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PERSPECTIVE



# Implementing a Managed Entry Agreement Framework in Cyprus

Olga Pitsillidou [a,b], Panagiotis Petrou [b,c] and M. J. Postma [a,d]

[a]Department of Health Sciences, Unit of Global Health, University of Groningen, Groningen, The Netherlands; [b]Health Insurance Organization, Nicosia, Cyprus; [c]Pharmacoepidemiology-Pharmacovigilance, Pharmacy School, School of Sciences and Engineering, University of Nicosia, Nicosia, Cyprus Health Insurance Organization, Nicosia, Cyprus; [d]Department of Economics, Econometrics and Finance, Faculty of Economics and Business, University of Groningen, Groningen, The Netherlands

**ABSTRACT**

**Introduction:** The aim of this study is to explore the current practice in Cyprus regarding the introduction and reimbursement of innovative pharmaceuticals through Managed Entry Agreements (MEA), assess its operational context, and suggest approaches toward spanning the knowledge gap consequential to these efforts, especially the barriers of a small country context.

**Areas covered:** The recent introduction of a National Health System (NHS), brought about fundamental reforms in Cyprus' Healthcare sector. Among such reforms, of particular interest, has been the introduction of a Managed Entry Agreements (MEA) mechanism. The first preliminary results indicate that despite being a small and unattractive market, Cyprus can apply a substantial MEA program. Concomitantly, it annotates the need to design an operational framework which should include, the definition of important technical parameters, clear demarcation of the scope, cooperation principles ensuring the effective operation of scientific committees, and clear delineation of what 'value' is. Moreover, in the context of the unified healthcare market, budget transfers should be considered, which could alleviate the inordinate budget impact of new products, which nevertheless will cut down on hospital expenditures. Narrative synthesis and health policy analysis-related resources were used.

**Expert opinion:** The implementation of MEA in Cyprus provides an ideal testing ground for innovative reimbursement approaches. This will streamline the country's efforts toward reimbursement of innovation, while concomitantly add to the collective MEA experience.

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Cyprus; cost-effectiveness; health system transition; HTA; MEA implementation; innovative pharmaceuticals; small country; value-based pricing

## 1. Introduction

### 1.1. The introduction of the NHS

Cyprus constitutes one interesting case, since it is one of the last EU countries to introduce a Universal Health Coverage (UHC) National Healthcare System (NHS). The introduction of the NHS in 2019, was one of the prerequisite structural reforms required by the bail-out agreement between Cyprus and the Troika in 2011 [1].

Prior to the NHS' introduction, the healthcare sector was segregated into two distinct sectors: the public and the private one, which formed a highly unequitable health environment. These sectors operated in parallel and never operationally merged. This situation led to the duplication of infrastructures and the inability to maximize the efficiency of the system, which was predominantly the negative blueprint of Cyprus' healthcare landscape [1]. The beneficiaries of the public healthcare sector had access to a vertical line of medical services in the form of public primary care, inpatient care at public hospitals, and free access to all pharmaceuticals prescribed by doctors employed by the Ministry of Health (MoH) which were only dispensed through public pharmacies. The criteria which granted eligibility to public healthcare benefits were either socioeconomic, or employment status-based (i.e. civil servants). The public sector was exclusively financed through the state budget. All employees of public healthcare facilities had the status of civil servants and were salaried employees of the state [2]. At any rate, this profoundly violated equity access.

Individuals who did not meet the socioeconomic or employment criteria necessary to attain public healthcare coverage, could only resort to the private sector, for timely care. All healthcare services that were provided privately in Cyprus had to be paid out-of-pocket (OOP), an attribute which explicates why Cyprus private OOP surpassed public funding and potentially exposed patients to catastrophic expenditure. Private insurances have also been available; nevertheless, the prevalently applied cherry-picking practice, deterred older persons, or persons with comorbidities to benefit from available health plans.

It hence comes as no surprise that Cyprus displayed a 43% public share of total health expenditure, the lowest and far below the 79% EU average [3]. Nevertheless, the highly centralized structure of the public health sector and the successful implementation of tendering contributed for a comparatively low public spending, albeit at the cost of lengthy procedures, small formulary, shortages which could not be tackled swiftly, and scientifically unjust decisions [4].

**CONTACT** Olga Pitsillidou o.pitsillidou@hio.org.cy Department of Health Sciences, Unit of Global Health, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

**Article highlights**

- The healthcare system in Cyprus is adopting a mainstream implementation of MEA
- This has highlighted the many opportunities arising from the transition as well as the threats
- A necessity exists of a robust and transparent framework to support the transition
- Cyprus as a late-comer, can draw on the experiences of other countries
- Cyprus can take advantage of its small market size while transitioning to the implementation of MEA.

The narrow scope of public formulary and the extended waiting lists, forced a substantial number of patients to resort to the private health sector for timely care, thus disproportionately burdening them with out-of-pocket expenditures.

The 2019 NHS introduction, merged the two formerly segregated healthcare sectors under the umbrella of a single-payer universal healthcare coverage (UHC) system. Beneficiaries of the system are all ordinary residents of the areas controlled by the Republic of Cyprus and their dependents. This term excludes people holding citizenship, but keeping their permanent residence and tax profile, in a different country or the parts of the island that are not under the control of the Republic of Cyprus due to the complex political situation in Cyprus.

The Health Insurance Organization (HIO), which serves as the single-payer of the NHS, was established in 2001. It is governed by a Board of Directors (BoD) which represents the social stakeholders of the system: the government, the patients, the employers, and the employees (trade unions) [1].

The healthcare system reform was introduced in two phases. Outpatient services were introduced in June 2019, while the introduction of inpatient care in September 2020, finalized the implementation of the reform, while currently only palliative care is yet to be added.

While reimbursement of pharmaceuticals is now solely provided by the HIO, pricing remains under the auspice of the Department of Pharmaceutical Services (DPhS) of the Ministry of Health (MoH). Pharmaceutical prices are set and regulated by the DPhS at all levels, through annual external price referencing (EPR) [5].

Within this new era, outpatient drugs are dispensed through community pharmacies. Day-case and hospital drugs, are dispensed through hospital pharmacies. This dispensing policy marks a major shift from the previous one, where all beneficiaries had to be served by a few scarcely located public pharmacies with all negative repercussions this entailed.

The HIO currently has three Positive Reimbursement lists (Figure 1):

(1) Direct use list, which includes a) outpatient pharmaceuticals and medical devices reimbursed by the NHS, and b) high-cost pharmaceuticals dispensed by hospital pharmacies to be self-administered by the beneficiary.
(2) Z-Drug Catalogue, which includes all pharmaceuticals reimbursed for day-case claims. Infusion costs and other administration-related costs that may arise, are reimbursed independently.
(3) Z-Consumables Catalogue, which includes all inpatient high-cost medical devices not reimbursed through the DRG.

There is currently no negative reimbursement list. However, lack of MEA for innovative pharmaceuticals will result in their listing in a negative reimbursement list.

Outpatient drugs are reimbursed at Pharmacy Purchasing Price (PPP). Subsequently, the reimbursement price is corrected through a rebate mechanism which is set forth in relevant decrees. Furthermore, the global budget for pharmaceuticals is protected via yearly claw-backs which are activated if the actual annual health expenditure exceeds the predefined budget. This eliminates any fiscal concerns, since the annual expenditure is hard-capped and any excess is redeemed by the industry [5]. Innovative pharmaceuticals are excluded from claw-backs, making the need for MEA implementation more pertinent.

### *1.2. Innovative and high-cost pharmaceuticals in the NHS*

As far as the reimbursement of innovative medicines is concerned, the issue has emerged as one of the most challenging topics for the NHS, and as such, it has been at the core of public debate. Departing from the preexisting tendering system, the policy implemented by the NHS provides that innovative products are fully reimbursed; thus, no personal contribution applies. This policy is nested in the fact that the high OOP costs resulting by the implementation of the internal referencing system, would act as a barrier to access. Moreover, the notion of OOP costs, is embedded in the assumption that patients are in the position of making informed selections, something not valid given the specific market.

It was previously postulated that Cyprus has high pharmaceutical prices, even though based on the reference basket the prices should be in the EU average [6]. Therefore, to compensate for the abandonment of the OOP policy, and toward ensuring the sustainability of the health care system (HCS), shielding it from the soaring fiscal pressures, while providing unobstructed access to high-cost pharmaceuticals, measures of cost containment and risk mitigation, became necessary.

Thus, the scope of this paper is to address the current environment with regard to reimbursement of innovative pharmaceuticals in Cyprus through MEA. As such, we deemed fit not to elaborate on the assessment and reimbursement of medical devices, which due to the breadth of the relevant catalog, would merit a separate study and commentary.

## 2. MEA: opportunities and weaknesses entailed for Cyprus

As in all health care systems, Cyprus' financial resources are not infinite while there is a constant stream of novel

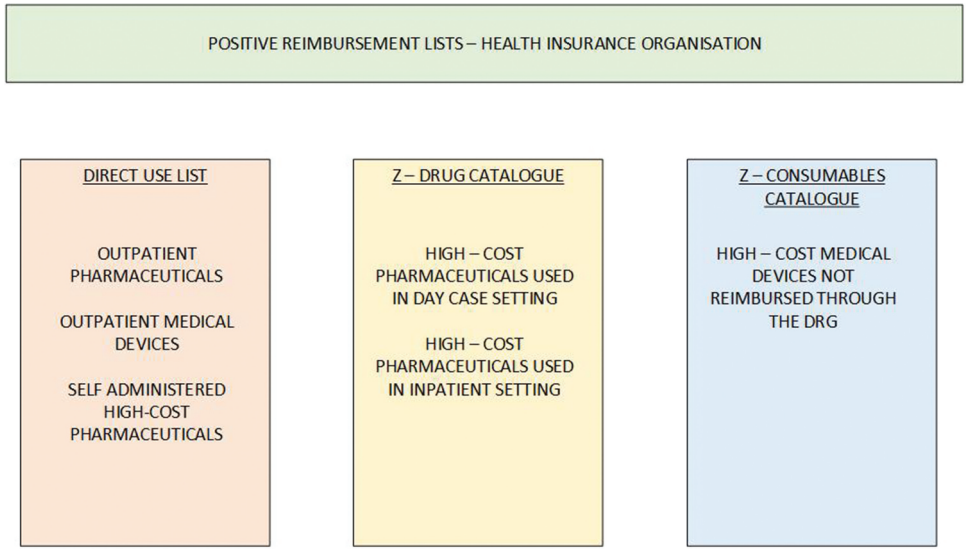


Figure 1. Reimbursement Lists.

pharmaceutical agents seeking reimbursement status. However, it has become apparent that the ever-increasing prices of new pharmaceuticals do not directly relate to their added value in existing therapeutic strategies. Therefore, Cyprus aims to apply a MEA targeted toward innovative therapies, in order to align the soaring prices of innovation with the added value it offers to the system in the most financially sustainable way [7,8].

We should primarily elucidate the several operational pillars of MEA. MEA should target the embedded uncertainty and not just rely on occasional price reductions for a product whose efficacy is low, with a myopic perspective [7]. This was an exemplar of tendering: several products with inferior results submitted steep price reductions and were awarded the tender. However, the majority of patients diverted this therapeutic option and opted for the individual patient committee, aiming to access the innovative therapeutic options that were excluded from the formulary for failing to win the tender. This served negatively bifold: the payer was obliged to buy certain guaranteed quantities (at least 70% of the agreed quantity) of a product through the tender, which could not be used, while additionally, the parallel market pathway implies that the other product is reckoned as superior. The perceived superiority resulted in shielding drug prices from further reductions. In the long-run, by perpetuating the tendering approach for innovation, the already unattractive market of Cyprus may transform to a no man's land for the industry, which can be aggravated by the obligations for a country-specific package, which do not fit the economies of scale operational framework, the industry seeks.

One major system evolution lies to the ability to reach MEA with the industry, thus allowing the HIO to consider other procurement schemes, apart from tendering. A MEA entails an array of tools that can be used to minimize uncertainty stemming either from lack of adequate evidence regarding the performance of a new therapy compared to standard care, or lack of resources to reimburse it, thus, enabling swifter patient access to innovative therapies [8,9].

MEAs can be drafted as financial agreements, outcome-based agreements, or a combination of the two [8]. Financial agreements are preferable in Cyprus' case because of both the lower technical skills necessary to design and implement them as well as the restrained recourses required to monitor them. Case in point, while the electronic prescribing system of the NHS collects and stores data according to General Data Protection Regulation (GDPR) and all relevant safety and privacy information, the debate on who will have access to this data, in which format and how will they be transferred is still ongoing.

Regarding financial-based MEA, Cyprus as a small country with low purchasing parity, faces the potential of achieving less favorable schemes, compared to bigger markets, since the industry is not willing to take stakes, given a possible spill-over effect on prices [10]. Where outcome-based MEA are concerned, Cyprus needs to overcome the lack of experience, the lack of infrastructure, and the lack of economies of scale as well, both from company's and payer's perspective.

On the other hand, Cyprus' small size can be capitalized upon by serving as testing ground for innovative approaches in MEA and risk sharing schemes. The country's small size and highly centralized NHS structure would allow for faster registry building and patient monitoring, while concomitantly not requiring the considerable resource investment necessary in the case of larger and more complex markets. This was broadcasted in the case of COVID-19 vaccination rollout in Israel [11]. The implementation of such schemes should be thoroughly evaluated even once experience is accrued, since the costs for the additional resources needed for managing them, might render their introduction cost-ineffective [8]. The information produced should be evaluated with caution at this early stage, and after elimination of potential biases, since the low number of patients could lead to skewed data.

This necessitates a thorough assessment prior to the introduction of MEA and highlights the implicit relationship between HTA and MEA [12].

## 3. Current framework

Currently, and until all MEAs are concluded, high-cost pharmaceuticals reimbursed by the NHS, continue to be procured through the existing centralized tendering process. As such, tenders for pharmaceuticals are awarded to the lowest bidder, while no other pharmacoeconomic criteria are applied [4]. As previously documented, tendering yields significant savings, but it is a blunt tool spiraling to lack of sensitivity in high-clinical-value products. The reduction is usually correlated with the volume and sales value, while the clinical value of the product, is not interrelated. This attribute conflicts with the value-based orientation outlook of the NHS [13].

Moreover, the tender employment method bequeathed to the HIO, hinders the implementation of updated clinical guidelines, as the preferred therapeutic modalities would raise costs to the detriment of winning the tender. According to the relevant NHS legislation [14], the reimbursement prices of high-cost pharmaceuticals must be set by the BoD, based on the recommendations of the Drugs Advisory and Drug Reimbursement Advisory Committees (DAC and DRAC). The DAC is appointed by the Ministerial Council, and consists of 10 members. It is an independent scientific expert committee The DRAC is comprised by both in-house experts and one representative from the Ministry of Health and Ministry of Finance, respectively. The DAC, which is an independent committee, bears the responsibility to assess and appraise the reimbursement status and conditions of pharmaceuticals and medical devices. The DRAC, which is appointed by the BoD, provides recommendations regarding the reimbursement price of products assessed by the DAC. DRAC has the responsibility of negotiating MEAs as the BoD proxy. Both committees offer their resulting recommendations to the BoD, who is tasked with rendering a decision regarding the inclusion of the modality on the positive reimbursement list.

## 4. Operational framework for MEA and the reimbursement of high-cost pharmaceuticals

### 4.1. HTA in Cyprus

The stepping stone to the implementation of a primarily MEA-based reimbursement system is the availability of data obtained through HTA. HTA aims to determine the consequences stemming from the adoption of a particular therapeutic modality, while safeguarding the most efficient pattern, to utilize the available monetary resources [12,15]. In the case of high-cost pharmaceuticals and innovative treatments whose reimbursement counters both significant costs and uncertainty, Cyprus, uses HTA data as the determinant of the status and conditions based on which new technology should be reimbursed [16]. HTA can safeguard the transparency of pricing and reimbursement decisions. As such, decision makers may use HTA complementary to their decision mechanism rather than solely relying on short-term budget impact-centered approaches, the latter being the most relevant for Cyprus [16,17].

Rudimentary HTA is performed by DAC through data collected and analyzed by dedicated HTA institutions, such as NICE, SMC, IQWIG and the Canadian HTA agency. The final assessment of the agency is also taken into consideration, but it is not an explicit factor on whether a reimbursement recommendation will be given. Rather, the raw data are used which are available at a much earlier time than decision publication, and will be used by the DAC [18].

While HTA is not institutionalized in Cyprus, early steps toward capacity building and framework design are evident by the albeit, slow introduction of innovative technologies in the NHS' positive reimbursement list. Human and fiscal resources should be invested in the design and apposite implementation of a transferability and adaptation of assessments framework that will in turn serve as the foundation to support the design and implementation of robust MEAs from a technical perspective [19].

However, the transferability of data is not a straightforward process. As previous authors argued, there are many country-specific issues which must be considered before an explicit transfer is done. Evaluating the adaptability and subsequently adapting an HTA assessment to a different economic and social environment, requires an advanced level of specific expertise. Transferring HTA and economic evaluation decisions from larger bodies to smaller ones needs to be done after evaluating the sensitivity-prone issues and thorough assessment of the added value [19,20].

A collaboration by which Cyprus could benefit in these early steps in MEA is EUnetHTA, the European initiative on joint HTA assessments. Joint European HTA assessments along with a suggested transferability framework will benefit Cyprus by streamlining access to data. However, use of joint assessments assumes an alignment in therapeutic guidelines between member states [21].

The question that is usually raised is whether Cyprus can fully operate a functional HTA, which has been an elusive target. It seems that currently the solution is to invest in the capacity planning for MEA and strengthen the networking with other HTA bodies focusing on the transferability of data. In view of the 2025 EU HTA initiative, any other single-handed approaches of Cyprus may prove futile [18].

### 4.2. Fiscal assessment framework

Abiding by the recommendations of ISPOR, Cyprus requires the submission of a Budget impact model, for products whose sales are anticipated to exceed the threshold of 250.000 euros on their first year in the market [22,23]. The BI model must be set based on a 5-year horizon and no discounts apply. This allows for a more thorough assessment and it is also a stepping stone toward budget correction in the future, i.e. shifting budget across health segments [24].

No economic evaluations are required for the assessment, which is interlaced with the absence of WTP threshold in Cyprus. Indicatively, an implicit maximum threshold for willingness-to-pay (WTP) is determined as three times the per capita domestic product. Any value surpassing this threshold is deemed as not cost-effective, and it is suggested that resources could be better allocated to other therapeutic areas to generate greater health utility [24–27]. While this approach gives due consideration to the financial capacity of Cyprus, we should underline that the definition of threshold is

still in its outset, and therefore this threshold serves only indicatively. More research and social discussion are needed to further corroborate the WTP threshold.

Because of the distortion caused in the standard of care offered in Cyprus by the late adoption of a UHC system, this implicit threshold is used as a guide, while the system's ability to pay is better represented by the necessary BI analysis [28]. There are no methodological guidelines for economic evaluations, which certainly is a gap that must be covered. Nevertheless, due to the dynamic oscillations of the Cyprus economy, which in 2013 was in the brink of bankruptcy, certain indicators may be trivial to generate, i.e. discounting [29].

Budget allocation must be interpreted from the perspective of each modality's cost and benefit decomposition. As discussed, health benefits are disseminated across health segment, or even as social benefits, which construe an intangible estimate. There are numerous examples, one of which is the case of anti – tumor necrosis factor products and the new hypolipidemic agents, which confer reductions in hospital stays and imaging costs. Budget reallocation between cost centers due to better pharmaceutical care may not be feasible practically even under the auspice of a single health care payor [30]. However, the medical benefit of a modality leading to an increase in life-years-gained and decrease in costs outside the pharmaceutical care cost center, should be incorporated in the valuation of the modality and factor in as a counter weight on the budget impact. This solicits a correction in the budget allocation process within cost-centers over time, following the shift of costs that will result by the adoption of a new modality for each of them. Considering that the abolishment of the silo mentality between different cost centers is achieved, an attainable solution would be the implementation of an adjustment factor that would incorporate the shift of costs within one cost center, arising from the adoption of a new modality in a different one. This factor would compensate the pharmaceutical budget for excessive fiscal pressures, given that other sectors redeem financial benefits borne out of the reimbursement of innovative pharmaceutical products. This should primarily focus on products with a strong societal impact, as in the case of new agents aiming to reduce blood transfusion, a public good but with a high significant societal opportunity cost. Overall, this provision would integrate the financial value of these estimates and enable allocation of more resources to the pharmaceutical budget during the health care budget allocation process. We do not assert for a universal implementation since the increase in life expectancy yielded by new products, will actually perpetuate to an increase of utilization of health care in the elderly. Nevertheless, it is possible that the medical needs will be diverted to chronic needs, rather than the primary more severe conditions. Reallocation of funds within cost-centers due to cost alterations in different cost-centers, could not be captured in the previously segregated healthcare sector but will need to be accounted for now, notably with regard to the reimbursement of innovative pharmaceuticals which bid higher prices in exchange to savings in hospital costs or social costs. This is the case of CAR-T therapy and the novel PCSK-9 inhibitors.

All the above mandate a better understanding of deliverables of new products, in order to define to which extent, they can extenuate existing burden of disease.

### 4.3. Negotiation framework

The DAC assessment and the budget impact analysis are passed on to the DRAC in order to apprise the framework on which price negotiations for Managed Entry Agreements (MEA) are performed. The DRAC proceeds with designing a negotiation framework based on the recommendations of the DAC. The DRAC has an array of MEA tools to implement, based on the characteristics of each product, as well as its target condition. The benefits that this approach yields are multidimensional. Primarily, it enables the HIO to align the reimbursement price with the perceived benefit and thus, correct high market prices [31]. Additionally, it allows for an innovation welcoming environment since more pharmaceutical products can enter reimbursement based on therapeutic guidelines. In the previous setting, only the cheapest therapeutic option was available and only people who could not tolerate, or would not respond to it, were able to switch to an alternative treatment. This came as an addition the therapeutic guideline update stalemate, which was initiated in 2016 pending the NHS implementation. This therapeutic option void was remedied by the individual patient committee, and formed a leeway for a parallel market access pathway for innovative pharmaceuticals. Since this conduit was set up to serve – in theory – a small number of patients, pharmaceuticals were procured at their PPP or close to their PPP. Therefore, the effective weighted price for agents targeting a specific disease, is far less impressive than the official tender price of the winner. This annotated the need for a more inclusive formulary, which has emerged a key indicator for the sustainability of the industry in a small and unattractive market. Finally, a competitive market will be quite difficult to convert to a monopoly one, a constant long-term drawback of the tendering system.

The pricing and reimbursement process in Cyprus are represented schematically in Figure 2. The different authorities are assigned different colors.

### 4.4. Operational framework

The extended procrastination in the introduction of the NHS, has led to a stalemate in the updates of therapeutic guidelines and the introduction of innovative therapies in therapeutic algorithms. Therefore, currently Cyprus travails to handle an array of reimbursement submission for new products, along with the task to identify therapeutic options that should be disbursed. This is further complicated by the legal obligation to assess and calculate the opportunity costs of the options reimbursed.

In order to achieve this, it is necessary to structure a robust operational framework where the obligations and responsibilities of all stakeholders are clearly demarcated. At the same time, it must be ascertained that all stakeholders endorse priority setting on a multi-criteria basis that will accommodate not only payer's fiscal concerns, but also diverging

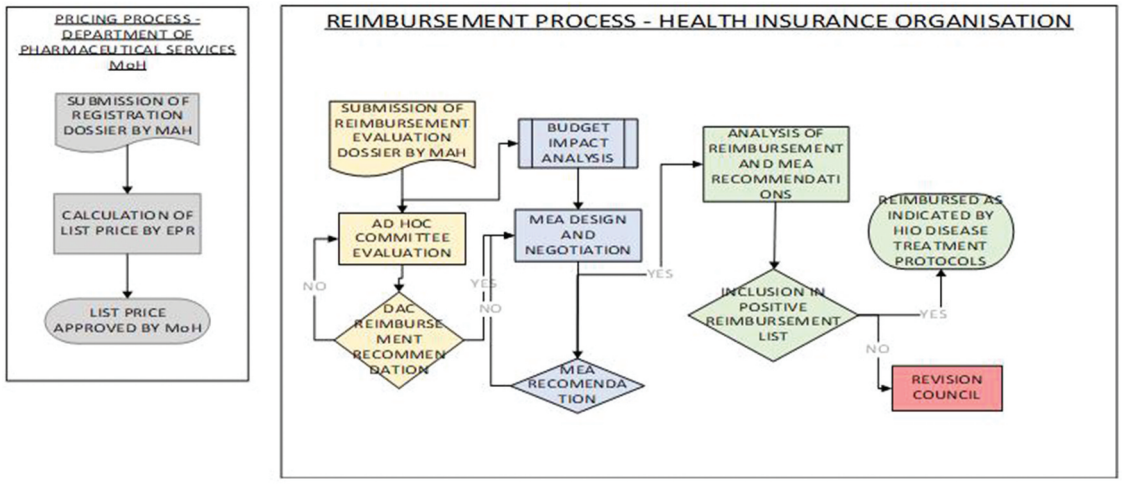


Figure 2. Pricing and Reimbursement Process in Cyprus.

stakeholders' perspectives as well. In order to do so, societal preferences should be clear and quantifiable. The definition of innovative value that each technology has to offer, and the degree to which this is relative and complementary to the existing therapeutic context in Cyprus must be distinctly defined [31–33].

The operational framework needs to accommodate orphan medicines. Apart from the definition of value, HIO is working toward societal preferences, assigning weight to the rarity of the disease and the disease-related unmet needs. This is further compounded by the absolute low number of patients, which abolishes any economies-of-scale efforts pertaining to the supply chain. This implies that for certain conditions, a multidimensional approach must be taken, extending well beyond ICER, which in almost all rare diseases is unfavorable [12]. Moreover, any negotiations should incorporate previous or parallel agreements in the same or similar therapeutic protocols regardless of whether they concern treatment or preventive care. Within the context of orphan drugs and gene therapies, the costs of administering such therapies within the country should be juxtaposed to the costs of treating patients in other countries.

Although a nascent committee, the DRAC already designed and negotiated 10 MEA by March 2022. The agreement duration proposed by the committee is usually 1 year, however a preference of the industry to longer agreements was noted, with 3 years being the maximum. Agreements with duration exceeding 1 year were approached cautiously in lieu of the combination of experience deficit and lack of a robust horizon scanning system.

Because of the limited experience, a preference in financial agreements is noted. The negotiation and subsequently agreement designs that were considered by March 2022 are presented in Table 1 [34,35].

The MEA schemes implemented, are Cyprus' first steps toward procurement methods that deviate from public tendering. Further elaboration on the reasoning behind the design choice could hinder the confidentiality of these agreements and will therefore not be elaborated upon.

Table 1. MEA Schemes Implemented.

| MEA Schemes Implemented |
|---|
| Price Reduction |
| Value Based MEA |
| Price Reduction and Cap |
| Price- Volume Agreement |
| Price Reduction and Flat Price Combination |

### 4.5. Orphan drugs framework

While Cyprus struggles with delayed reimbursement decisions and efforts to implement MEA to procure the modalities that will align the country's therapeutic guidelines with those of the EU, in order to address unmet medical need, the European Medicines Agency (EMA) has introduced fast-track regulatory processes for innovative therapies. In theory, this would facilitate patients' access to innovative therapies [34]. However, regulatory approval of a new technology does not imply reimbursement. The reimbursement of a new technology entails that adequate data are available in order to substantiate the value the technology adds to the management of an indication, and the impact it will have on the HCS budget.

Practically, the DRAC will have to assess products which are not supported by robust clinical data including products which were granted conditional marketing authorization. This comprises a litmus test since the expectations and the corresponding pressure from patients' association to the newly formed organization is mounting.

In Cyprus health context, this is an original endeavor and there is no basis upon to build on. In order to facilitate the transition to a primarily MEA reimbursement system for innovative pharmaceuticals, the HIO will have to assess and make use of the available external resources while ensuring that the experience gained is accompanied by sufficient training and networking of in-house experts. Moreover, validation of both data and procedures should be performed and comparisons with decisions of other agencies would pinpoint discrepancies, which may merit further scrutiny.

## 5. Threats

The array and pace of changes in the healthcare sector that trailed after the introduction of the NHS carry several political implications. As with all major legislative changes, it is imperative that the tools necessary for the realization of this change are not distorted into becoming blunt for short-term political gains. In the case of the introduction of innovative pharmaceuticals, the key tool is the MEA. The way to safeguard the ability of the HIO to negotiate MEA is by warrantying the transparency of the operational frameworks of both committees, while at the same time safeguarding the confidentiality of the agreements [34,36].

The differentiation between confidentiality and transparency in decision making constitutes a challenge, primarily on a political level. Cyprus has been plagued by several financial scandals, in which prominent officers were involved. Hence, the public and specifically auditing entities, do not always differentiate between these two partially overlapping but in the case of MEA, distinct terms. The house of parliament has recently criticized confidential agreements, by mistakenly reproving them as nontransparent. Therefore, the need for demarcation and definition of these two terms in the context of MEA is imminent. The MEA are confidential and as such, a mutual trust between the industry and the HIO is imperative. Nevertheless, this confidentiality which is often misinterpreted as lack of transparency in the operational frameworks, does not equate with lack of transparency, especially by governmental stakeholders. The differentiation between the two terms is critical since deviations from standard practice of the previous systems such as a lack of publication in reimbursed prices may be scrutinized [32].

As argued by several authors, the NHS was affected by a long-standing procrastination, which almost came to the fore of a civil war [37]. This has heavily swayed many functions of the former public health care sector. Among them, stagnation in revision of guidelines was prevalent. In order to make-up, a committee, the Individual Patient Committee, was formed to meet the needs of individual cases. The mission of this fund was distorted and the rise in expenditure was exponential. Therefore, many innovative products found their way into reimbursement, by diverting the formal route. Consequently, this adds to the complexity of structuring the operational framework for MEA since pharmaceuticals available via this route, are not willing to discuss reimbursement. This leads to a contradiction in terms, and what was designed as a temporary solution for some, is transformed to permanent for the majority.

Moreover, the legal obligations that may stem-out of negative responses regarding reimbursement are not fully comprehended. This period comprises a litmus test and it should be closely monitored.

In addition, the governing body of HIO consists of several stakeholders with conflicting interests such as employers' associations, the government, the patients' associations. The stakeholders represented in the BoD directly influence the policy setting of HIO. A stand-off must be achieved between potentially undesirable decisions for them and the viability of the HIO.

## 6. Conclusion

It is a common conviction that reimbursement of innovative technologies on official prices is not feasible considering the soaring prices of innovation and the hard-cap budgets allocated for pharmaceutical expenditure [7]. The potential hazard arising from the combination of the two factors levitating over not only Cyprus pharmaceutical but on global level as well [5].

At the same time, the need to incorporate innovation into reimbursement systems in a swifter manner is a priority for all healthcare systems and it emerges as a key topic. In the case of Cyprus, resource allocation toward the generation of local HTA data cannot be justified. Evidence generation can be a lengthy process for a small patient population and by the time the data are gleaned, they will probably offer little utility to the system. Evidence synthesis also entails the obligation of the payer to fully reimburse the product, considering the new data, and as such, the payer cannot recuperate the expenses.

Arguably, the development of operational frameworks for both MEA and HTA transfer seems to be the way forward. Also, investment should be made in identifying the knowledge and experience gaps, and seek to bridge them via appropriate training and exposure.

## 7. Expert opinion

The HIO should streamline the implementation of MEA while assessing innovative approaches to risk sharing methods used by more experienced systems. An example of such would be the French approach, which provides that the proceedings of an innovative pharmaceutical are deposited in a bank and the outcomes of the coverage with evidence development (CED) agreement define whether the payer or the company will be credited [38]. Another interesting example, is the case of annuity payments in tandem with outcome-based schemes. Such methods could be especially targeted toward technologies whose budget impact would be detrimental for almost all healthcare systems, such as gene therapies [39].

Registries should also be considered as the case of Greece, which has implemented two, for Chronic Lymphocytic Leukemia and Hepatitis C Virus [40,41]. The electronic system of NHS can provide the technical pillars for such initiatives. Nevertheless, it is imperative that the difficulty ingrained in non – financial-based agreements, does not deter the consideration and implementation of such [36].

A potential solution would be the creation of a joint MEA committee with Greece. This will boost negotiating power and provide a stepping stone for Cyprus to claim more favorable agreements.

Voluntary cross-country collaborations are one of the solutions discussed to address the increasing prices in pharmaceuticals since such initiatives are seen as ways to improve transparency in pricing and reimbursement [21]. In the case of Cyprus, a joint negotiation committee with Greece, will take advantage of the existing knowledge and experience on Greece's site, thus, making the process more accessible for Cyprus. The cooperation will be enhanced by the language. Still, many hurdles exist before such an endeavor can be

realized. Previous experience on similar efforts has shown that for cross-country collaborations to bear results, countries agreeing to participate need to show flexibility in legislative alterations. Such flexibility is essential because of the diversity in the legislative framework and healthcare system organizational structure between countries [21,42].

Evidently, one of the most imperative measures that need to be taken moving forward, is the formation of strong networking connections with more experienced systems that will be able to share their expertise. What Cyprus can offer in return, is the utilization of the country's small size as a testing ground in the application of innovative financing methods that will perhaps arise from a cross-country endeavor. Results of this nature can be captured with much more ease, and less risk, in Cyprus' centralized micro-environment, and if favorable, they can then be adapted to larger HCS.

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## Author contributions

O Pitsillidou designed and drafted the article. P Petrou and M Postma provided study material and revised the initial article. All authors read and approved the final manuscript for publication.

## ORCID

Olga Pitsillidou http://orcid.org/0000-0002-2463-3131
Panagiotis Petrou http://orcid.org/0000-0002-4881-720X
M. J. Postma http://orcid.org/0000-0002-6306-3653

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