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Published in	PharmacoEconomics
Publication Date	2025
Link	https://dspace.library.uu.nl/handle/1874/473390
Citation	Callenbach, M H E, Vreman, R A, Leopold, C, Mantel-Teeuwisse, A K & Goettsch, W G 2025, 'Managed Entry Agreements for High-Cost, One-Off Potentially Curative Therapies : A Framework and Calculation Tool to Determine Their Suitability', PharmacoEconomics, vol. 43, no. 1, 103433, pp. 53-66. https://doi.org/10.1007/s40273-024-01433-4
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Managed Entry Agreements for High-Cost, One-Off Potentially Curative Therapies: A Framework and Calculation Tool to Determine Their Suitability

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Accepted: 29 August 2024 / Published online: 5 October 2024

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Abstract

Objective To construct a framework and calculation tool to compare the consequences of implementing different payment models for high-cost, one-off potentially curative therapies and enable decision making to ultimately enhance timely patient access to innovative health interventions.

Methods A framework outlining steps to determine potentially suitable payment models was developed. Based on the framework, a supporting calculation tool operationalised as an Excel-based model was constructed to quantify the associated costs for an average patient during the timeframe of the intended payment agreement, the total budget impact and associated benefits expressed in quality-adjusted life-years for the total expected lifetime of the patient population. To demonstrate the potential of the framework, three case studies were used: onasemnogene abeparvovec (Zolgensma[®]), brexucabtagene autoleucel (Tecartus[®]) and etranacogene dezaparvovec (Hemgenix[®]). A hypothetical case study was used to illustrate the output of the calculation tool.

Results Part 1 of the framework presents steps for matching a suitable reimbursement and payment model with the disease and treatment characteristics. The reimbursement and payment models are further specified in Part 2. Part 3 guides end users through the setup of a calculation tool with which the financial impact can be calculated of two payment models: a price discount model and an outcome-based spread payment model with a discount. Part 4 concerns the output of the calculation tool, showing how different payment models lead to different financial consequences under three assumptions of longer term effectiveness.

Conclusions The presented framework provides decision makers with insight into the financial consequences of their chosen payment model under different assumptions. This can aid reimbursement negotiations by clarifying the optimal choice given a therapy's characteristics.

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Key Points for Decision Makers

Highly priced, one-off potentially curative therapies with large clinical uncertainties challenge healthcare reimbursement systems.

To mitigate these challenges, there is a growing interest in using more complex innovative outcome-based reimbursement and delayed payment models, although simpler models, for example, discounts, are currently most common.

With the practical framework described in this paper, decision makers can clarify the consequences of the financial consequences of their chosen payment model under different assumptions.

Using a developed framework specific to national settings could support the decision-making process of when a more complex model may have advantages or when a simple model is good enough.

1 Introduction

Innovative one-off therapies, such as cell and gene therapies, are increasingly entering the healthcare market. Though these therapies often promise to have long-term effects, they are frequently accompanied by uncertainties about the durability of their effects, while requiring large upfront payments [1–5]. This brings challenges in assessing a therapy's practical value and decisions on reimbursement [6, 7]. To overcome these challenges, the desirability of innovative managed entry agreements (MEAs) is frequently debated in both the literature and among national competent authorities for pricing and reimbursement [8–13]. Managed entry agreements are commonly defined as any agreement beyond a 'yes' or 'no' decision on reimbursement between the manufacturer of a therapy and a healthcare payer [11]. A MEA can include various combinations of reimbursement and payment models [14]. As such, reimbursement models may be categorised as purely financial or as outcome dependent. In the former, treatment reimbursement is determined solely based on financial aspects, independent of health outcomes, while in the latter, reimbursement is linked to the treatment outcome(s). Furthermore, payment models are usually broken down into upfront or delayed payment models (e.g. annuity payment and payment at outcomes achieved) [11–13, 15–18]. Additionally, payment and reimbursement models can be implemented on a patient or on a population level [14–16]. For example, when implementing an outcome-based annuity payment on a patient level for each (annual) payment, individual patient outcomes will be used to determine the height of the payment made to the manufacturer by the healthcare payer.

Outcome-based reimbursement and delayed payment models have often been hailed as the future of pricing and reimbursement, Simultaneously, however, they are criticised for being too complex to implement [4, 17–19]. Complexities concern, for example, difficulty in determining appropriate patient-relevant outcome measures to which payments can be linked and data deficiencies owing to the lack of registries and confidentiality issues [14, 19]. The result has been a preference for relatively simple, financially based reimbursement provided via upfront payment models [10, 17, 19]. Nonetheless, in some situations, more complex MEAs might create windows of opportunity, granting patients earlier access to therapies while financial risks are shared among stakeholders. Managed entry agreements have therefore gained favour, especially for high-cost one-off therapies, to address their large long-term clinical uncertainties and limit their upfront budget impact [14, 16, 18–22].

When to use which type of payment and reimbursement model and the economic and clinical advantages of specific agreements often remains unclear for decision makers. Outcome-based reimbursement and delayed payment models may be the most suitable option under certain circumstances, yielding preferred outcomes for healthcare systems [8–13, 23]. Several frameworks are available to ease the negotiation process and provide insight into suitable agreements [23–31]. However, these frameworks and tools are often country specific, while bypassing many of the economic and clinical advantages that specific agreement types can offer. Moreover, none of the available frameworks elaborates in detail the steps and decisions that stakeholders need to take when considering innovative complex MEAs.

To support national competent authorities for pricing and reimbursements in deciding when complex MEAs can be of added value and when simpler models are sufficient, this paper is organised as follows: Section 1 presents a decision support framework and calculation tool for quantifying and evaluating the costs and benefits associated with different MEAs for highly priced, one-off potentially curative therapies; Section 2 provides a user guide. Here, a theoretical approach is taken to outline key decision points on data sources for end-users. This is followed by Section 3, which describes a 'proof-of-concept', showcasing the usability of the framework and the accompanying calculation tool. Retrospective and hypothetical cases are compared to determine which type of agreement is most suitable given the particularities of the health innovation under consideration.

2 Section 1: A Framework and Accompanying Calculation Tool to Support MEA Decision Making

A narrative review in September 2023 was conducted to detect the relevant literature on how to construct an MEA, what components such agreements comprise, what elements are part of successful agreements and what agreements are most suitable. Both positive and negative experiences with particular MEAs were examined. Search terms included, but were not limited to, 'gene and cell therapies', 'ATMPs' and 'orphan medical products' in combination with 'managed entry agreements', 'outcome-based reimbursement', 'delayed payment models', 'pay-for-performance', 'reimbursement decision-making', 'risk-sharing agreements' and 'financial-based models' (see Annex I of the Electronic Supplementary Material (ESM), for the full list of consulted papers). The literature was included when covering MEAs for one-off therapies or when reimbursement challenges for uncertain, highly priced novel therapies were described. The literature was excluded when

covering MEAs for therapies where the administration is not one-off or when not covering the structure of the MEA, barriers, best practices or how specific reimbursement challenges can be mitigated. Based on findings from the literature and internal discussions with the co-authors, a four-part ten-step framework was developed (Fig. 1) [32–34]. Moreover, the experiences from the real-life case study of atidarsagene autotemcel (Libmeldy®) were used to align the framework with input from experts in the field [32–35]

Part I follows the PICO [Patient, Intervention, Comparator, Outcome(s)] structure to define the basic characteristics of the disease [36, 37]. Using existing MEA taxonomies (see Annex II of the ESM for the complete taxonomy [14, 16–22, 35, 38]), suitable reimbursement conditions and the moment of payment (payment models) should be identified that have the potential to mitigate the clinical uncertainties and/or financial challenges relevant to the reimbursement decision [14, 16, 19, 21, 38]. Part 2 of the framework guides the user through decisions about the setup of the MEA. The details of the included reimbursement and payment models under Part 1 are further specified (e.g. the timeframe of the agreements, whether there is an infrastructure in place to collect and share data). For the sake of this practical application, an upfront paid discount, hereafter called a simple payment

model, is included as the base-case model and compared to one or more outcome-based spread payment models on a patient level combined with a discount, hereafter called the innovative payment model(s). Part 3 of the framework guides end users in determining the input parameters needed to operationalise the calculations. An accompanying calculation tool that can demonstrate the effects of different choices was constructed as part of the framework. This tool enables the comparison of the effects of different choices directly, which is important given that there is not always a clear preference for a single model and because of the interdependence of the different parameters. In Part 4, guidance is given on how the results from the calculation tool can be interpreted [27, 28].

In the framework and calculation tool, costs are expressed in euros or other applicable currency, and the benefits are expressed in quality-adjusted life-years or other appropriate outcome measures. The calculation tool facilitates outputs for three scenarios, reflecting different assumptions namely (A) a positive scenario in which all patients respond better than assumed, (B) a base case where patients respond according to the response assumptions made at the time of the reimbursement decision and (C) a negative scenario in which all patients respond worse than assumed. The

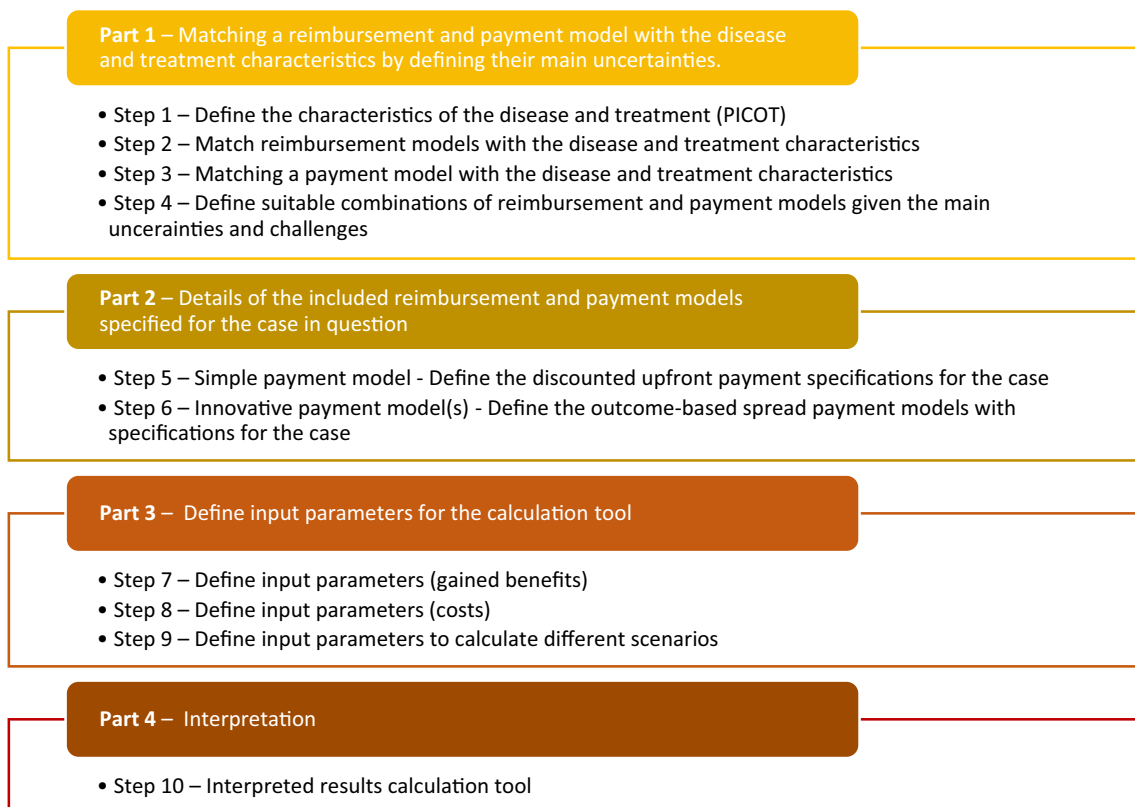


Fig. 1 Outline of the framework for selecting a suitable payment model for high-cost, one-off potentially curative therapies

calculation tool was operationalised as an Excel-based model [39]. For a complete overview of the developed framework, see Annex III of the ESM. To support end users, Annex III of the ESM also provides suggestions and practical applications for each step and guidance on whether the information needed for the step should come from external sources or are decisions that end users have to make themselves.

3 Section 2: User Guide

The framework and supportive calculation tool can be adopted at several moments in the lifecycle of a MEA. They can for example be used to define and compare relevant MEAs in the initial reimbursement negotiations and decisions. However, they can also be applied at a later stage, for example to evaluate implemented arrangements after the timeframe of the payment agreement has ended. The information can then be used to enter potential renegotiations. To support end users of the framework and calculation tool, a list of key decision questions per framework part is outlined in Fig. 2.

3.1 Are the Clinical Uncertainties and Financial Challenges Pressing Enough to be Decisive in the Reimbursement Decision? Part 1

The level of uncertainty in clinical evidence (e.g. the quality of evidence, the efficacy [precision of the effect size or the durability of the effects] and length of follow-up) can be seen as a main driver when choosing what type of reimbursement model might be suitable [10, 17, 19]. In line with the previous literature, clinical uncertainty is defined as ‘any explicitly or implicitly reported unresolved shortcoming, concern, question, or issue in the clinical evidence’ [40, 41]. To determine which reimbursement model could be relevant to compare in the calculation tool, Part 1 of the framework focuses on whether there are uncertainties in the clinical evidence [7, 15, 36]. Given that not necessarily all uncertainties can be mitigated nor are relevant to the reimbursement decision, the framework questions which clinical uncertainties are pressing enough to be decisive to the reimbursement decision and if an additional data collection could be of added value [33, 34, 36]. If there is already an indication that uncertainties may not be resolved over time irrespective of the

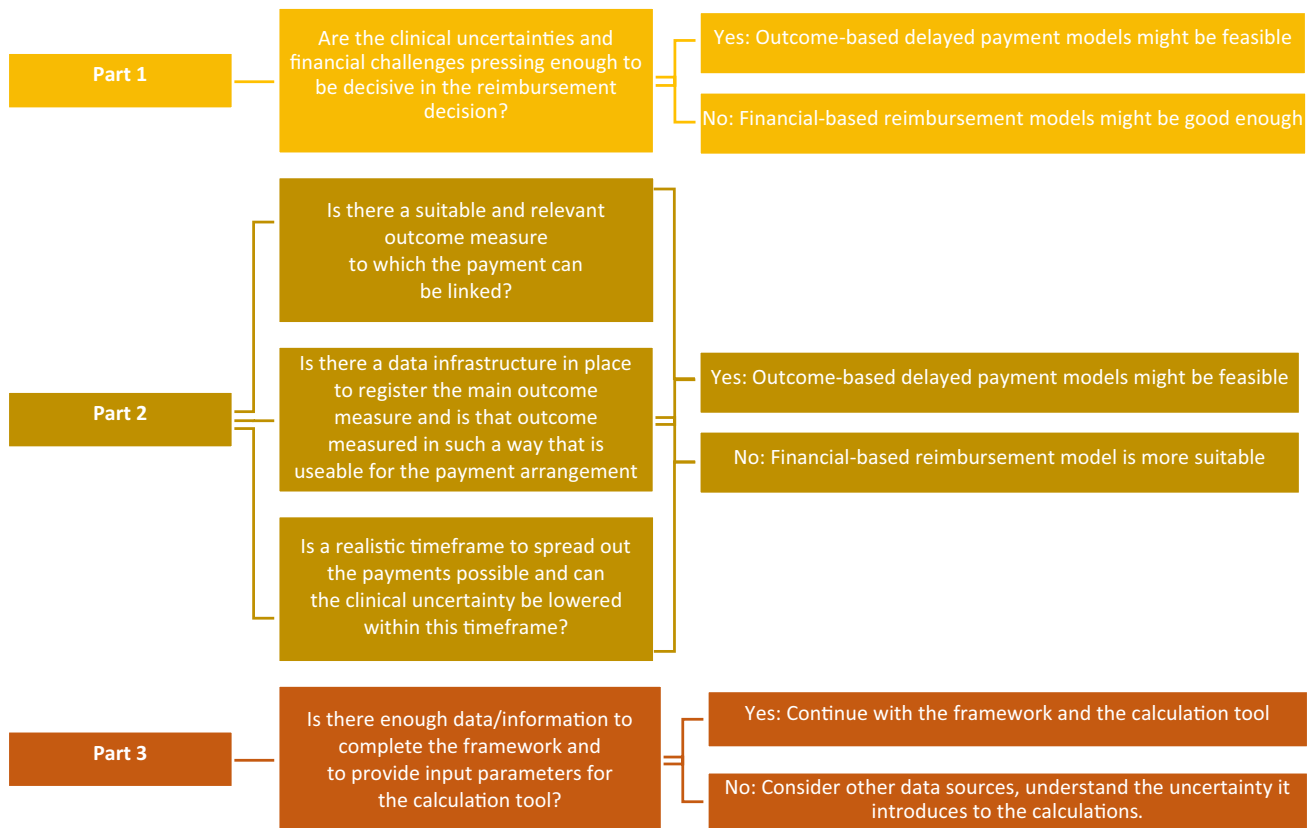


Fig. 2 Key decision questions for end users per part of the framework and calculation tool

reimbursement or payment model applied, or if the clinical uncertainties do not seem to hamper the reimbursement decision, a financial-based reimbursement model could be more suitable. This model facilitates that the financial risk of reimbursing the therapy under the existing clinical uncertainties is shared and the financial-based model can be updated over time when e.g. the perception about the remaining uncertainties change [42]. When a financial-based reimbursement model is deemed more suitable, the next steps of the framework do not need to be taken, and end users are advised to consider multiple discount rates based on, for instance, their cost-effectiveness thresholds to determine what they find agreeable under the circumstances.

When the reimbursement model has been defined, the type of payment model that might be relevant needs to be determined. Multiple strategies have been described in the literature [14, 16, 19, 21, 38]. If financial challenges need to be mitigated, delayed payment models should be considered. Suitable types of delayed payment models may depend on the uncertainties relevant to the reimbursement model. For example, to account for the financial risk of possible non-responders or an unexpected large deterioration in patient outcomes of the main outcome measure annuity payments would be a potentially suitable payment model. Payments will be then spread over time where the height of the payments is linked to outcomes achieved. When clinical uncertainties are extremely large, payments at outcomes achieved can be considered where payments are only made after specific results have been achieved [14, 19, 43–47].

3.2 What is a Suitable and Relevant Outcome Measure to Which the Payment Can be Linked and How is Success Defined? Part 2

In Part 2 of the framework, when a MEA is linked to outcomes, involved stakeholders (e.g. healthcare payers and healthcare professionals) need to come to a consensus about when a therapy is effective to define to what extent the treatment can be considered a success and is thus ‘worth’ paying for. To evaluate product performance, the different possible levels of outcomes should be outlined (binary or ordinal), and the minimum and maximum success score of the main outcome measure per subgroup should be defined [6, 18, 19]. When selecting which outcome measure is suitable, the literature denotes the importance of frequently collected outcome measures that are both clinically relevant and relevant to the patient [6, 18, 19]. To enhance the feasibility of successfully implementing an outcome-based reimbursement model, it is advised to focus on one outcome (if possible) that does not pose a large administrative burden to the healthcare provider.

Finally, the end users need to decide whether successful outcomes can/should be defined on a population, sub-population or individual level. The literature denotes that when the payment model is linked to specific outcomes, a successful implementation is most feasible at an individual patient level [13, 16]. This feasibility is specifically high when there is a small patient population, which is often the case for high-priced one-off therapies [14–16]. If no suitable and relevant outcome measure can be found, end users are advised to consider financial-based reimbursement models.

3.3 Is There a Data Infrastructure in Place to Register the Main Outcome Measure and is that Outcome Measured in Such a Way That is Useable for the Payment Arrangement? Part 2

To capture the collected data correctly, efficiently and in a trustworthy manner so that they are usable for payment schemes, it is important to ensure that an infrastructure is in place [18, 19, 48, 49]. In the literature, the importance of aligning and sharing data between involved stakeholders to increase the feasibility of successfully implementing outcome-based reimbursement models is underlined [18, 19, 47]. Moreover, given that reimbursement and payment negotiators often have a tight timeframe, there might not be enough time to set up a new register. Therefore, the literature denotes the importance of having an existing registry when entering an outcome-based agreement [18, 19, 48]. If a registry is not in place, the feasibility of setting one up within the timeframe of the first outcome measurement should be explored, or the possibilities of collecting, registering, and sharing data through other means or sources. Therefore, in Part 2 of the framework, a key decision point is establishing this feasibility, for which experts in the field should be consulted. If there is no data infrastructure in place, and the feasibility of creating one is considered low, implementing financial-based reimbursement models is more feasible.

3.4 Is a Realistic Timeframe to Spread Out the Payments Possible and Can the Clinical Uncertainty Be Lowered Within this Timeframe? Part 2

Determining at what moment the main outcome measure should be measured depends on its application in clinical practice. In Part 2 of the framework, healthcare providers should be consulted on when the outcome is measured in clinical practice. Additionally, if it is not a routinely collected outcome measure, patient representatives can be consulted on how likely patients are willing to come back for non-routine appointments for measurements necessary for the payment model. The frequency of how often this main

outcome is measured will determine the frequency of the spread payments during the timeframe of the payment agreement. In the literature, it is emphasised that the timeframe of the payment agreement should be long enough to allow for a reliable clinical assessment and adequate data collection, but, at the same time, must not be so long that the agreements become difficult to enforce or execute. In light of this, it is often noted that the timeframe should preferably be no longer than 5 years [16, 19, 50–53].

3.5 What Input is Needed to Perform the Calculations to Compare the Different Models? Part 3

Various input parameters for the calculation tool need to be defined in Part 3 of the framework. End users should know that in principle most steps can be completed using (publicly) available information to stakeholders involved in the reimbursement process of a health innovation (e.g. available health technology assessment [HTA] reports, clinical trials, European public assessment reports and/or available effectiveness data). Nonetheless, some information might be context specific or country specific and experts in the field, for example clinicians and patient representatives, need to be asked to provide input. Moreover, national procedures, political or societal discussions, and stakeholder preferences will shape the inputs and results of the calculated payment models and scenarios.

To determine how patients respond to the therapy, it was chosen to express the calculation of benefits in quality-adjusted life-years using information frequently available in reimbursement dossiers. Nevertheless, if other outcome measures are relevant, the calculation tool allows end users to choose their preferred country-relevant approach. To calculate the benefits gained within the timeframe of the payment agreement, transition probabilities (e.g. per month) and utilities (e.g. per year) need to be defined for each subpopulation for the best supportive care and the therapy under consideration. If further assumptions are relevant to determining how patients respond, this can be added to the tool (e.g. the transition between the health states depends on specific response classifications).

To calculate the associated costs expressed in euros (or any other applicable currency) per payment model, the (public list) price of the therapy needs to be defined, whereafter (outcome-related) discount rates are applied to this (list) price. In the framework, the simple payment model is further specified by determining a suitable discount rate applied over the defined therapy's price to establish which amount of the treatment costs will be paid in the upfront payment. To select this discount rate, end users can consult previously recommended discount rates in HTA reports for similar health innovations or apply any rate they find relevant or

suitable given the circumstances of the health innovation under consideration. For the innovative more complex payment model, the discount rates for each predefined outcome measure score need to be determined (e.g. depending on how success is defined in the therapy). By setting discount rates per outcome measure score, the payments can be adapted categorically with a fixed decrease in payment if patient responses drop below a certain threshold in a stepped manner and will be made after the patient response has been measured [19, 54, 55]. Consequently, it can be ensured that the payments made will relate to the outcomes achieved.

4 Section 3: Proof of Concept

To demonstrate the potential of the framework, two case studies in which common reimbursement challenges for one-off potentially curative therapies exist were selected: onasemnogene abeparvovec (Zolgensma[®]), indicated for patients with type 1 symptomatic spinal muscular atrophy and patients with presymptomatic spinal muscular atrophy with up to three copies of the *SMN2* gene, and brexucabtagene autoleucl (Tecartus[®]), indicated for adult patients with relapsed or refractory mantle cell lymphoma after two or three lines of systemic therapy, including a Bruton's tyrosine kinase inhibitor. These are two retrospective cases for which we used information from relevant clinical studies and HTA assessments from well-established HTA organizations; the National Institute for Health and Care Excellence from the UK, the Dutch National Health Care Institute (Zorginstituut Nederland) and the French National Authority for Health (HAS). An additional case study was selected, etranacogene dezaparvovec (Hemgenix[®]), indicated to treat patients with severe hemophilia B, as one upcoming gene therapy identified through the Dutch Horizonscan to illustrate how the framework can be used in an early phase using information from relevant clinical studies and the publicly available HTA report from the Institute for Clinical and Economic Review in the USA [56], a jurisdiction in which this gene therapy had already been approved at the time of the development of this framework.

4.1 Part 1: Matching a Reimbursement and Payment Model with the Characteristics of Onasemnogene Abeparvovec (Zolgensma[®]), Brexucabtagene Autoleucl (Tecartus[®]) and Etranacogene Dezaparvovec (Hemgenix[®])

In Fig. 3, a summarised overview of completing Part 1 of the framework for the three case studies is presented. Following Step 1, for each of them, the PICO framework, commonly used for structuring clinical questions capturing key elements; Patient, Intervention or exposure, Comparison or

control Outcome(s), was completed. For example for brexucabtagene autoleucel, the main outcome measures were overall survival, quality of life, and severe adverse events [42, 57, 58]. Hereafter, in Steps 2 and 3, the main clinical uncertainties and financial challenges are outlined in order to match potential suitable reimbursement and payment models. The case study of onasemnogene abeparvovec shows that there is uncertainty in the exact medium-term and long-term efficacy (including cognitive development and quality of life) because of a limited follow-up [59]. However, for brexucabtagene autoleucel, several clinical uncertainties are described in the Zorginstituut Nederland report, [42, 57–59] but they do not seem to be pressing enough to influence the reimbursement decision. In this case, a financial-based reimbursement model could be more suitable in which the financial risk of reimbursing the therapy under the existing clinical uncertainties is shared [42]. In this case, the next steps do not need to be taken, and end users are advised to consider multiple discount rates based for instance on their cost-effectiveness thresholds to determine what they find agreeable under the circumstances.

In Step 4, the potentially suitable reimbursement and payment model combination, thus the MEA, should be determined by combining the reimbursement and payment models that follow from the previously described consideration. For the cases of onasemnogene abeparvovec and etranacogene dezaparvovec, an outcome-based reimbursement model, i.e. pay-for-outcome with a discount in combination with an annuity-based payment model (the innovative payment model), is relevant to give further consideration given the clinical uncertainties and financial challenges associated with their use. For brexucabtagene autoleucel, a financial-based reimbursement model, a discount with an upfront payment (simple payment model) could be considered as most suitable. For this reason, brexucabtagene autoleucel was not included in the next parts of the framework. Given that both onasemnogene abeparvovec and etranacogene dezaparvovec are orphan-designated products and patient numbers are small, payments at a patient level are suggested [59, 60, 62, 63].

4.2 Parts 2 and 3: Details of the Included Reimbursement and Payment Models: the Simple and Innovative Payment Model and Defining the Input Parameters to Calculate the Consequences of Different Payment Models

In Fig. 4, Parts 2 and 3 of the framework are summarised for the case studies. In Step 5, the details of the simple payment model are outlined. In the case of onasemnogene abeparvovec, a 50% discount rate was advised in the HTA report by Zorginstituut Nederland, which can be used for the simple payment model. For etranacogene dezaparvovec, no public

discount advice was found. Because both therapies have large list prices, a similar discount rate was used for further calculations.

Considering the innovative payment model under Step 6, the main outcome measure for onasemnogene abeparvovec could be the functional motor score as it is patient relevant and routinely measured [59, 61]. To capture this outcome measure, several registries for spinal muscular atrophy could be explored to be used, for example RESTORE or SMARt-CARE, [64, 65]. In the case of etranacogene dezaparvovec, the Pettersson Score could be a relevant outcome measure [60]. Determining when which score(s) are considered to be a success is dependent on the end users' point of view and should ideally be decided in consultation with experts, for example healthcare professionals. The level of payment (discount) rate per outcome measure is also flexible to the end users' preferences. In Step 7, utility and transition probabilities (per relevant subpopulation) need to be collected to calculate the gained benefits for the case studies. The yearly payment proportions can be determined by matching them to the disease and therapy concerned. In the cases of etranacogene dezaparvovec and onasemnogene abeparvovec, there is much uncertainty on how patients will respond in the first years. Therefore, the payment proportions could be relatively small in the first years to account for possible non-responders or unexpected large deterioration in patient outcomes of the main outcome measure (Step 8). For example, patients first need to stabilise, and prospected long-term effects of the treatment will extend beyond the duration of payments. Finally, in Step 9, input for the best-case and worst-case scenarios should be defined. Given that this is very context specific and dependent on stakeholder perspectives, end users should determine the input parameters (transition probabilities) based on what is relevant under the circumstances. [59, 61]

4.3 Part 4: Interpreting the Results from the Hypothetical Case Study Product X

Because final decisions on what relevant input parameters are and defining exact scenarios cannot be made without considering national procedures, stakeholders' preferences and expert input, a hypothetical case study, Product X, illustrative of recent gene and cell therapies, was developed to showcase the potential of the calculation tool (ESM). Even though no exact numbers are presented, the output of the calculation tool shows how different decisions and circumstances such as adjusting multiple input parameters, discount rates, and level of clinical uncertainty can lead to different results and interpretations of what might be most suitable.

In Fig. 5, the output of the calculation tool is shown for Product X using various input parameters. In Fig. 5A, and B, different assumptions are made about the uncertainty

Step 1 - Characteristics of the disease and treatment

onasemnogene abeparvec (Zolgensma)

- Patient*
- Symptomatic SMA type 1 patients and presymptomatic SMA patients with up to three copies of the SMN2 gene.
- Population*
- Approximate incidence rates: 10.5/100,000
 - Approximate prevalence rates: 16.7/ 100,000
- Intervention*
- A single dose intravenous infusion for treating spinal muscular atrophy (SMA)
- Comparator*
- Nusinersen (Spinraza®) or best supportive care
- Outcome*
- Survival, Ventilation free survival, Mobility / muscle function (Measured with motor milestones or CHOP-INTEND), Incidence treatment-related serious adverse events (SAEs) and discontinuation due to adverse events

brexucabtagene autoleucel (Tecartus)

- Patient*
- Adult patients with relapsed or refractory mantle cell lymphoma (r/r MCL) after two or three lines of systemic therapy, including a Bruton's tyrosine kinase inhibitor (BTK inhibitor)
- Population*
- Approximate Incidence Rate: 0.95/100,000
 - Approximate Prevalence Rate: 0.003/100,000
- Intervention*
- A single-dose intravenous infusion for treating relapsed or refractory mantle cell lymphoma (MCL)
- Comparator*
- Multiple treatment options
- Outcome*
- OS, QoL, severe AE

Hemgenix®

- Patient*
- Treatment for patients with severe hemophilia B
- Population*
- Approximate Incidence Rate: 3.33 to 5/100,000
 - Approximate Prevalence Rate: 3.8/100,000
- Intervention*
- A single dose intravenous infusion in the treatment for severe and moderately severe hemophilia B
- Comparator*
- Intravenous coagulation factor IX concentrate
- Outcome*
- Reduction of annualized Bleeding Rates and no longer need to inject factor VIII into a vein one or more times a week, QoL (ICFR report)

Step 2 and 3 - Clinical uncertainties and financial challenges

Onasemnogene abeparvec

Clinical uncertainties:

- Medium and long-term efficacy (including cognitive development and quality of life) are uncertain due to limited follow-up and methodological limitations of the indirect comparison
- Evidence presented was not generalisable to babies with type 1 SMA who were older than 6 months.
- Long-term safety profile is uncertain due to lack of data

€ 2 million per patient

brexucabtagene autoleucel

Clinical uncertainties

- Duration and quantity of effect is uncertain due to the lack of direct comparison and limits of the indirect comparisons
- Nonetheless, it is deemed unlikely that is not superior to the comparative treatment in practice.
- Better evidence in the form of a randomized study is difficult to conduct.

€ 0,4 million per patient

etranacogene dezaparvec

Clinical uncertainties (ICER report)

- Uncertainty in the long-term efficacy due to small number of patients treated in the clinical trial. There is significant uncertainty around the estimates for the outcomes, particularly for follow-up beyond 18 months.
- Effect size unclear due to small patient numbers and limited follow-up.

€ 3,5 million per patient

Step 4 - Potentially suitable reimbursement and payment model combination**

Reimbursement model

- Outcome-based:
 - pay-for-outcome*

Payment model

- Delayed payments: annuity

Payment level: Patient level

Reimbursement model

- Financial based: Discounts

Payment model

- Upfront payments

Payment level: Population level

Reimbursement model

- Outcome-based:
 - pay-for-outcome*

Payment model

- Delayed payments: annuity

Payment level: Patient level

◀**Fig. 3** Framework. Part 1: Matching a reimbursement and payment model with the disease and treatment characteristics by defining their main uncertainties [42, 57–63]^a. *AE* adverse event, *ICER* Institute for Clinical and Economic Review, *OS* overall survival, *QoL* quality of life. This is a summarised overview of how the framework can be used. The complete framework can be found in Annex III of the ESM. ^bSee Annex II of the ESM for definitions

of how well patients will respond in the first year (e.g. patients will transition relatively slowly to worse health states), leading to different needs in payment proportions over the years. The results of Fig. 5A present the situation where there is large uncertainty of how patients will respond, and the payment proportions are relatively small in the first years. Without implementing any form of MEA, the total assumed treatment costs when reimbursing Product X for 5 years will be highest. If patients will respond better than assumed (best-case scenario), implementing the innovative payment model is financially the least favourite option, from a healthcare payer perspective, whereas implementing a simple payment model will lead to considerably lower associated costs. When patients respond according to the predicted clinical pathway presented in HTA reports or clinical trials, reimbursement Product X using a simple or complex payment model will not lead to large financial differences. However, if patients respond worse than assumed (worst-case scenario), implementing the innovative payment model will lead to substantially lower costs compared with implementing the simple payment model. The calculations show that for this situation the innovative payment model can mitigate the financial risk of reimbursing Product X considerably over the simple payment model when clinical performance was similar to or worse than predicted. The results of Fig. 5B show a situation when there is less uncertainty in how patients will respond. Because of this relatively low uncertainty on the calculation tool, the payment proportions were chosen to be more evenly spread over the years. In this case, a simple payment model is the preferred option, from a healthcare payer perspective. Only under the worst-case scenario would a complex payment model be preferable.

In Fig. 5C and D, situations are shown in which the discount rate for the simple payment model has been altered (e.g. the healthcare payer had a stronger or weaker negotiation position towards the marketing authorisation holder). In Fig. 5C, a lower discount rate is applied, illustrating that in this case, implementing the innovative payment model can be seen as the favourable option, from a healthcare payer perspective. In contrast to Fig. 5D, applying a larger discount rate and implementing a simple payment model is a financially more preferable model compared with implementing a complex payment model from a healthcare payers' perspective.

5 Practical Considerations

5.1 Implications for Decision Makers

Using the framework and supportive calculation tool can support reimbursement decision makers, healthcare payers and marketing authorisation holders in easing the determination of what MEA might be suitable given the circumstances of the therapy under consideration. The case studies of onasemnogene abeparvovec, brexucabtagene autoleucel and etranacogene dezaparvovec indicate that one size does not fit all and a tailored approach, considering national procedures and input from relevant stakeholders, is necessary. The framework developed in this study can support the decision process. The results from the calculation tool for Product X demonstrated that different scenarios and input parameters lead to substantial differences in the suitability of MEAs (Fig. 5). With the calculation tool, the scenarios can be easily modified to match decision makers' preferences, meaning that decision makers can easily adjust scenarios and quickly see the consequences of their decisions. Stakeholder preferences, incentives and risk aversion, strategic behaviour and the ability to negotiate certain discounts will influence the desirability of the different payment models. In principle, simple models should be preferred over complex models. However, under large uncertainties or financial risks, our results indicate that outcome-based models do allow financial impacts to be delayed in anticipation of changing assumptions about effectiveness. Yet, implementing outcome-based spread payment models is more resource intensive (e.g. higher transaction and administrative costs). Therefore, we wish to highlight the importance of considering the feasibility of the implementation. When choosing this option, stakeholders need to be willing to collaborate more closely to determine each aspect of the payment structure in detail, where mutual trust and time and resource investment are needed to answer challenging questions regarding contracts, data collection and privacy [18, 19, 22, 25, 66, 67]. For further exploration of outcome-based reimbursement and payment models, all stakeholders need to be involved because only a win-win situation will, in the end, provide access to innovations at fair prices. More insight into the exact implementation costs associated with outcome-based delayed payment models and who will be responsible for this would be beneficial to support this discussion.

The visual output generated by the calculation tool can serve as a means to translate complex information for diverse audiences, for example health technology agencies, patient representatives or healthcare professionals. The framework and calculation tool are designed to engage multiple stakeholders, facilitating a collaborative exchange

	Onasemnogene abeparvovec (Zolgensma)	Etranacogene dezaparvovec (Hemgenix)
Step 5 - The simple payment model <i>Discount</i>	<i>Simple payment model:</i> 50%* discount of the (list) price with an upfront payment model (payment after treatment initiation)	<i>Simple payment model:</i> 50%* discount of the (list) price with an upfront payment model (payment after treatment initiation)
Step 6 - The innovative payment model <i>Outcome-based spread payment with a discount</i>	<p><i>The innovative payment model:</i></p> <ul style="list-style-type: none"> • Main outcome measure: Functional motor milestones • The functional motor milestones is yearly measured • 5 year payment agreement • Registry is in place • Payments made at: 12-, 24-, 36-, 48- and 60-months • Yearly payment proportions increase each year: T1=5%, T2=10%, T3=15%, T4=20%, T5=45% • Payment amount depends on measured functional motor milestones and associated discount rates ** 	<p><i>The innovative payment model:</i></p> <ul style="list-style-type: none"> • Main outcome measure: Pettersson Score • Pettersson Score is measured every one to two years or as clinically indicated • 5 year payment agreement • Registry is in place • Payments made at: 12-, 24-, 36-, 48- and 60-months • Yearly payment proportions increase each year: T1=5%, T2=10%, T3=15%, T4=20%, T5=45% • Payment amount depends on measured Pettersson Score and associated discount rates **
Step 7, 8 and 9 - Input needed for the calculation tool	<ul style="list-style-type: none"> • Transition probabilities per health state (per sub population) • Utility scores per health state (per subpopulation) • Yearly payment proportions • Define the best- and worst-case scenarios. Set the patient response for each of different scenarios (transition probabilities) 	

Fig. 4 Parts 2 and 3: details of the included reimbursement and payment models: the simple (base case) and innovative payment model and defining the input parameters to calculate the consequences of different payment models. *This is a summarised overview of how the framework can be used. The complete framework can be found in the ESM. **Given that the authors of this paper are not aware of

previously agreed upon confidential discounts or agreements, the discount rates were set arbitrarily or based on what was described in the health technology assessment reports. The calculation tool enables easy modification of these scenarios to match decision makers' preferences

of different knowledge and perspectives. By adopting a more visual approach, it aims to illustrate the ways in which decisions influence budget considerations. We wish to highlight a need for more transparency on the structures of implemented MEAs and how they are perceived (without disclosing any financial specifics). Though more openly sharing this information, future development of the framework and calculation tool can be even more aligned with best practices and perceived barriers from practice. Additionally, we hope that the framework and calculation tool will be used in real-life case studies, which will allow for further refinement based on these experiences. Moreover, this transparency could also create more insight into the regulatory constraints or requirements that could influence the selection and implementation of payment models

for high-cost therapies. The research on the consequences of these hurdles is currently limited, largely owing to a lack of publications evaluating implemented payment models. Consequently, we do not yet have a comprehensive understanding of the impact of various regulatory decisions on the process of choosing and implementing a more innovative payment model.

Finally, if the end user decides that an outcome-based reimbursement model is preferred to a discount, multiple practical aspects need to be considered to determine whether the agreement is fit to fly. To ensure that it is a compelling deal for all stakeholders, the recent literature can be consulted to gain an understanding of potential barriers and how they might be overcome [17–19]. Moreover, teaching stakeholders in the principles of MEAs can

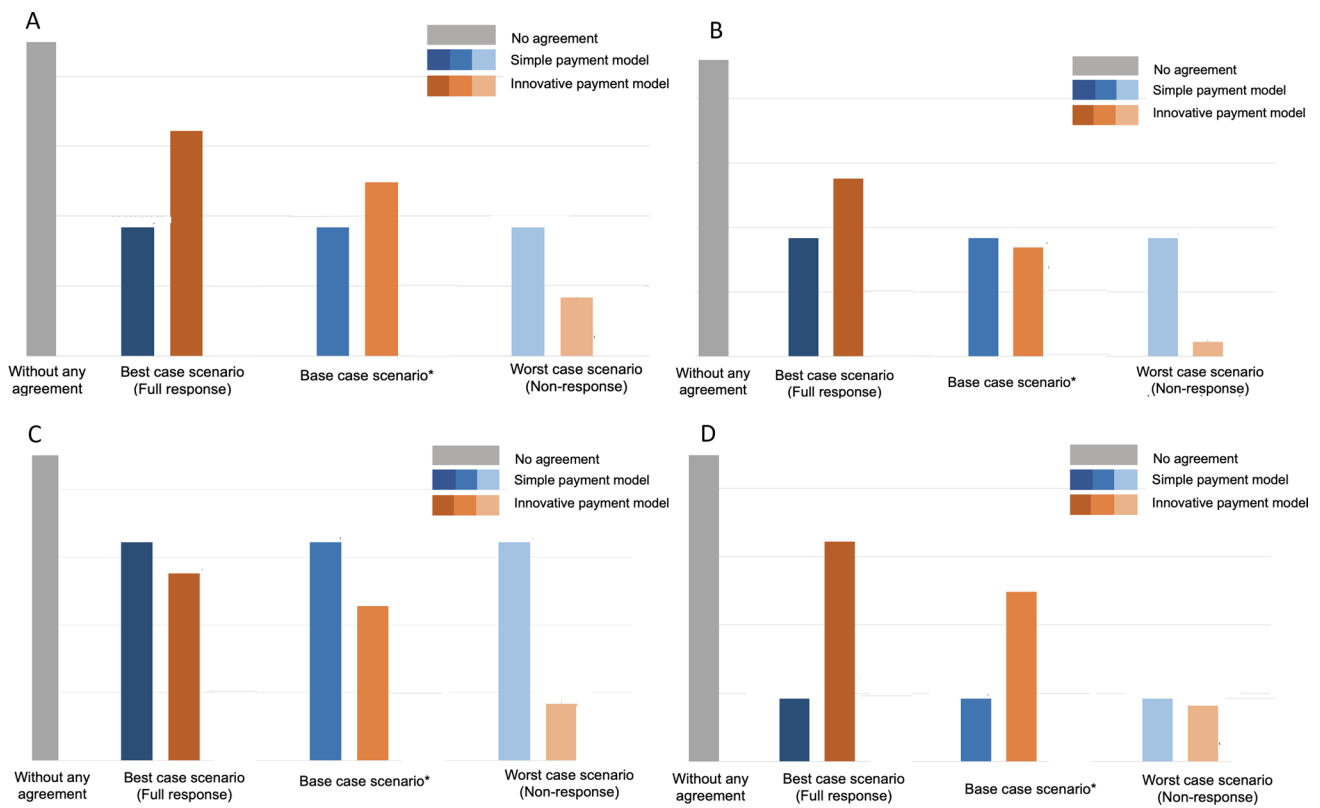


Fig. 5 Total calculated treatment costs within the agreement duration associated with reimbursing Product X (*y-axis*) according to the different payment scenarios (*x-axis*) using different input parameters. **A** large uncertainty treatment effect in the first years; **B** small

uncertainty treatment effects in the first years; **C** high discount rate simple payment model; **D** small discount rate simple payment model. *Patient response according to the predicted clinical pathway presented in health technology assessment reports or clinical trials

support better alignment during the negotiation and implementation period. Training stakeholders to understand the calculation tool and its interpretation in detail could support this even further. [17, 18, 18, 19, 22, 53, 68]

5.2 Limitations

Although the presented calculation tool enables easy modification of the scenarios to match decision makers’ preferences, there are some limitations to be taken into account. First, the calculation tool is structured in such a way that the main outcome measure is also used to define the different health states to which the outcome-based payments (innovative payment model) will relate. The transition probabilities and utilities of the specific health states corresponding to the main outcome measure therefore have to be known to calculate the consequences of the different payment scenarios. Moreover, the output from the calculation tool and the conclusions made on the feasibility of successfully implementing the preferred MEA are only as good as the included data are, for example when choosing outcomes, decision makers need to know if registers are in place and

whether these outcome parameters are being (correctly) collected. The framework applies to a wide range of high-cost one-off therapies with varying characteristics and uncertainties. Nevertheless, stakeholders should be aware that certain therapies or specific contexts may require additional considerations not covered in the framework. Additionally, the generalisability of the framework and calculation tool to therapies that are not one-off might be limited. However, the framework and calculation tool offer the flexibility to make them applicable to other types of therapies.

Second, the current calculation tool includes two MEAs. However, for other cases, different MEAs might be identified in the framework as relevant for inclusion in the calculation tool. In the presented tool, therefore, adjustments can be easily made according to the preferences of end users.

Third, while the results of the calculation tool represent the financial impact of different MEAs under different effectiveness scenarios, they do not say anything about the likelihood of these scenarios. Future research could include this aspect in further development of the calculation tool. To gain insight into a scenario’s likelihood, end users are advised to examine clinical data and consult with clinicians. The

intention of the presented framework and calculation tool is to provide stakeholders with more insight into the possible financial consequences of implementing different MEAs. However, no clear price recommendation or recalculated incremental cost-effectiveness ratios follow from the tool.

6 Conclusions

Designing an outcome-based managed entry agreement is a complex task that requires careful consideration. To deal with these complexities, this study developed a framework and supporting calculation tool to provide decision makers-insight into which type of agreement could be the optimal choice, given the characteristics of the disease, the therapy and stakeholders' preferences.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40273-024-01433-4>.

Declarations

Funding This project was funded by the Dutch National Health Care Institute (Zorginstituut Nederland) as part of the Research Network for Health Technology Assessment.

Conflicts of Interest/Competing Interests Rick A. Vreman reports that at the time the study was conducted, he was working in accordance with the above-mentioned affiliations. He is now employed by Roche. He reports no other conflicts of interest that are directly relevant to this study. Marcelien H.E. Callenbach, Christine Leopold, Aukje K. Mantel-Teeuwisse and Wim G. Goettsch declare that the research was conducted in the absence of any commercial interests that could be construed as a potential conflict of interest.

Ethics Approval This study did not require ethics approval because no patient data were used.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

Code Availability Not applicable.

Authors' Contributions Concept and design: MHEC, CL, RAV, AKM-T, WGG. Analysis and interpretation of data: MHEC, RAV, AKM-T, WGG. Drafting of the manuscript: MHEC. Critical revision of the paper for important intellectual content: Leopold, RAV, AKM-T, WGG.

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References

1. EUR-Lex. 32007R1394-EN-EUR-Lex. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L_.2007.324.01.0121.01.ENG&toc=OJ%3AL%3A2007%3A324%3AFULL. [Accessed 29 Nov 2021].
2. Jørgensen J, Kefalas P. The use of innovative payment mechanisms for gene therapies in Europe and the USA. *Regen Med*. 2021;16(4):405–21. <https://doi.org/10.2217/RME-2020-0169/FORMAT/EPUB>.
3. Danzon PM. Affordability challenges to value-based pricing: mass diseases, orphan diseases, and cures. *Value Health*. 2018;21(3):252–7. <https://doi.org/10.1016/j.jval.2017.12.018>.
4. van Overbeeke E, Michelsen S, Toumi M, et al. Market access of gene therapies across Europe, USA, and Canada: challenges, trends, and solutions. *Drug Discov Today*. 2021;26(2):399–415. <https://doi.org/10.1016/J.DRUDIS.2020.11.024>.
5. Herring WL, Gallagher ME, Shah N, et al. Cost-effectiveness of lovotibeglogene autotemcel (Lovo-Cel) gene therapy for patients with sickle cell disease and recurrent vaso-occlusive events in the United States. *Pharmacoeconomics*. 2024;42(6):693–714. <https://doi.org/10.1007/S40273-024-01385-9/TABLES/5>.
6. Eichler H, Trusheim M, Schwarzer-Daum B, et al. Precision reimbursement for precision medicine: using real-world evidence to evolve from trial-and-learn to track-and-pay to learn-and-predict. *Clin Pharmacol Ther*. 2022;111(1):52–62. <https://doi.org/10.1002/CPT.2471>.
7. ten Ham RMT, Frederix GWJ, Wu O, et al. Key considerations in the health technology assessment of advanced therapy medicinal products in Scotland, the Netherlands, and England. *Value Health*. 2022;25(3):390–9. <https://doi.org/10.1016/J.JVAL.2021.09.012>.
8. Antonanzas F, Juárez-Castelló C, Lorente R, Rodríguez-Ibeas R. The use of risk-sharing contracts in healthcare: theoretical and empirical assessments. *Pharmacoeconomics*. 2019;37(12):1469–83. <https://doi.org/10.1007/S40273-019-00838-W>.
9. Callenbach MHE, Adam L, Vreman RA, Németh B, Kaló Z, Goettsch WG. Reimbursement and payment models in Central and Eastern European as well as Middle Eastern countries: a survey of their current use and future outlook. *Drug Discov Today*. 2023;28(1): 103433. <https://doi.org/10.1016/J.DRUDIS.2022.103433>.
10. Efthymiadou O, Kanavos P. Determinants of managed entry agreements in the context of health technology assessment: a comparative analysis of oncology therapies in four countries. *Int J Technol Assess Health Care*. 2021;37(1):1–7. <https://doi.org/10.1017/S0266462321000039>.
11. Piatkiewicz TJ, Traulsen JM, Holm-Larsen T. Risk-sharing agreements in the EU: a systematic review of major trends. *Pharmacoecon Open*. 2018;2(2):109–23. <https://doi.org/10.1007/S41669-017-0044-1>.
12. Koleva-Kolarova R, Buchanan J, Vellekoop H, et al. Financing and reimbursement models for personalised medicine: a systematic review to identify current models and future options. *Appl Health Econ Health Policy*. 2022;20(4):501–24. <https://doi.org/10.1007/S40258-021-00714-9>.

13. Vreman RA, Broekhoff TF, Leufkens HGM, Mantel-Teeuwisse AK, Goettsch WG. Application of managed entry agreements for innovative therapies in different settings and combinations: a feasibility analysis. *Int J Environ Res Public Health*. 2020;17(22):1–20. <https://doi.org/10.3390/IJERPH17228309>.
14. Wenzl M, Chapman S. Performance-based managed entry agreements for new medicines in OECD countries and EU member states: how they work and possible improvements going forward. *OECD Health Working Papers*. 2019;1-115. <https://doi.org/10.1787/6e5e4c0f-en>.
15. Vreman RA, Leufkens HGM, Kesselheim AS. Getting the right evidence after drug approval. *Front Pharmacol*. 2020;11: 569535. <https://doi.org/10.3389/fphar.2020.569535>.
16. Hanna E, Toumi M, Dussart C, et al. Funding breakthrough therapies: a systematic review and recommendation. *Health Policy (New York)*. 2018;122(3):217–29. <https://doi.org/10.1016/j.healthpol.2017.11.012>.
17. Callenbach MHE, Vreman RA, Mantel-Teeuwisse AK, Goettsch WG. When reality does not meet expectations: experiences and perceived attitudes of Dutch stakeholders regarding payment and reimbursement models for high-priced hospital drugs. *Int J Environ Res Public Health*. 2022;20(1):340. <https://doi.org/10.3390/IJERPH20010340>.
18. Bohm N, Bermingham S, Grimsey Jones F, et al. The challenges of outcomes-based contract implementation for medicines in Europe. *Pharmacoconomics*. 2022;40(1):13–29. <https://doi.org/10.1007/S40273-021-01070-1/TABLES/4>.
19. Michelsen S, Nachi S, van Dyck W, Simoens S, Huys I. Barriers and opportunities for implementation of outcome-based spread payments for high-cost, one-shot curative therapies. *Front Pharmacol*. 2020;11:1. <https://doi.org/10.3389/fphar.2020.594446>.
20. Dunlop WCN, Stauffer A, Levy P, Edwards GJ. Innovative pharmaceutical pricing agreements in five European markets: a survey of stakeholder attitudes and experience. *Health Policy (New York)*. 2018;122(5):528–32. <https://doi.org/10.1016/j.healthpol.2018.02.008>.
21. Carlson JJ, Sullivan SD, Garrison LP, Neumann PJ, Veenstra DL. Linking payment to health outcomes: a taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers. *Health Policy (New York)*. 2010;96(3):179–90. <https://doi.org/10.1016/j.healthpol.2010.02.005>.
22. Garrison LP, Towse A, Briggs A, et al. Performance-based risk-sharing arrangements: good practices for design, implementation, and evaluation: report of the ISPOR good practices for performance-based risk-sharing arrangements task force. *Value Health*. 2013;16(5):703–19. <https://doi.org/10.1016/j.jval.2013.04.011>.
23. Angelis A, Kanavos P. Multiple criteria decision analysis (MCDA) for evaluating new medicines in health technology assessment and beyond: the advance value framework. *Soc Sci Med*. 2017;188:137–56. <https://doi.org/10.1016/J.SOCSCIMED.2017.06.024>.
24. NEWDIGS. Toolkit. Available from: <https://newdigs.tuftsmedialcenter.org/toolkit/>. [Accessed 14 Dec 2022].
25. Whittall A, Jommi C, De Pourvoirville G, et al. Facilitating more efficient negotiations for innovative therapies: a value-based negotiation framework. *Int J Technol Assess Health Care*. 2022;38(1): e23. <https://doi.org/10.1017/S0266462322000095>.
26. Kolasa K, Kalo Z, Hornby E. Pricing and reimbursement frameworks in central Eastern Europe: a decision tool to support choices. *Expert Rev Pharmacoecon Outcomes Res*. 2015;15(1):145–55. <https://doi.org/10.1586/14737167.2014.898566>.
27. Holleman MS, Uyl-de Groot CA, Goodall S, van der Linden N. Determining the comparative value of pharmaceutical risk-sharing policies in non-small cell lung cancer using real-world data. *Value Health*. 2019;22(3):322–31. <https://doi.org/10.1016/J.JVAL.2018.08.007>.
28. Efthymiadou O, Kanavos P. Impact of managed entry agreements on availability of and timely access to medicines: an ex-post evaluation of agreements implemented for oncology therapies in four countries. *BMC Health Serv Res*. 2022;22(1):1066. <https://doi.org/10.1186/S12913-022-08437-W>.
29. Zaric GS. How risky is that risk sharing agreement? Mean-variance tradeoffs and unintended consequences of six common risk sharing agreements. *MDM Policy Pract*. 2021;6(1):1–15. <https://doi.org/10.1177/2381468321990404>.
30. Antonanzas F, Juarez-Castello C, Rodriguez-Ibeas R. Should health authorities offer risk-sharing contracts to pharmaceutical firms? A theoretical approach. *Health Econ Policy Law*. 2011;6:391–403. <https://doi.org/10.1017/S1744133111000016>.
31. Gamba S, Pertile P, Vogler S. The impact of managed entry agreements on pharmaceutical prices. *Health Econ*. 2020;29(Suppl. 1):47–62. <https://doi.org/10.1002/HEC.4112>.
32. Claxton K, Palmer S, Longworth L, et al. A comprehensive algorithm for approval of health technologies with, without, or only in research: the key principles for informing coverage decisions. *Value Health*. 2016;19(6):885–91. <https://doi.org/10.1016/J.JVAL.2016.03.2003>.
33. Walker S, Sculpher M, Claxton K, Palmer S. Coverage with evidence development, only in research, risk sharing, or patient access scheme? a framework for coverage decisions. *Value Health*. 2012;15(3):570–9. <https://doi.org/10.1016/j.jval.2011.12.013>.
34. McCabe CJ, Stafinski T, Edlin R, Menon D. Access with evidence development schemes: a framework for description and evaluation. *Pharmacoconomics*. 2010;28(2):143–52. <https://doi.org/10.2165/11530850-000000000-00000/METRICS>.
35. Callenbach MHE, Schoenmakers D, Vreman RA, et al. Illustrating the financial consequences of outcome-based payment models from a payers perspective: the case of autologous gene therapy atidarsagene autotemcel (Libmeldy®). *Value Health*. 2024;27(8):1046–57. <https://doi.org/10.1016/J.JVAL.2024.05.010>.
36. Hogervorst M, Vreman R, Heikinen I, et al. Uncertainty management in regulatory and health technology assessment decision-making on drugs: guidance of the HTAi-DIA Working Group. *Int J Technol Assess Health Care*. 2023;39(1):1–25. <https://doi.org/10.1017/S0266462323000375>.
37. Nishikawa-Pacher A. Research questions with PICO: a universal mnemonic. *Publications*. 2022;10(3):21. <https://doi.org/10.3390/PUBLICATIONS10030021>.
38. Vreman RA, Broekhoff TF, Leufkens HGM, Mantel-Teeuwisse AK, Goettsch WG. Application of managed entry agreements for innovative therapies in different settings and combinations: a feasibility analysis. *Int J Environ Res Public Health*. 2020;17(22):8309. <https://doi.org/10.3390/ijerph17228309>.
39. Microsoft. Excel spreadsheet software: Microsoft 365. Available from: <https://www.microsoft.com/nl-nl/microsoft-365/excel>. [Accessed 20 Jan 2022].
40. Vreman RA, Naci H, Goettsch WG, et al. Decision making under uncertainty: comparing regulatory and health technology assessment reviews of medicines in the United States and Europe. *Clin Pharmacol Ther*. 2020;108(2):350–7. <https://doi.org/10.1002/CPT.1835>.
41. Callenbach MHE, Goettsch WG, Mantel-Teeuwisse AK, Trusheim M. Creating win-win-win situations with managed entry agreements? Prioritizing gene and cell therapies within the window of opportunity. *Drug Discov Today*. 2024;29(7): 104048. <https://doi.org/10.1016/J.DRUDIS.2024.104048>.

42. Zorginstituut Nederland. Pakketadvies sluisgeneesmiddel brexucabtagene autoleucl (Tecartus[®]) voor de behandeling van bepaalde patiënten met recidiverend of refractair mantelcellymfoom (MCL). Available from: <https://www.zorginstituutnederland.nl/publicaties/adviezen/2022/09/09/pakketadvies-sluisgeneesmiddel-brexucabtagene-autoleucl-tecartus>. [Accessed 21 Dec 2023].
43. Facey KM, Espin J, Kent E, Link A, Nicod E, O'Leary A, Xoxi E, van de Vijver I, Zaremba A, Benisheva T, Vagoras A, Upadhyaya S. Implementing outcomes-based managed entry agreements for rare disease treatments: nusinersen and tisagenlecleucel. *Pharmacoeconomics*. 2021 Sep;39(9):1021-1044. <https://doi.org/10.1007/s40273-021-01050-5>. Epub 2021 Jul 7. PMID: 34231135; PMCID: PMC8260322.
44. Jørgensen J, Kefalas P. The use of innovative payment mechanisms for gene therapies in Europe and the USA. *Regen Med*. 2021;16(4):405-21. <https://doi.org/10.2217/RME-2020-0169>.
45. Jørgensen J, Kefalas P. Reimbursement of licensed cell and gene therapies across the major European healthcare markets. *J Mark Access Health Policy*. 2015;3(1). <https://doi.org/10.3402/jmahp.v3.29321>.
46. Carlson JJ, Gries KS, Yeung K, Sullivan SD, Garrison LP. Current status and trends in performance-based risk-sharing arrangements between healthcare payers and medical product manufacturers. *Appl Health Econ Health Policy*. 2014;12(3):231-8. <https://doi.org/10.1007/s40258-014-0093-x>.
47. Eichler HG, Adams R, Andreassen E, et al. Exploring the opportunities for alignment of regulatory postauthorization requirements and data required for performance-based managed entry agreements. *Int J Technol Assess Health Care*. 2021;37(1): e83. <https://doi.org/10.1017/S026646232100057X>.
48. Facey KM, Espin J, Kent E, et al. Implementing outcomes-based managed entry agreements for rare disease treatments: nusinersen and tisagenlecleucel. *Pharmacoeconomics*. 2021;39(9):1021-44. <https://doi.org/10.1007/s40273-021-01050-5>.
49. Dabbous M, Chachoua L, Caban A, Toumi M. Managed entry agreements: policy analysis from the European perspective. *Value Health*. 2020;23(4):425-33. <https://doi.org/10.1016/J.JVAL.2019.12.008>.
50. Jørgensen J, Kefalas P. Reimbursement of licensed cell and gene therapies across the major European healthcare markets. *J Mark Access Health Policy*. 2015;3(1):29321. <https://doi.org/10.3402/JMAHP.V3.29321>.
51. Maes I, Boufraioua H, Dyck W Van, Schoonaert L. Innovative solutions for paradigm changing new therapies. 2019. <https://hdl.handle.net/20.500.12127/7460>
52. Jönsson B, Hampson G, Michaels J, Towse A, von der Schulenburg JMG, Wong O. Advanced therapy medicinal products and health technology assessment principles and practices for value-based and sustainable healthcare. *Eur J Health Econ*. 2019;20(3):427-38. <https://doi.org/10.1007/S10198-018-1007-X>.
53. Wills A, Mitha A. Health policy analysis financial characteristics of outcomes-based agreements: what do Canadian public payers and pharmaceutical manufacturers prefer? *Value Health*. 2023. <https://doi.org/10.1016/j.jval.2023.12.011>.
54. Cole A, Cubi-Molla P, Pollard J, et al. Making outcome-based payment a reality in the NHS. 2019. Available from: <http://www.cancerresearchuk.org/>. [Accessed 17 Mar 2022].
55. Payer perspectives on reimbursement of one-time high-cost durable therapies. Available from: <https://www.pharmexec.com/view/payer-perspectives-reimbursement-one-time-high-cost-durable-therapies>. [Accessed 17 Mar 2022].
56. Horizonscan geneesmiddelen. Available from: <https://www.horizonscangeneesmiddelen.nl/>. [Accessed 1 Sep 2023].
57. NICE. Overview. Brexucabtagene autoleucl for treating relapsed or refractory mantle cell lymphoma: guidance. <https://www.nice.org.uk/guidance/ta677/chapter/1-Recommendations>. Accessed 8 Feb 2024.
58. Haute Autorité de Santé. TECARTUS (cellules autologues CD3+ transduites anti-CD19). Available from: https://www.has-sante.fr/jcms/p_3266354/en/tecartus-cellules-autologues-cd3-transduites-anti-cd19. [Accessed 8 Feb 2024].
59. Zorginstituut Nederland. Pakketadvies sluisgeneesmiddel onasemnogene abeparvovec (Zolgensma[®]) bij de behandeling van spinale musculaire atrofie (SMA). Available from: <https://www.zorginstituutnederland.nl/publicaties/adviezen/2021/05/06/pakketadvies-sluisgeneesmiddel-onasemnogene-abeparvovec-zolgensma>. [Accessed 16 Dec 2022].
60. ICER. ICER publishes final evidence report on gene therapies for hemophilia A and B. Available from: <https://icer.org/news-insights/press-releases/icer-publishes-final-evidence-report-on-gene-therapies-for-hemophilia-a-and-b/>. [Accessed 21 Dec 2023].
61. NICE. Overview. Onasemnogene abeparvovec for treating presymptomatic spinal muscular atrophy: guidance. <https://www.nice.org.uk/guidance/hst15>. Accessed 8 Feb 2024.
62. NICE. Overview. Onasemnogene abeparvovec for treating spinal muscular atrophy: guidance.
63. Haute Autorité de Santé. Zolgensma (onasemnogene abeparvovec). Available from: https://www.has-sante.fr/jcms/p_3224937/en/zolgensma-onasemnogene-abeparvovec. [Accessed 8 Feb 2024].
64. Pechmann A, König K, Bernert G, et al. SMARtCARE: a platform to collect real-life outcome data of patients with spinal muscular atrophy. *Orphanet J Rare Dis*. 2019;14(1):1-6. <https://doi.org/10.1186/S13023-019-0998-4/TABLES/1>.
65. Finkel RS, Day JW, De Vivo DC, et al. RESTORE: a prospective multinational registry of patients with genetically confirmed spinal muscular atrophy: rationale and study design. *J Neuromuscul Dis*. 2020;7(2):145-52. <https://doi.org/10.3233/JND-190451>.
66. Herholz H, Ofierska-Sujkowska G, Adamski J, et al. Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers. *BMC Health Serv Res*. 2010;10:153. <https://doi.org/10.1186/1472-6963-10-153>.
67. Adamski J, Godman B, Ofierska-Sujkowska G, et al. Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers. *BMC Health Serv Res*. 2010;10:153. <https://doi.org/10.1186/1472-6963-10-153>.
68. Owen AJ, Spinks J, Meehan A, et al. A new model to evaluate the long-term cost effectiveness of orphan and highly specialised drugs following listing on the Australian Pharmaceutical Benefits Scheme: the Bosentan Patient Registry. *J Med Econ*. 2008;11(2):235-43. <https://doi.org/10.3111/13696990802034525>.