME countries.

This study was designed to gain understanding of and to provide future directions for the implementation of innovative payment and reimbursement models in CEE and ME countries. Through a survey, the experience, preferences, and barriers reported by stakeholders experienced in pricing and reimbursement from CEE and ME countries towards the current and future use of (innovative) payment and reimbursement models was investigated.

2. Methods

2.1. Survey participant selection

The survey was aimed at experts in pricing and reimbursement, most notably those with current or former payer experience or involvement in CAPR processes from multiple CEE and ME countries. Depending on their jurisdiction the stakeholders fell into the below categories: current or former members of regional or national healthcare payers and health technology assessment agencies, academic experts, or consultants in healthcare financing. Selecting the response group across these categories allowed opinions from different perspectives and experiences to be captured. The specific stakeholder representatives were selected based on their seniority and on their involvement in pricing and reimbursement mechanisms. The targeted stakeholders were invited to take part through a standardized email between May and July 2021. The invitation included a `Word' document of the survey as well as an online link. To secure that all participants had the same definition in mind when answering the survey, a knowledge clip was shown when opening the survey and a definition list of the different payment and reimbursement models was included (Supplementary materials). The survey was followed up by a workshop of which the results are reported elsewhere. Both are part of the HTx project.

2.2. Survey content and design

The survey was divided into two parts according to the split of managed entry agreements into reimbursement models as well as payment models. The first part questioned the current use of, future preferences for, and perceived barriers with reimbursement models while the second part questioned these three elements for payment models. These questions where both asked for in- and outpatient pharmaceuticals to detect whether differences exist between them for these three

elements. To supplement the main two sections of the survey, information was gathered about the individual stakeholders and the healthcare systems, and there was room for additional comments. Thus, in total, the questionnaire included 22 questions arranged according to five domains: (i) the role of the respondent within the healthcare system; (ii) how the healthcare system of the respondent is organized; (iii) the use of reimbursement models; (iv) the use of payment models; (v) arrangements beyond those included in this survey (Questionnaire available in Supplementary Appendix A). The included reimbursement and payment models (

Box 1) and taxonomy was based on previous work (17), with minor adaptations to reflect the setting of lower income countries. The developed survey was tested on content and construct validity by the authors and was pilot tested to verify the format, clarity, length, and usability of the survey for the setting in question (23,24). Any comments were used to make revisions. The survey instrument was programmed in Lime Survey. The results were generated from completed surveys, however if some answers were missing but the survey was still completed to the end, those responses were included.

Box 1. Included reimbursement and payment models

Financial based reimbursement models	
Discounts / rebates	Simple price discounts, publicly or confidentially agreed upon between the payer and manufacturer.
Budget threshold / dedicated funds	Maximum amount of reimbursement for an individual innovative treatment (budget threshold) or therapeutic area (dedicated funds) to cap total expenditures. Translates into maximum number of patients treated per year (utilization capping) or sharing of costs with the manufacturer or patients after pre-defined budget threshold has been exceeded.
Price-volume agreements	Drug prices are progressively lowered as more patients receive the treatment.
Outcome-based reimbursement models	
Value-based pricing	Setting the price of a new medicine and/or decide on reimbursement based on the therapeutic value that a therapy offers, usually assessed through health technology assessment (HTA). To compare value across healthcare domains incremental cost-effectiveness ratios and willingness to pay-thresholds can be used.
Pay-for outcome / outcome guarantees	The level of reimbursement is related to the future performance of the product in either a research or a real world (performance-based) environment. Therapy costs are fully or partially covered by the manufacturer if outcomes are not achieved.
Conditional treatment continuation	Continuation of coverage for individual patients is conditioned upon meeting short-term treatment goals. When agreed conditions are not met, coverage will end.

	Coverage with evidence development	Provisional reimbursement of promising technologies with limited clinical evidence. Temporary reimbursement is granted with an obligation for the manufacturer to obtain and provide additional data. Can be organized either with patients only having access when included in the study (only in research) or with an obligation to generate data and unrestricted access (only with research).
Upfront payment		Agreement to pay treatment costs upfront to the manufacturer at time of treatment delivery. This is the most common payment model.
Delayed payment models		
	Payments at outcome achieved	Paying treatment costs only after pre-defined results have been achieved.
	Annuity Payments	Spreading payments over multiple years, with an agreement upon amount of treatment or outcomes delivered.
	Health leasing / subscription	Paying for unlimited use of a therapy during a predefined period.

2.3. Survey analysis

The collected information was of both a qualitative and quantitative nature. Quantitative questions included reimbursement and payment models are currently used and which models are preferred to be used more often for in- and outpatient pharmaceuticals by indicating this on Likert scales. If no large differences were found between the results for in- and outpatient pharmaceuticals the results where combined and presented in one figure. Country characteristics were questioned using multiple choice questions where the results were analysed individually. Qualitative information focused specifically on the introduction of innovative models, i.e., the perceived barriers with outcome-based reimbursement models and delayed payment models. These open questions where analysed using NVivo 12 Pro (QRS International, Burlington, MA) (25) where a node structure was used to structure the barriers that where perceived, shown in **Figure 1** below. The basis of this node was both inductive and deductive as the main categories ware based on previous literature (17,26,27), but if mentioned barriers fell outside these predefined categories new categories were added. The results are presented by first discussing the current use of both reimbursement and payment models, followed by the preferred use and perceived barriers respectively.

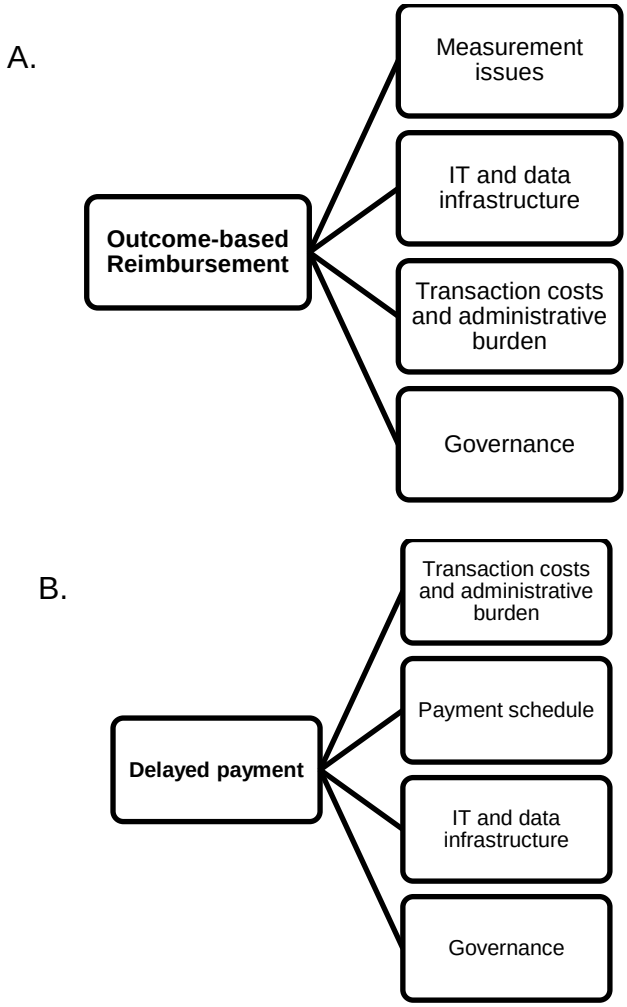

Figure 1. Decision tree for the categorisation of perceived barriers for the implementation and use of outcome-based reimbursement models (A) and delayed payment models (B).

3. Results

3.1. Sample characteristics

Out of the 37 stakeholders invited to fill out the survey a total of 27 participants completed the survey (response rate 73%). In total, stakeholders from 11 different countries completed the questionnaire (Figure 2). More than half of the stakeholders who filled out the survey were current members of regional or national healthcare payers (N=15). The other stakeholders were mainly former members of regional or national healthcare payers who now have a position at a health technology assessment agency (N=4) or work as consultants in healthcare financing (N=5) or academia (N=3).

Figure 2. Stakeholders' nationalities.

Country	Overall (N=27)
Jordan	4
Turkey	4
Kazakhstan	3
Poland	3
Slovakia	3
Croatia	2
Egypt	2
Slovenia	1
Czech Republic	1
Hungary	1
Ukraine	1
Romania	1

Table 1 shows that most respondents came from a country with a centralized HTA institution (N=12). Additionally, most HTA institutions have a weak influence on health decision-making (N=13). In over half of the countries there are multiple payer organizations to provide basis benefit package (N= 15).

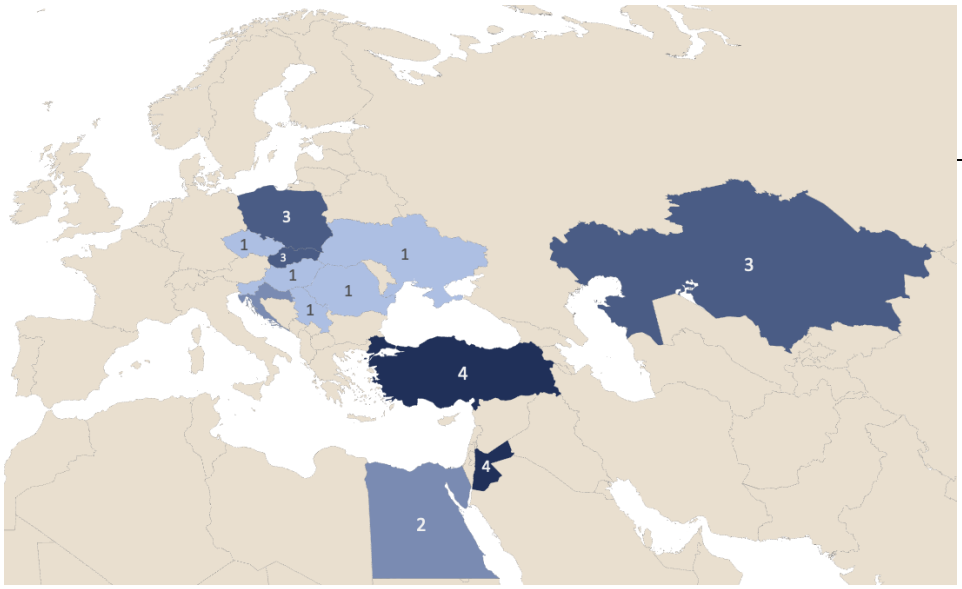

Table 1. Respondents' healthcare system descriptions

Characteristics	Overall (N= 27)

Centralized HTA institution	
No	6 (22%)
Yes	12 (44%)
No HTA institution exists	9 (33%)
Influence HTA institutions on healthcare decision-making	
Strong HTA institution	5 (19%)
Weak HTA institution	13(48%)
No HTA institutions exits	9 (33%)
Number of payer organizations to provide basic benefit package	
One	12 (44%)
Multiple	15 (56%)
Difference between inpatient and outpatient pharmaceuticals in the types of reimbursement models that are applied	
Yes	15 (56%)
Difference between inpatient and outpatient pharmaceuticals in the types of payment models that are applied	
Yes	14 (52%)

3.2. Current use of reimbursement models

In Figure 2 we merged data on in- and outpatient pharmaceuticals because overall no large differences were seen between those two categories. In the experience of the stakeholders the financial-based reimbursement models are more often applied compared to the outcome-based reimbursement models, specifically discounts/rebates are applied most. The outcome-based reimbursement models coverage with evidence development and pay-for outcome/outcome guarantee models are currently used very little with around 60% of the stakeholders indicating that these reimbursement models are currently never applied in their countries. One noteworthy difference in the current use of reimbursement models for in- and outpatient pharmaceuticals that we did find is that the outcome-based reimbursement model value-based pricing is more often experienced to be currently applied for outpatient pharmaceuticals (15%, often/always) compared to inpatient pharmaceuticals (4% often/always).

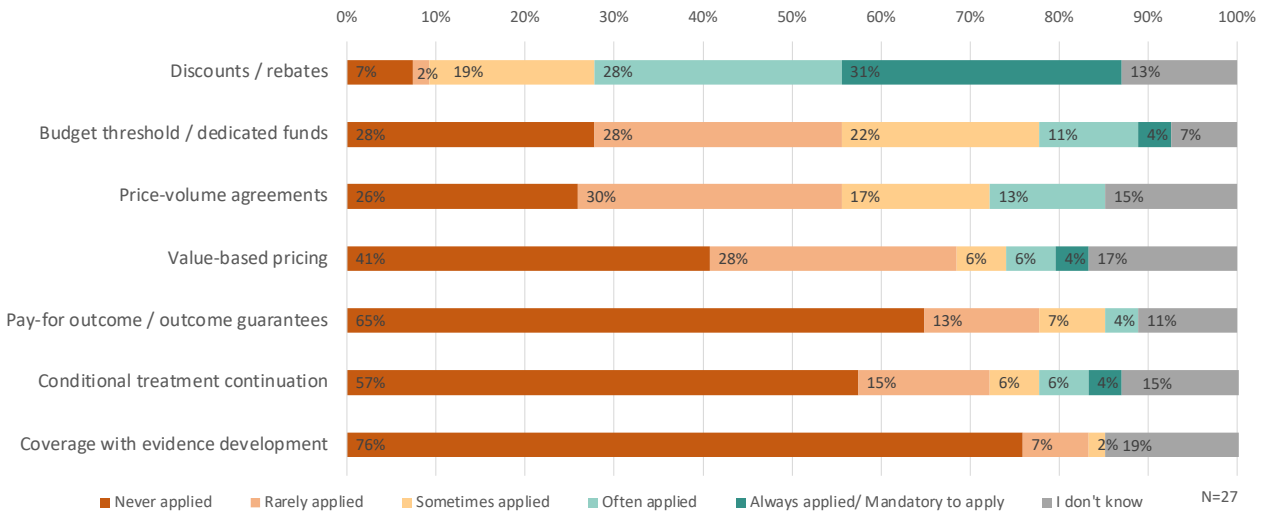

Figure 2. Current use of reimbursement mechanisms for inpatient and outpatient pharmaceuticals.

3.3. Current use of payment models

Again, no large differences in the current use of payment models between in- and outpatient pharmaceuticals were reported and therefore the results were combined in figure 3. It shows that upfront payment is clearly the most applied payment model, whereas more than half of the respondents indicated that in their experience the different delayed payment models are currently rarely to never applied. Only for the countries where a HTA institution exists, annuity payments and health leasing are sometimes or in a few cases rarely applied. In countries where no HTA institution exists only upfront payment models are applied.

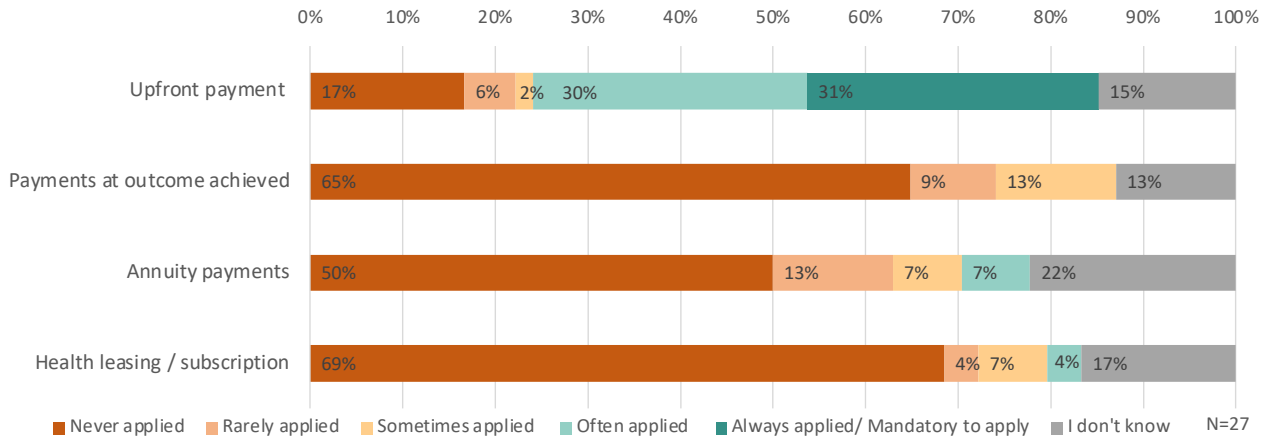

Figure 3. Current use of payment mechanisms for outpatient and inpatient pharmaceuticals

3.4. Preferences for reimbursement models

The respondents were asked to indicate which models they would prefer to be applied more often than currently, in 5 years from now. No large differences were found and the results where combined. The majority of the stakeholders indicated that they prefer the outcome-based reimbursement model pay-for outcome/outcome guarantees to be applied more often (Figure 4). A majority also preferred value-based pricing to be applied more often. A notable difference is that stakeholders from CEE countries prefer pay-for-outcome to be applied more often than ME countries for in- and outpatient pharmaceuticals. In those countries stakeholders the most preferred model was value-based pricing.

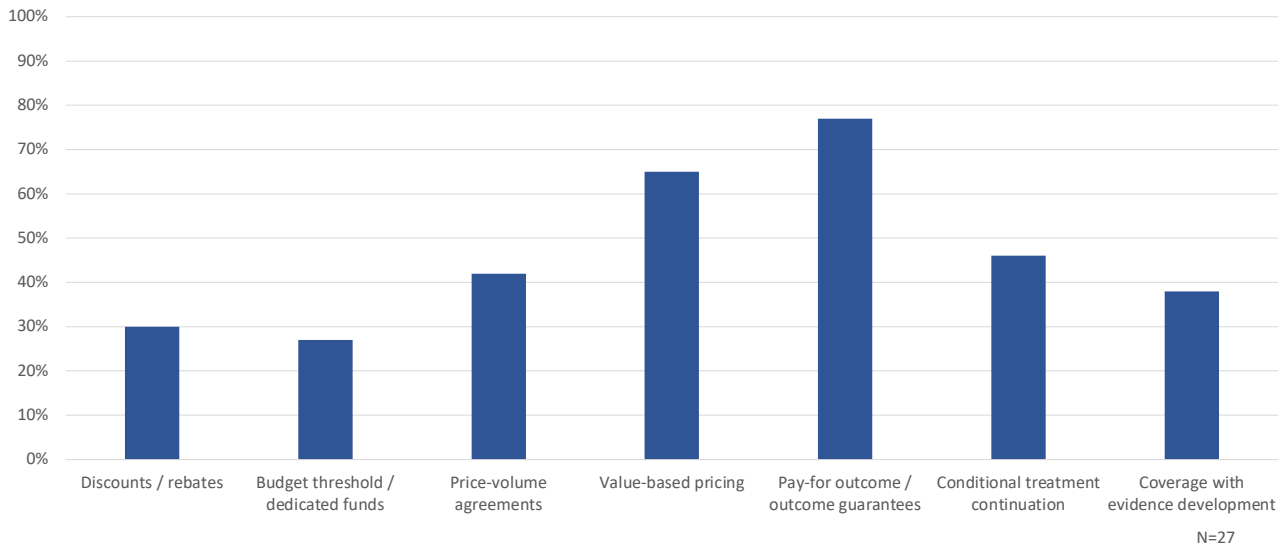

Figure 4. Percentage of stakeholders that indicated per reimbursement model whether they preferer the reimbursement models (Yes/No) to be applied more often than currently, 5 years from now.

3.5. Preferences for payment models

Stakeholders indicated a clear preference for certain payment models to be applied more often than currently. For both in- as outpatient pharmaceuticals almost 80% of the stakeholders indicated that they prefer the payments at outcomes achieved to be applied more often (N = 24). Both stakeholders from CEE and ME countries show similarities in their preferences for payment at outcome achieved, with both 80% of the stakeholders from these countries indicating this.

3.6 Perceived barriers for the implementation and use of outcome-based reimbursement models

To gain insight into what is currently preventing outcome-based models to be applied more often, the respondents were asked to elaborate which barriers are currently encountered with pay-for-outcome, conditional treatment continuation and coverage with evidence development (Table 2). The most often mentioned barriers experienced with pay-for-outcome reimbursement models are related to 'IT and data infrastructure', where especially 'the failure to capture the necessary data to reduce uncertainty within the current infrastructure' was mentioned often. Additionally, barriers regarding 'Transaction costs and administrative burden' were mentioned often with specifically the complex and timely negotiations on contractual terms with drug manufacturers was mentioned a lot. 'Measurement issues' given a lack of health economic and outcomes research expertise to define hard end-points and were also perceived a main barrier. For the reimbursement model 'conditional treatment continuation' this measurement issue was also the most mentioned barrier. Hereafter the most perceived barrier for conditional treatment continuation was related to 'Transaction costs and administrative burden' where especially 'the lack of resources to organize and implement the reimbursement model' such as lacking personnel, budget and capacities were mentioned as barriers hindering a more frequent use. However, the most barriers were perceived with coverage with evidence development reimbursement models. Especially barriers around 'IT and data infrastructure' again were mentioned often as a reason why this model is not implemented more often. Barriers surrounding the failure to capture the necessary data to reduce uncertainty within current infrastructure were perceived most, followed by a limited uptake of patient registries. Another mentioned barrier was related to 'Governance', where in the experiences of the respondents the regulatory framework of CEE and ME countries does not support coverage with evidence development models to be implemented more often.

3.6. Perceived barriers for the implementation and use of delayed payment models

When asked to elaborate on what the greatest barriers are that prevent delayed payments to be applied more often in their country. The stakeholders mentioned the most barriers with the payment at outcome achieved models. The greatest barriers with this payment model were perceived with its 'transaction costs and administrative burden' where respondents especially mentioned the costly implementation and the complexity of the contracts as barriers hindering the implementation of payments-at-outcome achieved models more in the future. Barriers with the 'IT and data infrastructure' were also mentioned frequently, especially the lacking infrastructure to monitor patient statuses, in addition to barriers with 'the payment schedule, due to limited experience with determining the optimal amount and/or duration of payments. Looking at the delayed payment model annuity payments and health leasing the most perceived barrier relate to the 'Payment schedule' where difficulties are experienced with conflicting financial flows of both parties due to 12-month budgetary cycles.

Table 2. The most frequently perceived barriers with outcome-based reimbursement and delayed payment models.

Outcome-based reimbursement barriers		Delayed payment barriers	
IT and data infrastructure	Failure to capture the necessary data	*IT and data infrastructure*	Lacking infrastructure to monitor patient statuses
Transaction costs and administrative burden	Complex and timely negations on contractual terms The lack of resources to organize and implement the reimbursement model	*Transaction costs and administrative burden*	Costly implementation and the complexity of the contracts
Governance	Regulatory framework of CEE and ME countries does not support	*Payment structure*	Conflicting financial flows of both parties due to 12-month budgetary cycles Limited experience with determining the optimal amount and/or duration of payments.
Measurement issues	Lack of expertise to define hard endpoint and to capture them		

4. Discussion

Our inquiry shows that the stakeholders from CEE and ME report that financial-based reimbursement models, specifically discounts, are currently applied most in CEE and ME countries. The respondents indicated to prefer using outcome-based reimbursement models more in the future, where particularly pay-for-outcome models were preferred most. Upfront payments are currently the most frequently applied payment model in CEE and ME countries. However, delayed payment models are preferred to be applied more often. The respondents especially preferred payment at outcome-achieved models to be applied more often in the future. A payment model that works well with the preferred pay-for-outcome reimbursement model as it enforces the moment of payment of the therapy to be only after certain results have been achieved. The barriers of implementing outcome-based agreements were mostly relate to IT and data infrastructure for payment at outcome-achieved models and coverage with evidence development models whereas the perceived barriers for conditional treatment continuation mostly related to measurement issues. Barriers preventing a more frequent implementation of delayed payments are mostly related to transaction costs, IT and data infrastructure when applying payment at outcome achieved models. Barriers concerning the payments structures were perceived most often for annuity payments and health leasing. Considering that there is still a limited amount of available literature surrounding payment and reimbursement models in CEE and ME countries, the gained insights into which payment and reimbursement models are currently applied in CEE and ME

countries, in addition to exploring future preferences and barriers perceived by stakeholders this study, are of added value. The presented overview can provide stakeholders from CEE and ME countries with future direction when implementing innovative reimbursement and payment models.

The results are in line with previous reported findings from both CEE and ME countries as Western countries, where various studies confirm that financial-based reimbursement models and upfront payments are currently applied more often than outcome-based reimbursement models and delayed payments respectively (21,28–30). Ferrario et al. (2017) showed that the most common MEA's in CEE countries are confidential discounts (22), a conclusion that was also found by Rotar et al. (2018) where finance-based MEA's are used frequently whereas performance-based MEAs are scarce and used to a limited extent in CEE countries (29). Similar results are shown for ME and North African countries. The study of Maskineh et al. (2018) concluded this as well (21). Giving the complexities typically involved in outcome-based and delayed payment models as well as the necessary infrastructure to undertake such models, these results are not surprising (26,30,31). Many countries, including CEE and ME but also Western countries, appear to still be in their infancy when it comes to the necessary preconditions for such models, e.g. a mature information infrastructure (21,28–30,32,33). Multiple studies argue that the best practices for more complex reimbursement and payment models such as outcome-based agreements and delayed payments are developed in countries with solid government mechanisms for reimbursement decisions and health outcomes research (21,29,33,34). Given that more than half of the stakeholders from different CEE and ME countries indicated having a weak or no HTA organization, it is understandable that financial-based models are being applied most often.

Several studies illustrate a similar preference for outcome-based reimbursement models over financial-based models and delayed payment models over upfront payment (8,21,26). Previous literature shows that these models are seen as promising alternatives to improve/ensure patient access, diminish the budget impact, reduce uncertainty, manage utilization, and address payers' concerns of affordability in the pharmaceutical market (26,33,35). Nevertheless, other studies show an increasing use more financial-based reimbursement models and upfront payment due to the administrative burden and complexity of outcome-based agreements and delayed payments (36,37).

Consistent with previous literature, we found that barriers relating to IT and data infrastructure, transaction costs, and governance, hinder the implementation of outcome-based reimbursement models (8,27,30,34,36–39). However, other literature highlighted more concerns about bureaucracy and burden mainly for clinical personnel (34,39,40). In the recent literature review of Michelsen (2020) the different barriers hindering spread payments are outlined in detail (26). In this review it is concluded that the main identified barriers for the implementation of spread payments are reaching an agreement on financial terms while considering 12-months budget cycles and the possible violation of

corresponding international accounting rules. These results differ somewhat from ours where also other barriers preventing a more frequent implementation of delayed payments were mentioned that related to the transaction costs, the IT and data infrastructure and the limited experience with determining the optimal amount and/or duration of payments.

4.1. Recommendations

Some preliminary recommendations can be made on how to overcome these barriers and to provide future direction. First a greater dialogue between experts in pricing and reimbursement, clinical opinion leaders, industry, governmental organizations, health technology assessment (HTA) agencies, and patient representatives capturing different perspectives is encouraged, both at the initiation and follow-up of agreements. Through enhanced insight into each other's perspectives, more awareness is created about what the feasible options are and how each stakeholder group can contribute. This includes dialogues on both national and international level. Through more European collaboration and by joining international initiatives, learnings can be taken from each other's best practices. Secondly, if difficulties are expected with the data collection within the current infrastructure, a pilot phase to compare and evaluate different methods could be considered. Given that the stakeholders indicated to experience barriers with how the current IT and data infrastructure supports the implementation of the preferred outcome-based reimbursement models and delayed payment models, a lot could be gained by investigating how the existing infrastructure could be optimally used. Finally, the promotion of a national platform for outcome-based reimbursement models and delayed payment models could aid to overcome barriers related to the transaction costs and administrative burden. By providing an implementation framework, contract archetypes for most common reimbursement and payment schemes and legal guidance the implementation of the preferred models would be more accessible.

4.2. Further research

Our findings lead to some areas for further research. By including a broader range of involved stakeholders, such as stakeholders from pharmaceutical companies or patient organizations, a more comprehensive overview can be given of the current situation, future preferences, and perceived barriers. Given that it is still debated (22,34,35) on how much is exactly gained by implementing more complex outcome-based reimbursement and delayed payment models, a frequent update on current use and experiences of CARP stakeholders is of value to provide future direction in successfully implementing the most feasible models. Better knowledge of the effects of these agreements would help to improve the design of future agreements. Therefore, it is necessary to analyze whether the agreements are fit-for-purpose, while keeping the characteristics of governmental structures of CEE and ME countries in mind. This could be achieved by initiating pilots to systematically review the consequences of

implementing outcome-based and delayed payment models in CEE and ME countries. Finally, the application of the studied models is not mutually exclusive, therefore future research should focus on the possibility to combine elements in the same agreement and address different issues at the same time (e.g., budget impact and use, access, and cost-effectiveness), specifically for CEE and ME countries (17,26,41).

4.2. Limitations

The survey was targeted at stakeholders from CAPRs in CEE and ME countries, but it was not possible to contact stakeholders from all CEE and ME countries. Additionally, the general response rate from some countries was low. Both of these factors emphasize that caution should be taken with generalizing the results to the entire CEE and ME region. However, our outcomes show a high level of homogeneity, and we aimed to invite key stakeholders with a vast knowledge of their fields, therefore they probably provide an adequate picture regarding the experiences and preferences for these models in these countries.

5. Conclusions

Despite the preference healthcare payers have for using outcome-based reimbursement models and delayed payment models more often in the future, currently they are rarely applied. For future use, stakeholders have indicated a specific preference for applying pay-for-outcome reimbursement models and payment at outcome achieved models more often. These insights can provide stakeholders from CEE and ME countries with future direction when implementing innovative reimbursement and payment models. Attention should be paid to which barriers are currently perceived as this could aid a successful implementation. Further research is required and should focus on exploring which combinations of reimbursement and payment models are most likely to be successful in CEE and ME countries.

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7. Appendices

Appendix A: Questionnaire

Questionnaire on the transferability of reimbursement and payment models throughout Europe

Survey payment models
Questionnaire on the transferability of reimbursement and payment models throughout Europe. Thank you for taking the time to answer this survey.

Aim
The questionnaire will focus on the current situation of payment and reimbursement models in your country and barriers of transferring selected novel payment models to your country.

Research context
This questionnaire is part of broader research in the HTx project. The University of Utrecht and the Syreon Research Institute are involved to the European Commission funded H2020 HTx project (Next Generation Health Technology Assessment) project.
Work Package 4 of the HTx project covers payment models of new health technologies and sustainable healthcare funding. In this work package, we would appreciate your valuable contribution.

Knowledge clip and factsheet
Because the terms for the different payment and reimbursement models are often used and interpreted differently in practice, you will be shown a knowledge clip at the start of the questionnaire explaining how the concepts have been defined in this survey. These definitions can always be found throughout the questionnaire by opening the factsheet in the index button at the top right or can be downloaded here.

Estimated time to complete
The questionnaire has been tested and we estimate that you will need about 20 minutes to complete it.

Questions or comments
For any questions or remarks you can contact Marcelien Callenbach from Utrecht University by e-mailing to M.H.E.Callenbach@uu.nl.

Again, thank you very much for taking the time to provide us with your valuable knowledge.

Kind regards,

On behalf of the collaborating partners,

Syreon Research Institute (SRI)
Zoltán Kaló (HTx H2020 Transferability Workpackage Leader)
Bertalan Németh (HTx H2020 Payment Model Workshop Coordinator)
Ildiko Adam, PhD candidate

Utrecht University (UU)
Wim Goettsch (HTx H2020 Project Leader)
Rick Vreman (Assistant professor)
Marcelien Callenbach (PhD Candidate)

Data protection
Please note that we could not fully anonymize this questionnaire due to organizational and analysis purposes. We would like to assure you that we will handle your information with care, and will not publish or share with others any data that can be traced back to you personally or your position, according to European legislation (EU) 2016/679. By accepting our survey data policy below, you agree to these terms.

- **I accept the terms**

Knowledge clip

By clicking on **this link** you will see the knowledge clip (viewing time 4 minutes). This knowledge clip explains the different reimbursement and payment models that will be mentioned in this survey.

Next Generation Health Technology Assessment

Factsheet
Reimbursement and Payment models

Discounts / rebates	Simple price discounts, publicly or confidentially agreed upon between the payer and manufacturer.
Budget threshold / dedicated funds	Maximum amount of reimbursement for an individual innovative treatment (budget threshold) or therapeutic area (dedicated funds) to cap total expenditures. Translates into maximum number of patients treated per year (utilization capping) or sharing of costs with the manufacturer or patients after pre-defined budget threshold has been exceeded.
Price-volume agreements	Drug prices are progressively lowered as more patients receive the treatment.
Value-based pricing	Setting the price of a new medicine and/or decide on reimbursement based on the therapeutic value that a therapy offers, usually assessed through health technology assessment (HTA). To compare value across healthcare domains incremental cost-effectiveness ratios and willingness to pay-thresholds can be used.
Pay-for outcome / outcome guarantees (performance-based)	The level of reimbursement is related to the future performance of the product in either a research or a real world environment. Therapy costs are fully or partially covered by the manufacturer if outcomes are not achieved
Conditional treatment continuation	Continuation of coverage for individual patients is conditioned upon meeting short-term treatment goals. When agreed conditions are not met, coverage will end.
Coverage with evidence development	Provisional reimbursement of promising technologies with limited clinical evidence. Temporary reimbursement is granted with an obligation for the manufacturer to obtain and provide additional data. Can be organized either with patients only having access when included in the study (only in research) or with an obligation to generate data and unrestricted access (only with research)

Upfront payment to the manufacturer	Agreement to pay treatment costs upfront at time of treatment delivery. This is the most common payment model.
Payments at outcome achieved	Paying treatment costs only after pre-defined results have been achieved.
Annuity payments / over-time payments / staggered payment	Spreading payments over multiple years, with an agreement upon amount of treatment or outcomes delivered.
Health leasing / subscription	Paying for unlimited use of a therapy during a predefined period.

Topic 1: Role of the respondent within the healthcare system

The following questions are designed to gather general information about your role regarding payment and reimbursement models within the healthcare system of your country.

From which country are you?

……..……..……..……..

From what perspective do you fill out this survey? (i.e. where is your main job)
Choose one of the following answers

- Health Technology Assessment (HTA)
- Health care payer
- Governmental (ministry or other)
- Health care provider (e.g. hospital, outpatient clinic)
- Pharmacy
- Academia
- Health care consultancy
- Industry
- Other _____

In a few words, what is your role within this institute (e.g. assessor, advisor, decision-maker, health care professional)?

……..……..……..……..

How would you describe the role of your organization within the implementation of reimbursement models and payment models?

……..……..……..……..

Topic 2: How the healthcare system of the respondent is organized

The following questions are designed to gather information about how the healthcare system in your county is organized.

Do you have centralized Health Technology Assessment (HTA) or decentralized HTA in your country?
Choose one of the following answers

- Centralized HTA
- Decentralized HTA
- No HTA institution exists in my country

How would you rate the HTA institution(s) in your country in terms of its influence on healthcare decision-making?
Choose one of the following answers
- Strong HTA institution(s)
- Weak HTA institution(s)
- No HTA institution exists in my country

Do you have one payer organization or multiple payers to provide the basic benefit package in your country?
Choose one of the following answers
- One major payer organization
- Multiple payer organizations

Is there a difference between how pharmaceuticals and non-pharmaceuticals (devices, apps) are priced and reimbursed in your country?
Choose one of the following answers
- No
- Yes, please give a short explanation

……..……..……..……..

Topic 3: Use of reimbursement models

The following questions are designed to explore your experiences with the current use of different reimbursement models and how this use might differentiate between inpatients and outpatients. All further questions apply specifically to ***pharmaceuticals (not devices or other technologies)****.*

How often are each of the following mechanisms currently being applied in your country for inpatient (in-hospital) pharmaceuticals? Please select one option in each row.

	Never applied	**Rarely applied**	**Sometimes applied**	**Often applied**	**Always applied/ Mandatory to apply**	**I don't know**
Discounts / rebates						
Budget threshold / dedicated funds						
Price-volume agreements						
Value-based pricing						
Pay-for outcome / outcome guarantees						

Conditional treatment continuation						
Coverage with evidence development						

Is there a difference between inpatient and outpatient pharmaceuticals in the types of reimbursement models that are applied in your country?
Choose one of the following answers

- No
- Yes, namely

……..……..……..……..

If no, please answer the following questions.

Which of the following arrangements would you prefer to be applied in your country more often than currently, **5 years** from now? Please only select 4 at most.

- Discounts / rebates
- Budget threshold / dedicated funds
- Price-volume agreements
- Value-based pricing
- Pay-for outcome / outcome guarantees
- Conditional treatment continuation
- Coverage with evidence development
- Other_____

If yes, please answer the following questions

How often are each of the following mechanisms **currently**, being applied in your country for **outpatient** (out-hospital) pharmaceuticals? Please select one option in each row.

	Never applied	**Rarely applied**	**Sometimes applied**	**Often applied**	**Always applied/ Mandatory to apply**	**I don't know**
Discounts / rebates						
Budget threshold / dedicated funds						
Price-volume agreements						
Value-based pricing						

Pay-for outcome / outcome guarantees						
Conditional treatment continuation						
Coverage with evidence development						

Which of the following arrangements would you prefer to be applied for **inpatient** (in-hospital) in your country more often than currently, **5 years** from now? Please only select 4 at most.

- Discounts / rebates
- Budget threshold / dedicated funds
- Price-volume agreements
- Value-based pricing
- Pay-for outcome / outcome guarantees
- Conditional treatment continuation
- Coverage with evidence development
- Other_____

Which of the following arrangements would you prefer to be applied for **outpatient** (out-hospital) in your country more often than currently, **5 years** from now? Please only select 4 at most.

- Discounts / rebates
- Budget threshold / dedicated funds
- Price-volume agreements
- Value-based pricing
- Pay-for outcome / outcome guarantees
- Conditional treatment continuation
- Coverage with evidence development
- Other_____

Outcome-based arrangements are rarely applied in the Central and Eastern European regions. In your opinion what are the greatest barriers preventing **pay-for outcome / outcome guarantees (performance-based)** arrangements from being used more often? (Please list 1-3 barriers)

……..

Outcome-based arrangements are rarely applied in the Central and Eastern European regions. In your opinion what are the greatest barriers preventing **conditional treatment continuation** arrangements from being used more often? (Please list 1-3 barriers)

……..

Outcome-based arrangements are rarely applied in the Central and Eastern European regions. In your opinion what are the greatest barriers preventing **coverage with evidence development** arrangements from being used more often? (Please list 1-3 barriers)

……..……..……..……..

Topic 4: Use of payment models

The following questions are designed to explore your experiences with the current use of different payment models and how this use might differentiate between inpatients and outpatients.

How often are each of the following payment models **currently** being applied in your country for **inpatient** (in-hospital) pharmaceuticals? Please select one option in each row.

	Never applied	Rarely applied	Sometimes applied	Often applied	Always applied/ Mandatory to apply	I don't know
Upfront payment to the manufacturer						
Payments at outcome achieved						
Annuity payments						
Health leasing / subscription						

Is there a difference between inpatient and outpatient pharmaceuticals in the types of payment models that are applied in your country?

- ○ No
- ○ Yes, namely

……..……..……..……..

If no, please answer the following questions.

Which of the following arrangements would you prefer to be applied in your country more often than currently, **5 years** from now? (multiple choices are possible)

- ○ Upfront payment to the manufacturer
- ○ Payments at outcome achieved
- ○ Annuity payments
- ○ Health leasing / subscription
- ○ Other_____

If yes, please answer the following questions

How often are each of the following mechanisms **currently**, being applied in your country for **outpatient** (out-hospital) pharmaceuticals? Please select one option in each row.

	Never applied	Rarely applied	Sometimes applied	Often applied	Always applied/ Mandatory to apply	I don't know
Upfront payment to the manufacturer						
Payments at outcome achieved						
Annuity payments						
Health leasing / subscription						

Which of the following payment models would you prefer to be applied for **inpatient** (in-hospital) in your country more often than currently, **5 years from now**? (multiple choices are possible)

- Upfront payment to the manufacturer
- Payments at outcome achieved
- Annuity payments
- Health leasing / subscription
- Other:_____

Which of the following payment models would you prefer to be applied for **outpatient** (out-hospital) in your country more often than currently, **5 years from now**? (multiple choices are possible)

- Upfront payment to the manufacturer
- Payments at outcome achieved
- Annuity payments
- Health leasing / subscription
- Other:_____

Upfront payment may not be a viable option for the most expensive treatments. In your opinion what are the greatest barriers preventing the use of the payment model **payments at outcome achieved**? (please list 1-3 barriers)

……..

Upfront payment may not be a viable option for the most expensive treatments. In your opinion what are the greatest barriers preventing the use of the payment model **annuity payments**? (please list 1-3 barriers)

……..

Upfront payment may not be a viable option for the most expensive treatments. In your opinion what are the greatest barriers preventing the use of the payment model **health leasing / subscription**? (please list 1-3 barriers)

……..……..……..……..

Topic 5: Arrangements beyond those included in this survey

Which managed entry agreements (reimbursement models, payment models, or other) regularly apply within your country that have not been listed previously in this questionnaire?

- ○ None
- ○ Yes, namely

……..……..……..……..

Thank you for completing this questionnaire!

Your answers have been saved (only press 'Exit and clear' if you want to delete your answers and exit the survey).

Please submit your survey via email: m.h.e.callenbach@uu.nl

SECTION 2

RECOMMENDATIONS FOR IMPLEMENTING DELAYED PAYMENT SCHEMES FOR NEW TECHNOLOGIES WITH HIGH UPFRONT COSTS IN CENTRAL AND EASTERN EUROPEAN AND MIDDLE-EASTERN COUNTRIES

1. Introduction

The focus of research and development in health care has been changing recently. As opposed to bringing new technologies to the marketplace in large disease groups typically managed in primary care, innovators are focusing more strongly on smaller target patient groups in specialty diseases (e.g. oncology, hematology, autoimmune diseases) or rare diseases. The complexity of new technologies has also increased, initially with the uptake of biological medicines, followed by combined personalized solutions (e.g. molecular diagnostics and precision medicines or pharmaceuticals supported by digital health solutions) and most recently with cell and gene therapies.

Previous research summarized innovative payment models for new health technologies, including those that might be able to manage the market access of potentially curative health technologies. These technologies may have the potential to be cost-effective, as they might prevent chronic treatments and negative clinical outcomes in the long-run. However, due to the high upfront costs and the relatively large uncertainty whether long-term effects will be realized, payers have significant concerns with the short-term budget impact of these therapies. The importance of affordability has been highlighted with the introduction of human papilloma virus vaccinations, direct antiviral agents to treat hepatitis C or advanced therapeutical medical products (Hampson, 2018). Instead of the standard upfront payment methods, in which manufacturers receive the payment from health care payers at the time of delivering the treatment, different types of delayed payment options were described by Vreman et al. (Vreman, 2020). These include a) paying treatment costs only after results have been achieved, or b) annuity or staggered payment methods, in which payments are spread over multiple years with an agreement upon amount of treatment or outcomes delivered, and c) health leasing or subscription methods, in which payment is made for the unlimited use of a therapy within a predefined period.

While a wide range of managed entry agreements have been extensively used in Central and Eastern Europe (CEE) and the Middle East (ME) (Ferrario, 2017; Maskineh, 2018), examples of delayed payment methods were mainly described in developed countries. As part of the European Commission funded HTx H2020 project, our objective was to explore the transferability of delayed payment methods for technologies with high upfront costs to lower income developing countries within and outside the European Union with special focus on countries in CEE and ME. The transferability assessment included listing potential barriers for implementing delayed payment models and making recommendations on how to address these barriers.

2. Methods

Three different sources were utilized in parallel to collecting information about potential barriers and solutions to implement delayed payment methods in Central and Eastern Europe or in the Middle East (see Figure 1). We retrieved information from a survey about the current status and potential barriers of innovative payment models in CEE and ME countries. Results of the survey are described in a different manuscript (REF). In parallel a targeted review was conducted to explore barriers and potential solutions from the scientific and grey literature. Finally, iterative discussions within HTx consortium members who represented multiple stakeholders (such as payers, HTA experts, researchers), complemented the list of barriers and recommendations. During these discussions the research team aimed to reduce overlaps in the list of barriers. As these steps were conducted in parallel, we have not tracked the origin of barriers and recommendations from the three described sources.

As a second step we planned to review draft list of barriers and recommendations with representatives of health care payers or health care financing experts (i.e. advisers of health care payers or former payers) from CEE or ME countries in a face-to-face policy workshop. Due to travel restrictions related to the COVID-19 pandemic it was a virtual meeting. The virtual workshop was organized in June 2021 with 16 members of the HTx consortium and 14 payer representatives and experts representing 8 Central and Eastern European countries (Bulgaria, Croatia, Hungary, Poland, Ukraine, Serbia, Slovakia, Slovenia), 4 Middle-Eastern countries (Egypt, Jordan, Lebanon, Turkey) and 3 Western European countries (The Netherlands, Sweden, The United Kingdom).

As a start, participants could benefit from relevant experiences in Sweden, the United Kingdom and The Netherlands, followed by a presentation about the draft list of barriers and recommendations. Then workshop participants were allocated to small working groups to discuss certain sections of the recommendations. Finally, rapporteurs provided feedback to all workshop participants and clarified all emerging questions.

As a third step the HTx research team prepared a draft report with the consolidated list of barriers and recommendations. The document was circulated among workshop participants, who had the opportunity to make final comments and amendments to the report. Following the workshop, experts were asked to confirm their input provided during the workshop. Finally, we reached a consensus in the list of barriers and potential solutions for innovative payment models among participants.

3. Results

After deduplication of barriers retrieved from different sources, 8 different barriers in 4 groups were established, including (i) transaction costs and administrative burden, (ii) payment schedule, (iii) IT and data infrastructure and (iv) governance. Based on those barriers 15 practical recommendations were drafted. Table 1 provides a summary of the barriers and recommendations.

3.1. Barriers of implementing delayed payment models in CEE and ME countries

Two challenges were described related to high transaction costs and administrative burden of delayed payment models. Compared with upfront payment models, solutions

for delayed payment are associated with complex and resource intensive negotiations on contractual terms, including not only the initial agreement but renegotiation of terms after the first contract is terminated. Secondly, the implementation of these agreements also requires significant resources, as the timing of service provision is not linked to the timing of payments.

Barriers could also be attributable to the payment schedule. Until sufficient experience is accumulated from delayed payment agreements for several different types of health technologies, both payers and manufacturers of health technologies need to take significant risks with determining the optimal amount and duration of payments. Even if there is an agreement on spreading the payment to more periods, it may result in conflicting financial flows with current accounting practices and regulations for both parties. Budget holders mostly have to consider 12-month budgetary cycles, while manufacturers are also liable to strictly follow international and national accounting rules and reflect revenues and liabilities annually (Michelsen, 2020).

Delayed payment schemes are usually linked to outcome-based agreements, as continuing payments after treatment failure makes no sense. Current IT and data infrastructure is prone to failure to monitor the patient status. In fact, collecting, organising or accessing data are one of the most frequently reported barriers of implementing outcome-based agreements, which is often linked with delayed payment schemes (Michelsen, 2020). Patient registries may alleviate the burden of data collection, however, in CEE and ME countries the availability and uptake of such registries is limited.

The final group of barriers is related to governance. First, current legal frameworks may not be appropriate to accommodate delayed payment schemes. And if this problem is solved, civil servants in national public sectors may not be prepared and incentivised to efficiently negotiate with multinational industry. This is especially true in countries with relatively small market potential, where headquarters of multinational companies may have limited interest in approving unique local proposals.

3.2. Recommendations for implementing delayed payment models in CEE and ME countries

Several practical recommendations were made to facilitate the adoption of delayed payment models in lower-income CEE and ME countries. Some recommendations may be a solution for multiple barriers, the connections between barriers and recommendations are presented in Table 1.

3.2.1. Recommendation #1 - Consider transferring the structure of existing agreements from higher income countries

Lower income countries (including CEE and ME countries) can benefit from experiences of higher income countries with delayed payment models. While some information may also be in the public domain on potential barriers and related solutions, direct exploratory discussion with health care payers in forerunner countries and manufacturers is also advocated. It has to be noted that transferring solutions from other jurisdictions without adjustment to local environment may not be feasible, however, existing structures from elsewhere may be a good starting point in designing the structure of delayed payment

schemes.

Similarly, review of practices and solutions of forerunner countries to adjust the regulatory and legislative framework to accommodate delayed payment schemes could be highly beneficial in lower income countries.

3.2.2. Recommendation #2 - Pharmaceutical industry should develop contract archetypes for most common schemes

Multinational manufacturers of health technologies should develop and publish a master document that can describe the adaptability of delayed payment methods to different archetypes of health care systems. Development of common solutions for similar systems can accelerate preparations for offerings and negotiations in different countries, and prevent failures related to “one size fits all” market access strategies. While the master document should be updated on a continuous basis with new experiences, too detailed description of contracts would result in the applicability of such schemes only to individual countries.

3.2.3. Recommendation #3 - When agreements are renegotiated, the latter agreement should be simpler than the first

As delayed payment agreements have to be renegotiated after their termination, there is an opportunity to simplify the original conditions based on the experiences in the initial period. For example, real world effectiveness data can help to clarify the expected payments in the second or third years after therapy initiation.

3.2.4. Recommendation #4 - Apply re-opener clauses of agreements after entry of competitive product

Recognition of market dynamics should be reflected in agreements with several years of duration. Therefore, it is recommended to add re-opener clauses to the agreement for the market launch of competitive technologies or if applicable, for the patent expiry of the health technology. Alternatively, for such cases a pre-defined adjustment of the payment may be considered (Vreman, 2020).

3.2.5. Recommendation #5 – In the short run, rely on existing infrastructure

Implementation of delayed payment schemes can be fairly complex, expensive and unreliable, if it necessitates the development of a new infrastructure (including data reporting system or data lakes) for its administration. Therefore, it is highly recommended that such schemes should rely on existing infrastructure.

3.2.6. Recommendation #6 - In the long run, adjust data infrastructure of health care payers to such agreements

Initial failures to monitor the patient status with current infrastructure can be considered as a need for changing the data infrastructure of health care payers. While changing the infrastructure cannot be justified based on a single case, in the long-run more and more potentially curative technologies with high upfront costs can be expected, therefore adjustment of the data infrastructure to accommodate delayed payment options in addition to alignment with international data standards is an inevitable step in the long-run.

3.2.7. Recommendation #7- Reuse of existing claims or medical data

Reusing existing claims data or electronic medical records for administering delayed payment schemes reduces the human or financial burden of implementation. Linking existing databases – e.g. patient registries with payer's databases – may require additional investment, however, the availability of such joint databases may open further opportunities in generating real world evidence to improve health policies. It should also be noted that reusing existing data for multiple purposes has the potential to increase data quality.

3.2.8. Recommendation #8 - Greater dialogue between payers and HE&OR experts

Health economic and outcomes research (HE&OR) experts, researchers in academic centers within and outside a country may accumulate broad experiences from previous or ongoing research projects (such as the current HTx H2020 projects), while HE&OR experts at multinational companies can draw negative and positive conclusions from establishing similar agreements in many different countries. In many CEE and ME countries there is little room for information exchange between payers and HE&OR experts, which may prevent knowledge transfer from research projects and generalisation of learnings from previous agreements. Greater dialogue between payers and HE&OR experts may improve the information exchange and has the potential to optimise payment schedules.

3.2.9. Recommendation #9 - Consider that upfront payment has higher present value than delayed payment

Time preference for payments should be reflected in the agreements, and so an appropriate discount factor should be applied to calculate the present value of future payments. Possibly a third party may be involved to mitigate financial risks of spread payments.

3.2.10. Recommendation #10 - Propose changes to international and national accounting rules (e.g. to allow accruals over several years)

Pharmaceutical companies and health care payers face challenges in spreading payments over a certain period due to national and European accounting rules. Therefore, a complex approach would be essential that would enable parties to choose spread or delayed payment. Maes et al. concluded that European System of Accounts ('ESA') is a real barrier in implementing annuity payments. Annuity payments should be recognized as debt in the year of delivering treatment, which has an impact on the government's deficit in the year of treatment (Maes, 2019). Hence, a general proposal to enable the international and national regulations allowing payments division over a certain period would improve the adaptability of delayed payment schemes to the accounting systems of both health care payers and multinational companies.

3.2.11. Recommendation #11 - If difficulties to collect data is expected, consider a pilot phase with adjustment according to early experiences

In any novel policy solution, it makes sense to introduce a pilot period with strict monitoring process of early experiences. The pilot phase would provide opportunity to adjustment in the first couple of agreements according to early experiences.

3.2.12. Recommendation #12 - Consider the implementation of pilot cases

Similarly to the pilot cases in individual agreements, pilot cases should also be considered before making changes in the regulatory and legislative framework to accommodate delayed payment schemes.

3.2.13. Recommendation #13 - Facilitate the establishment of patient registries

Collection of real-world health outcomes in patient registries is advocated for many reasons, and implementation of delayed payment schemes can also benefit from the establishment of patient registries. Training of health care professionals, manufacturers and payers is key in overcoming interpretation and analysis bias (Michelsen, 2020). Finally, enabling multi country cooperation could help in decreasing the burden of setting-up registries and eliminate duplicating the work of collecting data.

3.2.14. Recommendation #14 - Strengthen HTA system to promote value for money and affordability concepts

HTA facilitates policy decisions based on the best available evidence related to multiple criteria. Delayed payment schemes can improve the affordability of health technologies with high upfront costs in parallel with supporting value-based health care. Budget impact analyses may help to quantify how such schemes can contribute to the sustainability of health care financing. A prerequisite for informed decision-making around delayed payment models within a value-based health care environment is a strong HTA system.

3.2.15. Recommendation #15 - Joint procurement by smaller countries to increase the purchasing power

A few years ago, the MEAT (Most Economically Advantageous Tender) value framework concept was introduced, and a discussion started whether it could be a useful tool in purchasing high-cost health technologies jointly by multiple countries. The concept advocates the consideration of those health technologies - instead of the cheapest alternatives - that can bring benefits to the economy on a wider scale, to different stakeholders in the health systems, including patients, providers and health professionals, while taking into account advantageous financial solutions (MEAT, 2016). Delayed payment models for potentially curative technologies with high upfront costs can be a relevant subject for the MEAT framework.

4. Discussion

This study provided a consensus statement on important barriers related to delayed payment schemes in CEE and ME countries and practical recommendations to overcome those barriers. Some recommendations are specific only to lower income countries, while other recommendations apply more universally, but are especially crucial in developing countries.

The focus on CEE and ME countries is especially important for two reasons. At first, experiences about delayed payment schemes have been published about higher income countries, which may not be fully transferable to developing countries. Second, populations of these countries have poorer health status, so demand for potentially curative health technologies is greater. On the other hand, financial resources are more

limited, and improving sustainability of health care financing with delayed payment schemes may result in even more value in these countries.

5. Conclusion

Conclusions of this policy research can be considered as an initial step in a multistakeholder dialogue about implementing delayed payment schemes in CEE and ME countries. The authors recommend continuation of this work, as conducting research in a pandemic period reduced the opportunity of organising face-to-face focus group meetings. Similarly, initiation of discussions with health care payers, who were overwhelmed with managing health care financing in a difficult health and economic period, was challenging.

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7. Appendix

Figure 1. Process of creating policy recommendations for the implementation of delayed payment models for technologies with high upfront cost in Central and Eastern European and Middle Eastern countries

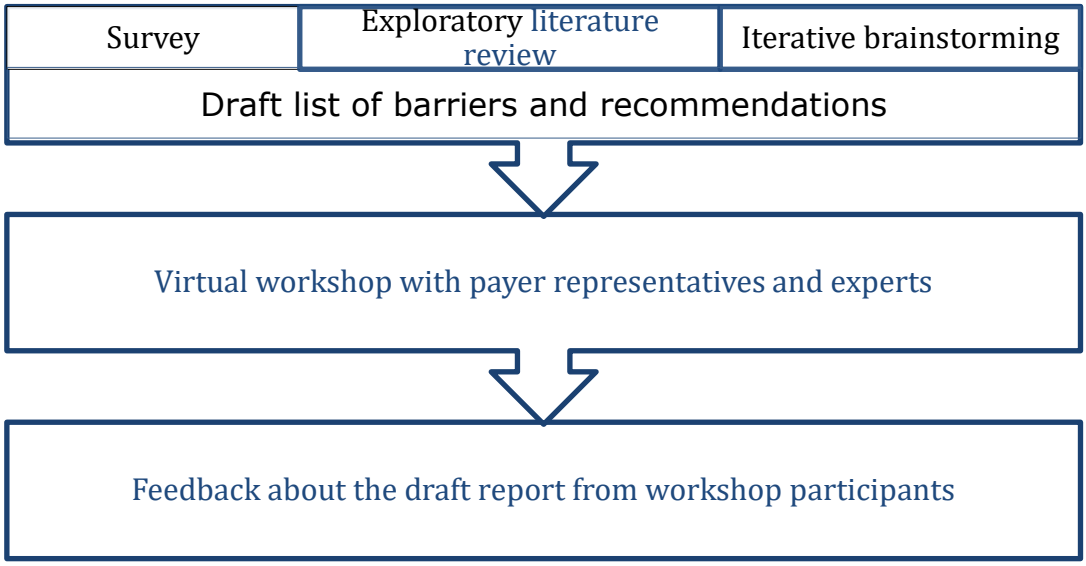

Table 1 - Summary of barriers and recommendations

Group of barriers	Barriers	Summary of recommendations
Transaction costs and administrative burden	Complex and resource intensive negotiations on contractual terms (including the first agreement and renegotiations)	1) Consider transferring the structure of existing agreements from higher income countries 2) Develop contract archetypes for most common schemes 3) When agreements are renegotiated, the latter agreement should be simpler than the first 4) Re-opener clauses of agreements after entry of competitive product
	Costly implementation of agreements with delayed payment	1) Rely on existing infrastructure 2) Reuse of existing claims or medical data 3) In the long-run, adjust payer's data infrastructure to such agreements
Payment schedule	Limited experience with determining the optimal amount and/or duration of payments	1) Greater dialogue between payers and HE&OR experts 2) Consider transferring the structure of existing agreements from higher income countries 3) Develop contract archetypes for most common schemes 4) When agreements are renegotiated, the latter agreement should be simpler than the first 5) Consider that upfront payment has higher present value than delayed payment
	Conflicting financial flows for both parties due to 12-month budgetary cycles	Propose changes to European and national accounting rules (e.g. to allow accruals over several years)
IT and data infrastructure	Failure to monitor the patient status with current infrastructure	1) If difficulties to collect data is expected, consider a pilot phase with adjustment according to early experiences 2) In the long-run adjust data infrastructure of health care payers to such agreements

	Limited uptake of patient registries	Facilitate the establishment of patient registries
Governance	Lack of regulation	1) Review regulatory frameworks in higher income countries 2) Consider the implementation of pilot cases, and prepare regulatory legal framework based on experiences in the pilot phase
	Weakness of public sector to efficiently negotiate with multinational industry	1) Consider transferring the structure of existing agreements from higher income countries 2) Strengthen HTA system to promote value for money and affordability concepts 3) Joint procurement by smaller countries to increase the purchasing power

SECTION 3

RECOMMENDATIONS FOR IMPLEMENTING OUTCOME-BASED REIMBURSEMENT MODELS FOR NEW TECHNOLOGIES IN CENTRAL AND EASTERN EUROPEAN AND MIDDLE-EASTERN COUNTRIES

1. Introduction

Lower income countries (LICs) generally have a worse health status than the more affluent countries according to various metrics (Boncz, 2014) (Bowry, 2015) (Marmot, 2012) (Bertuccio, 2015) (Stanifer, 2016). These issues go hand in hand with financing issues and access limitations to the more expensive innovative health technologies (Adam, 2012) (Hollis, 2016) (Pejcic, 2018) (Ozawa, 2019). This unmet medical need creates strong incentives from patient groups and the general public to push for the reimbursement of these innovative medicines despite the more restricted payer budgets in various LICs: from the Central and Eastern European (CEE) region to the LICs of the Middle East (ME), and several other parts of the world as well.

One possible solution to bridge this gap are the various types of confidential agreements between payers and manufacturers, known as managed entry agreements (MEAs) (Klemp, 2011) (Kanavos, 2017) (Fens, 2020). MEAs can be considered well-balanced compromises between the aforementioned two stakeholder groups (Németh, 2020a), and have shown promising results in granting access to innovative pharmaceuticals in Western European (WE) countries for example (Pauwels, 2017).

Outcome-based agreements are a subtype of MEAs (Carlson, 2010) (Wenzl, 2019), that link payments through various ways to the health benefits that patients realize due to the use of the particular health technology (such as pay-for outcome, conditional treatment continuation, coverage with evidence development, etc.). These can effectively reduce the risk of payers in cases when there is great uncertainty or heterogeneity regarding the clinical value of the pharmaceutical in question (Inotai, 2019). Outcome-based MEAs play an important role in the healthcare financing of several WE countries, for example

Italy (Xoxi, 2021). However, their uptake in LICs seems to be lagging behind (Ferrario, 2017) as these nations often rely more on other methods, such as volume restrictions, without accomplishing the potentially increased utilization due to outcome-based agreements (Inotai, 2019).

HTx is a Horizon 2020 (H2020) project supported by the European Union lasting for 5 years from January 2019. The main aim of HTx is to create a framework for the Next Generation Health Technology Assessment (HTA) to support patient-centered, societally oriented, real-time decision-making on access to and reimbursement for health technologies throughout Europe. Task 4.4 of the HTx project is dedicated to payment models and sustainable healthcare funding. A key result of this task has been the publication of a feasibility analysis of the application of MEAs for innovative therapies (Vreman, 2020).

As part of the European Commision funded HTx H2020 project, the objective of this study was to explore the transferability of outcome-based payment methods within and outside the European Union with a special focus on countries in the CEE region and LICs from the ME. This research aims to highlight the most important barriers that prevent the widespread use of these agreements, and to go a step further and recommend potential solutions to the identified barriers.

2. Methods

The first step in our research was the collection of information from relevant literature and the HTx network regarding the potential barriers and solutions for implementing outcome-based reimbursement models in CEE and in the ME (see Figure 1). Information collection was carried out in parallel through three different sources. Information about utilisation status and potential barriers of outcome-based agreements in these countries was collected through a survey, the results of which are described in a different manuscript (see Section 1). A targeted review of scientific and grey literature was carried out in parallel with the above mentioned survey, to identify and explore further barriers and potential solutions for the implementation of outcome-based reimbursement models. During iterative rounds of discussions with HTx consortium members representing different stakeholders in the HTA arena, the list of barriers and recommendations were expanded with their insights. The upcoming information from these sources were

reviewed continuously with the objective minimizing overlaps in the list of barriers and streamlining recommendations to each barrier. Considering the parallel and iterative nature of the exploratory process for these barriers and recommendations, the clear back-tracking from the various sources would be cumbersome as well as irrelevant for the next steps.

The second step in our approach was to review the draft list of barriers and recommendations identified in the earlier step, with representatives of health care payers and with health care financing experts (i.e. advisers of health care payers or former payers) from CEE and ME countries during a policy workshop. Considering the travel restrictions related to the COVID-19 pandemic, the workshop had to be organized as a virtual meeting. The virtual workshop took place in June 2021 with 16 members of the HTx consortium and 14 payer experts from Bulgaria, Croatia, Hungary, Poland, Ukraine, Serbia, Slovakia, Slovenia, representing 8 CEE countries and 4 ME countries, including Egypt, Jordan, Lebanon, Turkey and 3 WE countries (The Netherlands, Sweden, The United Kingdom).

In the first part of the workshop, participants received an introduction of relevant experiences in Sweden, the United Kingdom, and The Netherlands. This was followed by a presentation of the draft list of barriers and recommendations created by the research team. Participants were then allocated into working groups, consisting of 4 workshop participants and 4 representatives from the research team in each group. Finally, the rapporteurs summarized the findings of each working group, providing feedback to workshop participants and clarifying all emerging questions.

As part of the third and final step of our approach, the research team summarized their findings in a draft report containing the consolidated list of barriers and recommendations identified. Workshop participants were given an opportunity to make final comments and amendment suggestions to the report. After the workshop, we reached out to participating experts to confirm their inputs provided during the workshop.

The final outcome of the research carried out by the HTx team was a list of barriers and potential solutions for outcome-based reimbursement models, based on a consensus among the research team and workshop participants.

3. Results

After deduplication of barriers retrieved from different sources, the HTx research team concluded with 20 different barriers in 5 groups, including (i) transaction costs and administrative burden, (ii) measurement issues, (iii) IT and data infrastructure, (iv) governance and (v) perverse policy outcomes and made practical recommendations to address these barriers (see summary in Table 1).

Recommendations for barriers of implementing outcome-based reimbursement models in CEE and ME countries

3.1. Transaction costs and administrative burden

Unlike MEAs with financial terms only (such as rebate, price-volume agreement, manufacturer funded initial treatment period, etc.), the transaction costs and administrative burden of implementing outcome based agreements are more significant.

3.1.1. Complex and resource intensive negotiations on contractual terms

Outcome-based reimbursement models require complex and resource intensive negotiations on contractual terms. The complexity of negotiations can be reduced by considering transferring the structure of existing agreements from higher income countries. Multinational manufacturers, supranational organizations or international consortiums supported from the Horizon Europe framework program can facilitate the transfer of agreements by developing contract archetypes for the most common health care financing systems. Contracts should have clarity on foreseeable problems, for example re-opener clause has to be a standard section in the agreements to manage situations when a new product is entering the market. Finally, in parallel with the increasing evidence base of technologies, when agreements are renegotiated, the latter agreement should be simpler than the first, as there is limited benefit from maintaining complex agreements in managing less and less uncertain outcomes.

3.1.2. Costly collection of outcomes data without appropriate funding mechanism for data collection

The implementation of outcome-based reimbursement models may necessitate significant financial resources. Therefore, it is a relevant question how the incremental costs can be minimized and who should cover the costs of the additional data collection.

(Makady, 2019)

If feasible, payers should rely on the existing infrastructure that would minimize extra costs. Additionally, reusing the existing medical and/or reimbursement claim data could also contribute to data collection without significant extra costs. If these do not provide enough evidence, additional data collection is inevitable. The underlying costs should be covered by the pharmaceutical manufacturers. Payers should make sure that the pharmaceutical manufacturers take responsibility for the required extra data collection (and other costs e.g. administrative costs). It is also suggested that the data will be made publicly available.

3.1.3.Administrative burden on health care providers to collect data

Outcome-based agreements can be successful only if relevant real world data is collected. That cannot be achieved without the involvement of health care providers. As collecting data on the result of the treatment usually does not happen in the structured way that is required to derive evidence from the data during the treatment, that would require extra and significant commitment from the health care providers. (Stafinski, 2010) Payers should make it interesting for health care institutions to put effort into making outcome-based agreements a success (e.g. by financial or other rewards). Health care institutions should opt-in to prescribe medicines in outcome-based schemes. That would mean that they take the commitment to collect data as they would be eligible to prescribe the medicines only that way. Besides, involving leading centres in a network to publish real world data could also contribute to minimizing the administrative burden on health care providers if they would have access to such publications.

3.2. Measurement issues

The internal validity of real-world evidence is more limited to scientific evidence generated in clinical trials. On the other hand, the external validity of real-world evidence is greater, hence, with careful measurement of real-world outcomes in payment agreements valuable complementary data can be generated, which ultimately has strong potential to reduce the decision uncertainty of new technologies.

3.2.1.Lack of Health Economic & Outcomes Research expertise

Specifying and determining treatment effects in nonrandomized and observational settings are critical for outcome-based agreements. However, these processes are

resource intensive and very specialized. Therefore, an important step is to enable the training of payers and their advisors about health economics and outcomes research (HE&OR). In addition, the capacity of HE&OR experts should be increased in payer organisations. Capacity building can be facilitated by participation in international educational initiatives. Finally, the capacity constraints in HE&OR can also be reduced by implementing joint outcome-based reimbursement models at the regional level.

3.2.2. Surrogate outcomes are not warranties

Since a long time-frame is needed to capture hard end-points, surrogate outcomes are usually the second-best measures to support reimbursement decisions. (Dabbous, 2020) However, surrogate outcomes may not guarantee improvements in hard end-points. (Ciani, 2021)

In outcome-based reimbursement model only those surrogate endpoints should be selected which are valid predictors of patient outcomes. If such validation is not available upfront, additional data collection within the outcome-based reimbursement model can be considered to validate the surrogate outcome. A greater dialogue between clinical opinion leaders, HE&OR experts, payers and patient representatives can facilitate the consideration of different perspectives both at the initiation and follow-up of agreements. If outcome-based reimbursement models are designed by consensus of multiple stakeholders, there is a better chance for them to be successful.

3.2.3. Confounding factors of the treatment success

Even in the case of cooperation between relevant stakeholders, the success of the treatment cannot be guaranteed due to inefficiencies in the health care system, and confounding factors, such as poor adherence of patients, suboptimal patient pathways, or hidden access barriers to supplementary services (Inotai, 2020). Outcome-based reimbursement models create direct incentives to manufacturers to recommend and facilitate solutions for better patient selection, patient education, support of health care providers. Partnership between the payers and manufacturers in monitoring and improving health outcomes is recommended as that can contribute to reducing the inefficiency of health care delivery.

Given that there is a real human and financial resource restriction, outcome-based

agreements should not be the standard when simpler models can suffice. A very clear selection mechanism should be developed and implemented to make sure outcome-based agreements are applied rationally and sparingly.

3.3. IT and data infrastructure

As the current way of treatment and the underlying financing mechanisms are not set for measuring and reporting real-world health outcomes, IT and data infrastructure can be a barrier of implementing outcome-based reimbursement models.

3.3.1. Failure to capture necessary data

As outcome-based payments are usually not based on health outcomes in current health care financing systems, current IT infrastructure of health care payers is designed to collect and monitor electronic utilization records of health services and technologies. Hence, failure to capture necessary outcomes data is a real uncertainty of implementing outcome-based reimbursement models. (Michelsen, 2020)

If such difficulties are expected, a pilot phase of implementing outcome-based reimbursement models should be considered and adjustment to the agreement may be considered based on the relevant experiences. If the adjustments still do not provide a better solution, terminating the outcome-based agreement could be considered.

3.3.2. Fragmented health care financing and service provision

Outcome-based reimbursement models can be a real challenge in health care systems with multiple payers for many reasons. An ongoing agreement should not prevent patients from choosing another health care payer, however, such a change may complicate the outcome-based agreement. In addition, in some countries patients may have duplicate coverage, and so they can choose which is the simpler option for getting reimbursement to specific health care services or technologies. If an expensive medicine is covered from the public payer and diagnostics are covered from the private supplementary insurance, there is disconnect between the therapy and monitoring outcomes.

In health systems with fragmented health care financing limiting the scope of outcomes to hard end points can facilitate the feasibility of implementing outcome-based reimbursement schemes. Besides, promoting the national platform (e.g. coordinating

centre for outcome-based agreements serving for multiple payers) with system based incentives could contribute to a successful agreement scheme. It is recommended that outcome-based agreements are centrally coordinated, even in a fragmented system, and implemented with system-based incentives.

3.3.3.Limits in compatibility of system data

Usually medical, pharmacy and payer data systems are designed for different purposes. Hence, it is no wonder that the data structure is not identical. Compatibility of data from the different systems could result in a limit for outcome-based schemes. (Garrison, 2013) A general framework for the compatibility of health care data is key in implementing outcome-based data collection. Linkage of medical records, patient registries and payers' databases and reusing existing data can be an answer to the increasing need of real-world evidence for multiple research questions (Grigore, 2020). The payers in LICs should invest in linking the different data sources or require pharmaceutical manufacturers to pay for additional data collection.

3.3.4.Limited uptake of patient registries

Patient registries are key especially for rare diseases with high treatment cost (Boulanger, 2020). Although this is clear to all stakeholders, due to the barriers - such as lack of IT and data infrastructure, limited financial budget - countries are not setting up registries to all relevant patient groups. All stakeholders, who can be beneficiaries of patient registries, should be identified and encouraged by relevant incentives to facilitate the establishment of patient registries that are internationally aligned.

3.4. Governance

Implementation of financial MEAs, which are common even in LICs (Ferrario, 2017) (Maskineh, 2018), would not be possible without proper regulatory and legal background. As outcome-based reimbursement schemes are just about to be implemented, the regulatory and legal framework should be updated to enable that for payers and manufacturers as well.

3.4.1.Lack of regulation

The minimum criterion is to enable the possibility for health care payers to conclude outcome-based reimbursement models with the manufacturers in the legislative and regulatory framework. (Goodman, 2019)

Considering pilot outcome-based reimbursement schemes in the initial period would create an opportunity for more sustainable regulation. Based on the experience of the pilot cases a regulatory and legal framework should be proposed with recommendation for a rationale selection mechanism on when to apply outcome-based reimbursement models. Besides international collaboration on how to regulate the implementation of outcome-based reimbursement models would be beneficial. LICs can learn from each other especially if health systems are similar. Regional collaboration is a good opportunity to overcome the barrier of lack of regulation.

3.4.2. Contradicting motivation of limiting patient access

Incentives of health care professionals, patients and manufacturers to improve patient access limit their compliance to keep agreements. They would like to provide access to all patients. That motivation makes it hard to keep outcome-based reimbursement models, such as terminating a treatment, if the target in surrogate outcomes is not reached. Therefore, outcomes should be objective, clearly defined, reproducible and difficult to manipulate.

3.4.3. Unknown consequences of better results

Although clinical benefits measured in clinical trials can hardly be replicated in real world, in theory, the therapy can result in worse, the same or better outcomes in the real world than in the clinical trial. This leads to the question what happens if results are better than expected. For example, can the manufacturer increase the price? For such cases no special policy action is recommended, which has to be stated explicitly in the agreement, as better results can happen without outcome-based reimbursement models as well.

3.4.4. Limited trust between payers and manufacturers

Outcomes data of patients cannot be accessible for manufacturers (due to legal restrictions), which implies that health care payers have direct control over individual patient records with serious financial implications on manufacturers. The trust between payers and manufacturers has to be maintained by making outcome data available for independent audit. As the audit should be requested by the manufacturer, its cost should also be covered by them. Sales revenues or paybacks could be frozen until the audit confirms the outcome data, the ring-fenced budget can be released after the audit is completed. (Mahendraratnam, 2019)

3.4.5. Difficulties in excluding therapies from reimbursement and renegotiating prices

Exclusion of high-cost therapies from the reimbursement list due to lower-than-expected health benefits is a politically sensitive step, as even in such cases the technology may be the best alternative for several patients. Although adjustment of the price to the lower clinical value is a reasonable solution, pharmaceutical companies are reluctant to lower drug prices due to market externalities through the external price referencing system. Confidential price reductions should be part of the outcome-based agreement. Similarly, to the regulatory response related to safety concerns, clear legal foundation is necessary to support delisting therapies from public reimbursement, if real-world health benefits are proven to be worse than expected. Clinical and patient representatives should be involved to such sensitive decisions. (Makady, 2019)

3.5. Perverse policy outcomes

Even in case of the best legislative framework, complex contractual agreements can have negative implications beyond the improvement in the agreed health outcome. Such implications should be carefully evaluated prior to introducing the outcome-based schemes in partnership with all stakeholders.

3.5.1. Equity in patient access

If new therapies would be available only in those centres, which are involved in the outcome-based reimbursement models, equitable patient access may be compromised. On the other hand, patient access in at least a few selected centers is still better than no patient access to the new technology without the outcome-based reimbursement model. Still, in the selection process of prescribing centers the equitable geographical coverage should be considered both upfront and in the renegotiation phases.

3.5.2. No improvement if real world data remains unpublished

Outcome-based reimbursement models provide an opportunity to generate real world evidence about technologies with uncertain health benefits. However, if real-world data collected in such scheme remains unpublished (Garattini, 2015), there is no improvement in the evidence-base of health technologies for those stakeholders, who are not directly involved in the analysis of primary data or not getting access to aggregated results. No publication of real-world data from outcome-based schemes may not resolve the duplication of efforts among payers facing similar uncertainties in the

relative effectiveness of new health technologies.

Evidence gathering methods should be shared and implemented jointly by multiple health care payers in different countries. That would result in improvement in information quality and completeness and prevention of potential information bias. It should be highlighted that evidence about the effectiveness of health technologies should be considered a global public good, and so publishing real world evidence from outcome-based agreements should be an international standard. (Kalo, 2021)

3.5.3. Non-transparency of policy decisions

Certain elements of outcome-based agreements, especially the net price with the actual paybacks, are considered confidential, which reduces the transparency of the resource allocation decisions. The public confidence in policy decisions can be improved by increased transparency around the key components of the scheme, for example publication of the objectives, process and structure of agreements and the generated real-world data. (Wenzl, 2019)

3.5.4. True cost-effectiveness of health care interventions cannot be calculated

Implementing value-based health care is a challenge due to the confidentiality of actual prices, if the true cost-effectiveness of any health technologies cannot be calculated. (Nemeth, 2020a) However, this problem is already well-known from experiences of financial MEAs, so inclusion of outcome-based agreements to reimbursement models in countries with existing confidential price agreements would only marginally increase the problem. Two-way sensitivity analysis for the prices of compared technologies can make economic evaluations relevant to health care payers, who may have precise knowledge on the net prices both of the comparator and the new technology. Eventually the complexity of cost-effectiveness calculations may even be reduced by publishing HTA documents, with special focus on the newly generated real-world evidence.

3.5.5. Lower income countries pay more for medicines

Higher income countries usually have more resourceful HTA bodies and greater economic power when negotiating about confidential discounts, and so lower income countries may pay even more for medicines. The limited HTA capacity of late technology adopter lower income countries can be alleviated by re-using the transferable elements of joint HTA reports and focusing only the calculation of the local value based price.

(Nemeth, 2020b). The market potential of lower income countries can be increased if they set-up a joint procurement process, which can compensate manufacturers with a larger volume in case of successful agreements.

4. Discussion

Population health status is correlated with the economic status of countries, and so the capacity to benefit from innovative technologies may even be greater in lower income countries. However, the health gap between poorer and more affluent countries cannot be reduced, if policy-makers in the health care sector of lower income countries do not put more emphasis on selecting only those technologies for reimbursement, which can generate greater absolute health gain. The opportunity cost of the selection process for high-cost technologies can be mitigated by implementing outcome-based reimbursement models, in which the health gain is guaranteed. In other words, health care payers should have the opportunity to purchase health instead of purchasing health technologies. Such agreements may contribute to new standards in health care provision, in which health gain has primary importance over other objectives for health care providers, patients, pharmaceutical and medical device manufacturers. The importance of reaching target health gain creates incentives for all stakeholders to pay more attention to health outcomes not only by creating access, prescribing and utilising new health technologies, but also by streamlining patient pathways and improving other elements of care.

The momentum for outcome-based reimbursement models is strengthened by the ongoing initiative to enhance regulatory post-authorization requirements, especially in those cases where only conditional market authorization is granted for new medicines which respond to huge unmet medical needs with uncertain clinical value (Eichler, 2021). Implementation of outcome-based reimbursement models is challenging, especially in resource constrained health care systems of lower income countries. However, those challenges can only be resolved by making an effort to conduct at least pilot agreements and preparing for predictable barriers.

5. Conclusion

Our guidance paper can be considered only as an initial step in this process. The generalisability of our recommendations can be improved by monitoring experiences

from pilot reimbursement models in CEE and ME countries and continuing the multistakeholder dialogue at national levels, especially because the number of involved stakeholders in the consultation process of the HTx project was relatively limited partly due to the pandemic period.

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7. Appendix

Figure 1. Process of creating policy recommendations for the implementation of outcome-based reimbursement models for technologies with high upfront cost in Central and Eastern European and Middle Eastern countries

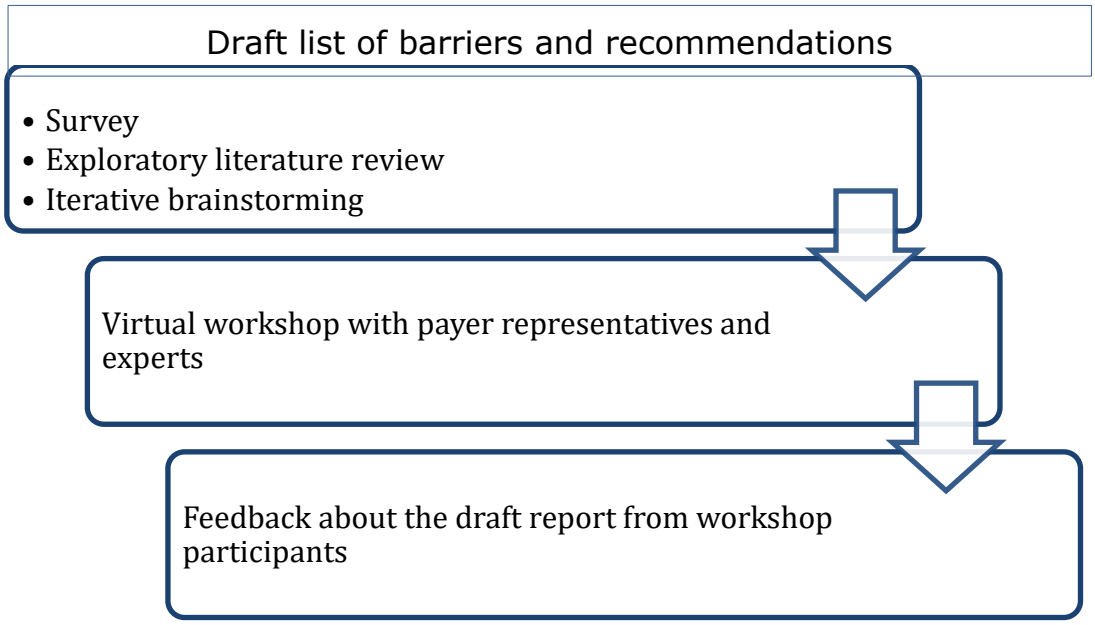

Table 1. Summary of barriers and recommendations

Group of barriers	Barriers	Recommendations
Transaction costs and administrative burden	Complex and resource intensive negotiations on contractual terms (including the first agreement and renegotiations)	1) Consider transferring the structure of existing agreements from higher income countries 2) Develop contract archetypes for most common schemes 3) Include re-opener clause into the agreements 4) When agreements are renegotiated, the latter agreement should be simpler than the first
	Costly collection of outcomes data without appropriate funding mechanism for data collection	If feasible, 1) rely on existing infrastructure 2) reuse of existing medical or claims data 3) cost of incremental data collection should be covered by pharmaceutical manufacturers
	Administrative burden on health care providers to collect data	1) Health care institutions should opt-in to prescribe medicines in outcome-based

		schemes 2) Involve leading centres in a network to publication of real world data
Measurement issues	Lack of HE&OR expertise to specify and determine treatment effects in nonrandomized and observational settings (especially in rare diseases)	Capacity building in HE&OR (including education and collaboration in international initiatives)
	Long-time frame to capture hard end-points, however, in surrogate outcomes may not guarantee improvement in hard endpoints	1) Greater dialogue between clinical opinion leaders, HE&OR experts, payers and patient representatives capturing different perspectives both at the initiation and follow-up of agreements 2) Surrogate endpoints should be valid predictors of patient outcomes. If such validation is not available upfront, additional data collection within the agreement can be considered to validate the surrogate outcome
	Treatment success is affected by confounding factors that cannot be controlled (e.g. inefficient health systems, local practice patterns, or poor treatment adherence)	Outcome based agreements provide incentives to manufacturers to address inefficiencies of health care delivery
IT and data infrastructure	Failure to capture the necessary data to reduce uncertainty within current infrastructure	1) If difficulties to collect data is expected, consider a pilot phase with adjustment according to early experiences 2) Terminate the agreement, if there is no better solution
	Fragmentation of healthcare financing and service provision makes it difficult to undertake outcome-based schemes	1) In fragmented health care system limit the scope of outcomes to hard end-points 2) Promote national platform for outcome based agreements with system based incentives even in fragmented health care systems
	Limited compatibility of medical, pharmacy and payer data systems restrict meaningful retrospective analysis	Invest into building pragmatic MEA implementation frameworks by 1) linkage of databases 2) reuse of existing data
	Limited uptake of patient registries	Facilitate the establishment of patient registries with incentives to all stakeholders
Governance	Lack of regulation	1) Consider the implementation of pilot cases 2) Consider rationale selection mechanism when to apply outcome based agreements 3) Prepare regulatory legal framework based on experiences in the pilot phase
	Incentives of health care professionals, patients and manufacturers to improve patient access limits their compliance to keep agreements	Outcomes should be objective, clearly defined, reproducible, and difficult to manipulate

	Unknown consequences of better results than expected (e.g. can prices be increased?)	No special action is needed 1) similarly to current practice outside outcome based agreements 2) such situation rarely happen, as clinical benefits measured in clinical trials can hardly be replicated in real world
	Limited trust between payers and manufacturers	1) Outcomes data should be made available for independent audit 2) Sales are frozen and be made available depending on the outcome to the payer or to the manufacturer
	Difficulties for health authorities to delist health technologies or renegotiate prices	1) Clear legal foundation to support delisting of medicines due to limited efficacy (similarly to existing safety issues) 2) Involve clinical and patient representatives into delisting decisions
Perverse policy outcomes	Equity in patient access may be compromised when the new technology is available only in selected centres	1) Consider that no agreement would result in no patient access to new technologies 2) Extend the scope of prescribing centres when renegotiating the agreement
	No improvement in the evidence based of health technologies, if real world data in outcome-based schemes remains unpublished	1) Evidence-gathering efforts can be shared and implemented jointly by countries to improve information quality and completeness and to counter potential information bias 2) Evidence about the effectiveness of health technologies should be considered a global public good. Publication of real-world evidence in outcome based agreements should be an international standard
	Non-transparency of policy decisions due to confidential nature of data captured in agreements	Increase transparency around key components of the scheme
	Difficulties to implement value based health care, as due to confidentiality of actual prices, true cost-effectiveness of any health care interventions cannot be calculated	1) Public availability of HTA documents 2) Two-way sensitivity analysis for the prices of compared technologies in economic evaluations
	Lower income countries may pay more for medicines, as higher income countries potentially have greater economic power when negotiating about confidential discounts	1) Strengthen HTA system to calculate the local value based price 2) Consider joint procurement by lower income countries