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Commentary

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Faciliating More Efficient Negotiations for Innovative Therapies: A Value-Based Negotiation Framework

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Abstract

Objectives: An increasing number of innovative therapies (e.g., gene- and cell-based treatments) have been developed in the past 20 years. Despite the significant clinical potential of these therapies, access delays may arise because of differing perspectives of manufacturers and payers regarding issues such as the value of the product, clinical and financial uncertainties, and sustainability. Managed entry agreements (MEAs) can enable access to treatments that would not be reimbursed by conventional methods because of such concerns. However, although MEA typologies exist, there is currently no structured process to come to agreements on MEAs, which can be difficult to decide upon and implement.

To facilitate more structured MEA negotiations, we propose a conceptual "value-based negotiation framework" with corresponding application tools.

Methods: The framework was developed based on an iterative process of scientific literature review and expert input.

Results: The framework aims to (i) systematically identify and prioritize manufacturer and payer concerns about a new treatment, and (ii) select a mutually acceptable combination of MEA terms that can best address priority concerns, with the lowest possible implementation burden.

Conclusions: The proposed framework will be tested in practice, and is a step toward supporting payers and manufacturers to engage in more structured, transparent negotiations to balance the needs of both sides, and enabling quicker, more transparent MEA negotiations and patient access to innovative products.

In the past two decades, an increasing number of innovative therapies have been developed, such as gene-, cell-, and RNA-based treatments. Since 2018, a 20 percent increase in development of gene and cell therapies was reported in the United States and a 23 percent increase is expected in Europe between 2021 and 2026 (1;2). Innovative therapies can be defined as those that provide a significant added therapeutic (clinical) value (3;4), often in diseases with high unmet need, such as rare diseases, in which the incremental health gains of orphan drugs have been found to be higher than that of nonorphan drugs (5). Many of these therapies are also single or short-term treatments with potentially curative effects (6). However, they often come with high prices and evidence gaps that can lead to evidential uncertainty or affordability concerns, and which translate into pricing and reimbursement (P&R) "risks" because of their impact on economic and clinical parameters. For instance, an evidential uncertainty concern might arise due to limited evidence on treatment effects in subgroups. This concern would have corresponding P&R "risks" in terms of the impact of the concern on real-world health outcomes, as well as budget/revenue implications based on a potential but unknown increase in the eligible population size.

Although some countries have specific appraisal pathways for particular therapies, such as orphan drugs (7), conventional approaches of market access and reimbursement bodies (hereafter referred to as "payers") to appraising value for money still predominate and have limitations in the case of innovative therapies. Such approaches generally require randomized controlled trials (RCTs) and a price below a certain threshold, yet innovative therapies often have higher prices and more uncertainties in the evidence. Their value can therefore be difficult to assess and may be largely impacted by how key concerns are viewed (8). Additionally, the goals of manufacturers and payers differ regarding the potential clinical value of a new product and its

P&R risks (real-world health outcomes, cost-effectiveness, cost per patient, and budget/revenue impact) (8;9). On the one hand, manufacturers necessarily aim to recover investment and secure revenues to finance future innovation and remunerate shareholders, often putting their price goals at the higher end of the negotiation range. On the other hand, payers aim to keep costs of treatments consistent with their perceived value and within available budgets, often putting their price goals at the lower end of the negotiation range (9). Despite the fact that manufacturers and payers do share a common goal to achieve reimbursement and patient access for promising products, these differences can cause a "negotiation gap," in which it is difficult to come to an agreement that manages evidential uncertainty and affordability concerns while bringing each side closer to its respective goals. This can make negotiations longer and prolong time to access, or prevent access altogether. This trend is increasing, with 93 percent of countries having a longer time to access in 2019 than 2018 according to the Patient W.A.I.T. Indicator, a survey capturing two key parameters in European countries: (i) rate of availability (number of medicines available to patients) and (ii) time to availability (average time between marketing authorization and availability to patients) (10). Although numerous factors can cause delays in access, it is the authors' belief that lack of common ground between manufacturers and payers plays a significant role. Globally, regulatory authorities have recognized the potential of innovative therapies and the need to eliminate access delays whenever possible. This has stimulated efforts to accelerate access to innovative therapies, such as offering expedited approval for marketing authorization (11;12). As innovative therapies move from the approval to reimbursement phase, such expedited approvals can result in additional uncertainties, making the decision-making process more difficult (11;13). A method for striking a balance between speeding up negotiations while addressing risks is needed in these situations, to facilitate patient access to promising, innovative therapies.

Managed entry agreements (MEAs) are arrangements between manufacturers and payers that allow for reimbursement of new medicines while managing uncertainty around their financial or clinical impact (8). MEAs between a manufacturer and a payer can be a useful approach to facilitate patient access and reimbursement of innovative therapies with high evidential concerns, high affordability concerns, and high clinical potential in areas of unmet need (14). Although there are numerous taxonomies around MEAs (15), the purpose of this paper is not to go into the details of these. Broadly speaking, financial-based MEAs represent a route to manage uncertainty around the budget impact of a new technology by setting and tracking usage or financial parameters. Outcomes-based agreements link the level of payment to defined therapeutic outcomes of the technology, therefore focusing on product performance and potentially enforcing real-world evidence (RWE) collection (9;14). For sustainable reimbursement, payers and manufacturers may consider a combination of multiple MEA "terms" or elements that comprise the different aspects the MEA will cover (14).

MEAs can be complex to agree on and implement, and are not suitable in every situation. The level of concerns related to P&R risks should determine the usefulness of an MEA, along with the product's potential value (16).

Despite interest in applying MEAs, key barriers to use have raised skepticism about their value (9;15). This may be the result of some key issues:

- *Lack of systematic identification of the type and magnitude of concerns*: Concerns are not only viewed differently by payers and manufacturers, but also not clearly identified and discussed (9;17).
- *Lack of consistent decision making and alignment of understanding:* Negotiations are generally not approached in a systematic way; negotiating parties often fail to understand each other's perspectives.
- *Lack of consideration of implementation burden:* The implementation challenges of the agreement terms are often not systematically considered when deciding on MEA terms. Examples of such challenges include financial costs of implementing MEAs, measuring, tracking, and assigning causality to outcomes or the need for complex IT (18–20).

Consequently, there has been an increasing trend of relying on financial-based instead of outcomes-based MEAs because they are simpler and easier to implement, despite the fact that *both* financial- and outcomes-based deals may offer better outcomes, depending on the concerns to address. Even in countries where outcomes-based agreements are possible, postmarketing evidence is often not used to discuss and determine price renegotiations or discontinue reimbursement. Essentially, financial MEAs appear to be the main MEAs in use, whereas outcomes-based MEAs are proving too complex to establish, inappropriate to address uncertainty (9) and delisting or price cuts based on the evidence collected is not sufficiently enforced (15;21).

With the arrival of new generations of innovative treatments targeted at a genetic level, there has been a renewed interest in MEAs, particularly more complex agreements, to address the concerns these products raise (9). However, given the lack of systematic identification of concerns and alignment between manufacturers and payers, we suggest that different *ways* of approaching MEA negotiations may be a more effective solution. We presume that payers already have sufficient tools (outcomes- and financial-based) to manage and address concerns, and that an efficient negotiation process could be more effective at improving access than more complex MEAs. This does not assume that current health systems can infallibly produce the right types of data in a timely manner, or that the associated methods to examine comparative effectiveness and cost-effectiveness are sufficient in light of poor or nonexistent RCT evidence. The topic of generating high-quality RWE, while of substantial importance, is beyond the aim of this framework.

Our aim instead focuses on structuring the negotiation process, based on the hypothesis that a more structured method for identifying uncertainties and corresponding P&R risks, and selecting appropriate MEA terms, can accelerate negotiation processes and facilitate patient access, by providing tools to enable greater convergence between manufacturers and payers on fair and reasonable ways to bear P&R risks. The framework is focused only on products that are considered "worthy" of MEAs. It is not intended to be a substitute to state-of-the-art clinical trials. We suggest that only products with reasonable supporting data would be considered appropriate for such discussions. However, even with state-of-the-art clinical development, innovative therapies are likely to have areas of uncertainties and concerns, both clinical and financial. Our goal is therefore to enable more constructive dialogue to ensure a faster agreement for products with potential added value.

The components of a more structured approach for MEA negotiations are not entirely new. For instance, efforts have been made to better classify uncertainty. The transparent uncertainty assessment (TRUST) was developed for systematically identifying, assessing, and reporting uncertainties, with the aim of making uncertainties and their impact on cost-effectiveness more explicit

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and transparent (22). The tool for reducing uncertainties in the evidence generation for specialized treatments for rare diseases (TRUST4RD) proposes a structure that explicitly names and addresses uncertainties that are common to treatments for rare diseases, but it does not link these to specific P&R risks and MEA terms that can address these risks (23).

There is currently no structured framework to support the process of evaluation and negotiation, including assessment of value, identifying and prioritizing sources of uncertainty and selecting MEAs with the highest potential effectiveness *and* feasibility to implement. Pouwels and colleagues have highlighted that a framework involving all stakeholders would help to systematically identify uncertainties and explore the impact of these uncertainties on the assessment results of a product (24). The need for identifying concerns and connecting them with potential MEA terms, while minimizing implementation burden, is further echoed in the literature; Annemans and Pani suggest that "techniques should be applied to assess the balance between the costs and benefits of applying an MEA" (16).

With the aim to facilitate a more structured, transparent, and evidence-based approach to MEA contracting for innovative therapies, we propose a value-based negotiation framework with corresponding tools.

By value-based (25), we mean:

- The focus should be on products with clear potential therapeutic value (e.g., product addresses an unmet need, is likely to have an impact on survival, other relevant clinical endpoints or quality of life (QoL). This should be based on regulatory and health technology assessment (HTA) assessments; the framework does not intend to substitute these processes.
- MEA terms need to be derived from a plausible and rational assessment of risks while balancing the impact of these risks between both negotiating parties. This assessment will vary depending on the method used and jurisdiction-specific priorities, but risks will primarily be related to four categories: *real-world health outcomes* (e.g., unclear actual impact of the therapy due to issues such as uncertainty around long-term effects, eligible population, and magnitude of effect), *cost-effectiveness* (e.g., potentially higher incremental cost-effectiveness ratio [ICER] than deemed acceptable due to issues such as uncertainty around size or durability of effect), *cost per patient* (e.g., risk of increase/decrease in cost per patient due to issues such as uncertainty around eligible population size), and *budget/revenue impact* (e.g., risk of budget/revenue increase or decrease due to issues such as uncertainty around eligible population size, effect durability, and adverse events).
- Appreciation that different stakeholders may have different priorities and different perceptions of risks in different jurisdictions.

The framework can be adapted to different countries and jurisdictions with different P&R frameworks. This enables more consistency in assessment while allowing flexibility for different priorities and perspectives toward risks. At the same time, it accommodates such country differences in a way that does not undermine or disincentivize access. Figure 1 portrays a schematic overview of the context and potential issues around application of MEAs, their role in bringing manufacturers and payers closer to a "solution space" in which the right agreement can bring each side closer to its respective goals by narrowing the negotiation gap, and where such a value-based framework fits in. The details of the

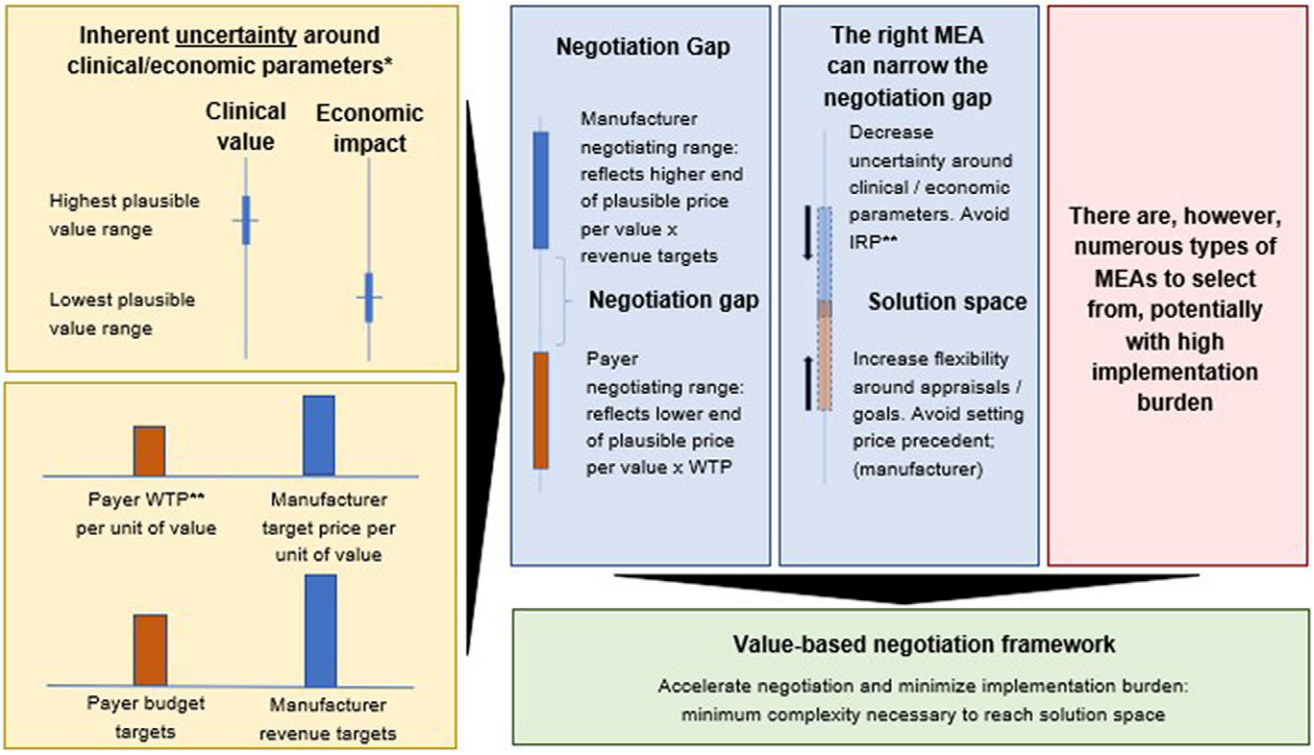

Figure 1. The context and potential issues around application of managed entry agreements.

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framework and how it can be applied in practice are then outlined.

Our proposed framework involves a stepwise process to facilitate more efficient MEA negotiations through the following:

- A structured and systematic approach to (i) identify evidential uncertainty or affordability concerns and corresponding priority P&R risks, (ii) quantify the impact of concerns on these risks in a meaningful way based on local priorities with a view to (iii) prioritize top risks, and (iv) more rapidly identify mutually acceptable MEA terms that allow a fair split of key risks acknowledged by payers and manufacturers.
- Minimize time to negotiate an MEA while being more transparent about the constituents of the negotiation process.
- Minimize implementation burden by evaluating the MEA terms for risk-mitigating capacity and implementation feasibility for both negotiating parties.

Although the scope of this work is not dedicated to determining how a company sets its price or what a fair price should be, the framework can be used by both negotiating parties to facilitate convergence on mutually agreeable cost-effectiveness and budget/revenue impact. These represent parameters which, depending on jurisdiction, are of primary importance for payers and manufacturers to ensure access to a therapy.

Methodological Approach

The methodological approach to designing the framework was as follows:

1. Literature review: A semistructured literature review was conducted by two members of the research team to identify the rationale for and components of the framework, including: identifying how concerns can be defined, how common understanding can be reached on these issues, and leveraging this common understanding to create a mutually acceptable MEA. Articles related to this topic and published within the past 10 years were included. The terms were searched in PubMed, Google Scholar, Microsoft Academic, and Google: "MEAs," "performance-based agreements," "outcomes-based agreements," "financial agreements," "P&R," "uncertainty," and "risk." Titles and abstracts were screened first, followed by full text reading of potentially appropriate articles. Reference lists of selected articles were checked by the two research team members for additional publications. Twenty-nine relevant articles were identified (seventeen original articles, four reviews, four reports, two masters theses, one policy paper, and one letter to the editor). Articles were read in detail by both team members, and relevant evidence was extracted. TRUST4RD was used as a basis for identifying which concerns and P&R risks are most frequently raised during the evaluation process. This was expanded based on commonly stated concerns in HTA reports (26). The literature review supported creation of a first draft of the framework and tools.
2. Expert opinion: The framework and application tools were further developed and refined based on stakeholder input. The framework and tools were presented to academic experts and industry representatives with hands-on P&R experience, who provided verbal or written feedback that was integrated into the materials. The experts that were consulted were invited to be coauthors on this paper.
3. Case study: To demonstrate how the framework structure can be applied in practice, an illustrative simplified case study of a chimeric antigen receptor T cell (CAR-T) therapy archetype was developed (27). A small sample of items from the framework tools were applied to exemplify how the framework might look in practice. Key uncertainties and quantification of concerns, risks, and potential agreement terms were inspired by published HTA reports, a "mock" evaluation of a CAR-T therapy conducted by NICE (27), and agreement terms used by EU5 agencies for CAR-T therapies (28;29). The case study was developed to demonstrate the application of the framework from a structural perspective, not to test it in anyway.

The resulting framework developed from Steps 1 and 2 is presented below. It is intended to be a *conceptual* starting point, with corresponding tools for practical future implementation. We have identified relevant areas of P&R risk, but these do not represent a one-size fits all approach; adaptations will be required depending on the priorities in the jurisdiction of application. The case study that was developed in Step 3, and which is presented after the conceptual framework, is intended to provide a simplified example of how the framework might look when applied.

It is important to note that although the framework and tools do allow for quality of evidence to be included as an uncertainty that could restrict reimbursement if not addressed through an MEA, they are *not* intended to determine or assess whether quality evidence was produced. Their value lies in providing a structured approach for identifying risks and coming to agreements in MEA negotiations as quickly and efficiently as possible.

Results: A Value-Based Negotiation Framework

The stepwise approach of the conceptual framework (Figure 2) aims to identify concerns, the influence of these concerns on P&R risks, and preferred agreement terms which can best address priority risks and minimize implementation burden for both negotiating parties.

Step 1 ("Assess") represents a necessary baseline step in which a thorough understanding of the product and disease profile must be attained. The corresponding tool (Supplementary Table 1) includes detailed information on disease background (epidemiology, patient population, standard of care, etc.) and product background (technology, regulatory background, safety, efficacy, etc.). The main significance of this step is to acknowledge that this information is essential to capture; we do not suggest that this template is the only way to do so. Discussion of this information should include magnitude of effect and uncertainties.

In Step 2 ("Prioritize"), negotiating parties identify individual elements from the disease and product profile (Step 1) which may constitute a source of evidential uncertainty or affordability concerns and could prevent conventional reimbursement, thus warranting consideration of an MEA. To prioritize concerns, we recommend quantifying their expected impact on four different P&R risks: (i) real-world (health) outcomes, (ii) cost-effectiveness, (iii) cost per patient, and (iv) budget impact. Although these four parameters inevitably overlap with each other, the intention of the framework is not to make them mutually exclusive. Rather, it is to separate out the parameters and enable a more fine-grained view of each. This allows, for instance, jurisdictions that prioritize cost-effectiveness to use the framework just as effectively as jurisdictions that prioritize budget impact.

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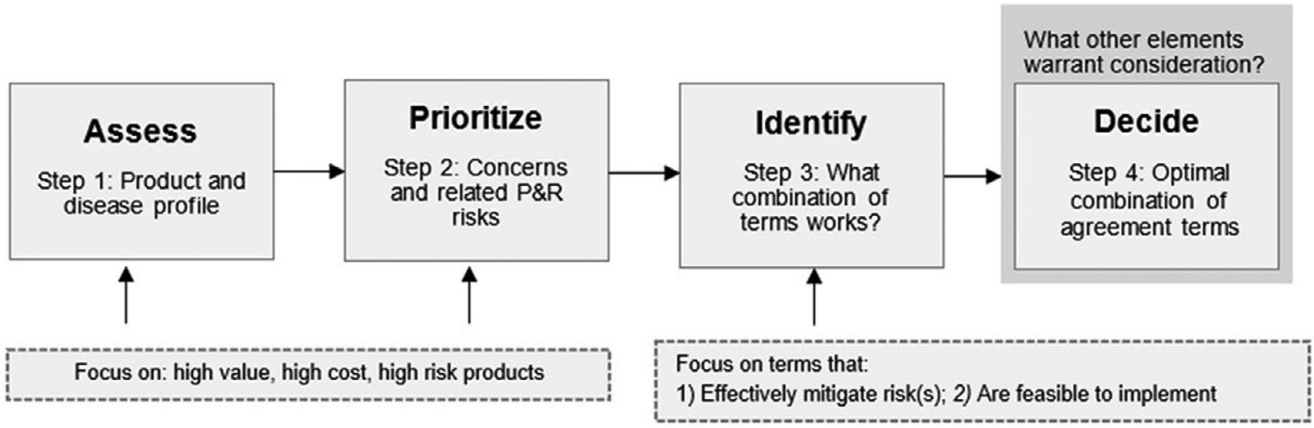

Figure 2. Stepwise value-based negotiation framework for innovative therapies.

A meaningful quantification of the impact of concerns on P&R risks is based on how sensitive one factor is to another. The aim is to first assess the baseline dossier submitted by the manufacturer and how core P&R risks may change relative to each concern raised. Consider the earlier example of uncertainty around eligible population size due to limited subgroup evidence. The magnitude of uncertainty regarding how many additional eligible patients may exist but are currently unknown would translate into an estimated corresponding P&R "risk" in terms of an increase in budget impact.

The risks that are most highly impacted by evidential or affordability concerns are then prioritized and ranked in order of importance. Prioritized risks will vary depending on context and the relative importance of each of the four risk parameters in a given country; for example, not all countries use the ICER as a key decision parameter, so will instead focus on the domain(s) which is(are) most relevant for them. The tool in this step (Supplementary Table 2) enables stakeholders to clearly describe their specific concerns and the impact of these on P&R risks. The prioritized concerns can then be used to determine the preferred terms of an MEA. It is important to acknowledge that we do not recommend a specific threshold to define what level of change should be consider important, or a particular way of quantifying concerns and corresponding risks; these are decisions to be made by the user.

In Step 3 ("Identify"), MEA terms to address the prioritized risks are selected. This step includes assessing the capacity of each potential MEA term to mitigate the concerns driving those risks and how feasible implementation is in a particular context. Like with Step 2, we do not suggest a specific method or threshold for ranking feasibility, but instead provide the structure and leave that decision to the user. Feasibility is a subjective measure; as such it cannot be prescribed, but it should be clear how the ranking was selected. The aim is to facilitate selection of terms that are most appropriate for addressing priority concerns, are feasible to implement, and are acceptable to both sides. The tool in this step (Supplementary Table 3) allows the user to outline various possible agreement terms that can potentially address their priority concerns. They can then assess the risk-mitigating capacity and implementation feasibility of these terms within their local system to minimize implementation burden and maximize risk-mitigating capacity.

At the end of this step, each negotiating party has their own preferred agreement terms and clearly described motivation behind them, which can be used as a basis for constructive, efficient negotiation discussions to eventually come to Step 4 ("Decide"). The decision step necessarily entails a compromise from both parties to arrive at a mutually acceptable agreement. Once this compromise has been made, additional strategic elements can be considered, such as evidence generation, spillover effects, and so on.

Simplified Example of Framework Application for a CAR-T Product

An illustration of how the framework could be applied in practice is outlined below for an archetype CAR-T therapy. The information provided is simplified for demonstration purposes of the framework structure only and does not include all information or potential risks and agreement terms. The quantification was inspired by the "mock" evaluation of a CAR-T technology by NICE (27), and agreement terms employed by EU5 agencies (28;29). The case study is not intended to be comprehensively representative of a real-world scenario, but to illustrate how the structure to the framework could look in practice.

Step 1: Assess (Product/Disease Profile)

Simplified disease and product overview: The disease has a high impact on mortality and QoL. Existing therapeutic options slow progression. The new treatment to be evaluated is a one-off injection that stops disease progression. Clinical trials only included early-stage patients and 2 years of follow-up data, which showed significant impact on overall survival in 65 percent of patients. Treatment requires specialized infrastructure and is associated with some severe adverse effects.

Step 2: Prioritize (Concerns Matrix)

Evidential uncertainty and affordability concerns should be identified, and impact on corresponding P&R risks should be assessed. These are then ranked based on impact and country system priorities, to identify the top three-to-five priority risks. For demonstration purposes, only *one* top concern (in bold) had been selected instead of three to five: long-term efficacy (Table 1).

Step 3: Identifying Agreement Terms (Solutions Matrix)

Each party uses the information table (Table 2) to identify which agreement terms could address the prioritized concern(s); in this case, the prioritized concern is: uncertain long-term efficacy.

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Table 1. Concerns and Corresponding P&R Risks for a Chimeric Antigen Receptor T-Cell Archetype (Nonexhaustive List)

Uncertainties	Description	Expected Influence on Real-World (Health) Outcomes	Expected Influence on Cost per Patient	Expected Influence on Cost-Effectiveness (Impact on ICER)	Expected Influence on BI/Revenue
Long-term efficacy	**Data on long-term efficacy are too immature to inform the expected life-long effect of the therapy.**	**Overall survival extrapolated from 2 year trial to >30 year time horizon; high uncertainty around long-term efficacy.**		**Base case ICER could increase between 60%.**	**Lack of medium-term efficacy could increase BI by 35%.**
Safety	The therapy is associated with some serious adverse events. It is unknown if additional adverse events will manifest in the long term.	Duration of short-term adverse events is uncertain; absence of long-term safety data; comparable products meet safety criteria.	Lack of long-term safety could increase cost per patient by 5%.	Adverse events duration may require treatment, increasing ICER of 5–10%.	Lack of long-term safety could increase BI by 15%.
Number of eligible patients	Size of eligible population is difficult to estimate; more patients might be eligible than expected.				If more than the expected 30 patients are treated, BI could increase by 25–45%.

Abbreviations. BI, budget impact; ICER, incremental cost effectiveness ratio.

Table 2. The Risk-Mitigating Capacity of a (Nonexhaustive) List of Agreement Terms, and Feasibility from the Manufacturer or Payer Perspective

		Risk-Mitigating Capacity				
Uncertainty	Potential Agreement Terms	Expected Influence on Real-World Health Outcomes	Expected Influence on Cost per Patient	Expected Influence on Cost-Effectiveness (Impact on ICER)	Expected Influence on Budget Impact/ Revenue	Feasibility
Long-term efficacy	Cost cap (by volume/ revenue)	No impact	No impact	No impact	25% decrease	Feasibility should be considered for each agreement term from each parties' perspective.
	Price volume agreement (by volume/revenue	No impact	15% decrease	10% decrease	15% decrease	
	Time-based price cut	No impact	No impact	No impact	20% decrease	
	Outcomes-based payment/rebate	50% decrease in uncertainty	15% decrease	30% decrease	35% decrease	
	Outcomes-based price change	50% decrease in uncertainty	15% decrease	30% decrease	25% decrease	

Note. In bold the agreement terms employed by EU5 agencies are indicated (23;24).
Abbreviation. ICER, incremental cost effectiveness ratio.

Possible agreement terms should be assessed for risk-mitigating capacity and implementation feasibility from a local system perspective, to minimize implementation burden and maximize risk-mitigating capacity (Table 2). Descriptions of agreement terms can be found in Supplementary Table 3.

In the example, the potential terms that best mitigate risks associated with long-term efficacy include outcomes-based payment/rebate or outcomes-based price change and coverage with evidence. Of these, all pose high potential risk-mitigating capacity, but coverage with evidence might be rated as less feasible due to considerable implementation burden for both parties. The preferable agreement term might be therefore outcomes-based payment/rebate or outcomes-based price change. Because outcomes-based payment/rebate is slightly more feasible for payers and offers a reduction in budget impact, although an outcomes-based price change might be slightly more feasible for manufacturers and offers a lower decrease in revenue, there may be different preferences regarding which to select, but for constructive discussion, both sides would have clearly motivated reasons for their preferred selection.

Discussion

Innovative therapies offer significant advances in clinical value while also posing challenges related to evidential uncertainty or affordability, emphasizing a need for innovative approaches to enable reimbursement of such treatments.

Although frameworks and guidance exist to supportive the broader deliberative process of decision making in healthcare (e.g., "the Evidence Informed Deliberative Process" (30) and "Evidence and Value: Impact on DEcisionMaking" (31)), there is no framework that aims specifically to structure the MEA negotiation process. The structured process of this framework addresses the

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need for a more systematic approach to better utilize MEAs for reimbursement of innovative therapies (24). The goal of the framework is to facilitate a faster, more predictable, and more transparent negotiation process, enabling parties to come to commonly acceptable agreements more quickly. It can be used at various stages throughout the development and P&R process of a therapy, such as:

- early in a product's development, for instance, in the context of scientific advice when some aspects related to the clinical developments could address some of the anticipated issues,
- upon submission of the dossier for evaluation, for instance, in the context of early dialogue, and
- in the context of MEA negotiations.

The flexibility of the framework enables it to be adapted accordingly to payers and manufacturers in a given national context. This flexibility could be extended to the ongoing discussions of a potential European-wide HTA process in terms of clinical evidence, in which case the first two stages of the framework may be valuable, whereas Stage 3 could be used either for joint negotiations, or during national-level negotiations.

It should further be recognized that the framework focuses on P&R risks as a *primary* area to address for effective negotiations, but this is not the only reason negotiations are delayed or fail. MEAs are not appropriate in every situation and even when they are potentially useful, employing the framework proposed in this paper would not in itself remove every cause of delayed purchasing agreements. The framework is intended to be applied for products with high potential, high evidential concerns and high cost, as these are the situations in which MEAs can provide substantial value for the required investment.

Different countries may use the framework for the same product in different ways and come to different conclusions based on their local contextual systems (32). MEAs are most effective when they are tailored to the specific circumstances in which they are being used. This should include careful consideration of the characteristics of the product in question, but also the characteristics of the healthcare system, the possibilities for different payment structures, and preferences regarding priority risks and types of agreements (14).

Finally, the framework in its current version remains primarily conceptual and has not yet been thoroughly applied in practice. The CAR-T case study was a simplified adaptation, and there might be value in a systematic assessment of recently introduced innovative products. This could be a topic for additional research, including its potential application to specific past cases.

In addition, empirical experience through "Mock-up" P&R assessments may be equally valuable. To this end, the framework has been introduced in various roundtable meetings at a preliminary stage in Italy, Belgium, and the Netherlands. An additional event took place in France, and more are planned in the United Kingdom and at a European level, as well as presentations at a number of conferences. This broad dissemination will enable input to be collected from country-specific perspectives, highlighting the nuances that would need to be considered in these different contexts.

The continuing evolution of the framework and practical validation seek to integrate these recommendations and strengthen its effectiveness for real-world application. The initial goal was to develop a potentially useful conceptual framework and tools. Moving forward, we intend to more rigorously test and validate the tools through different approaches, including an increased number of consistent empirical discussions between and across countries and products. If possible, a long-term research project would envision a clinical study applying the framework across a large group of individuals, using principles of behavioral and experimental economics.

On a broader scale, additional interventions beyond the framework itself may be needed to help drive the practical functionality of the framework in reality. For instance, national-level independent panels and/or voluntary collaborations between similar nations that can objectively support the process may be necessary.

Conclusions

Significant developments in innovative therapies offer high potential health gains in areas with high unmet need, but also evidential concerns and affordability issues. Ensuring timely patient access to new therapies has been a healthcare priority in the past decade, with several new regulatory initiatives being introduced at a European level, as well as at national levels. MEAs are recognized as tools than can address P&R risks for payers and manufacturers, but can be complex and must be chosen carefully. They should provide value by not only maximizing risk-mitigating capacity, but also minimizing implementation burden. There are a number of complexities of this process which we have not covered here in the interest of focusing on the conceptual framework, but which must be considered throughout the process. For instance, if RWE is part of the agreement, considerations regarding how this will be collected must be an integral part of the process.

The proposed framework is a first step toward an approach that can support payers and manufacturers to engage in a more structured, transparent negotiation process to identify effective MEAs that balance the needs of both sides, and enable quicker negotiations and patient access to innovative products.

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Supplementary Materials. To view supplementary material for this article, please visit http://doi.org/10.1017/S0266462322000095.

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