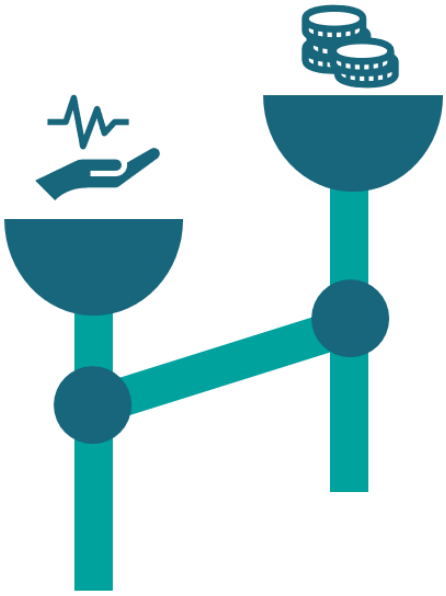
HEALTH INNOVATION NEXT GENERATION PAYMENT & PRICING MODELS (HI-PRIX):

Balancing Sustainability of Innovation with Sustainability of Health Care



HI-PRIX

M2: Within-country performance of novel payment/pricing schemes: costs and benefits of implementation

WP1 – Mapping of payment and pricing schemes for health innovation in the EU: implementation, barriers, and enablers

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Executive summary

Innovative payment models (IPMs) can offer solutions where uniform pricing and discounts fall short, balancing healthcare system sustainability with access to and incentives for innovation. However, IPMs are complex arrangements: while they provide benefits for patients, systems, and industry, they also involve significant implementation costs. It is therefore important for key stakeholders to better understand these costs and benefits to enable efficient and flexible use of IPMs across systems, therapy areas, types of innovation, and contexts. This research aims to capture and measure the full range of IPM implementation costs and benefits through a systematic analytic framework and case studies of IPMs in five different countries.

Methods

We analysed four case studies of distinct IPMs across five countries, using quantitative and qualitative methods to identify costs and benefits, map them to implementation phases, determine the most affected stakeholders, and estimate their magnitude.

We developed an analytic framework, grounded in implementation science, to characterise IPM implementation by phase and stakeholder group. The framework distinguishes four phases—inception & design, adoption & implementation, maintenance & sustainment, and wrap-up & closing—and includes payers/HTAs, providers, manufacturers, and patients. Four case studies were selected to cover distinct IPM types: instalments and amortisations (CAR-Ts in Spain and Italy), financial-based risk-sharing (antibiotics in Sweden), outcomes-based agreements (gene therapy in Germany), and portfolio/bundling agreements (oncology drugs in Lithuania). The framework was applied through a three-stage process. First, qualitative exploration via interviews and questionnaires built a structured cost–benefit repository. Second, data collection combined primary and secondary sources to populate quantitative and qualitative assessments. Third, analysis used direct quantification, reasonable approximations, and qualitative estimation as needed. This approach enabled a comprehensive evaluation of implementation costs and benefits across IPM types, phases, and stakeholder perspectives.

Results

Our case studies highlight a wide range of costs associated with IPM schemes. These include human resource (HR) costs from payers, manufacturers, and providers across the scheme lifecycle, as well as transaction costs such as monitoring, legal and financial input, IT, and infrastructure. Despite these, IPMs deliver major benefits: improved outcomes and earlier access for patients, cost savings for health systems, and revenue predictability for manufacturers. They also create broader value through knowledge spillovers, scientific progress, and stronger infrastructure.

The case studies show that IPM implementation costs and benefits vary by type and setting. In the CAR-T staged model in Spain and Italy (instalment and amortisation payment), the largest costs were HR-related, affecting payers and manufacturers across all phases, while providers' costs were mainly during adoption and implementation. Costs were higher in Spain, likely reflecting the relative efficiency of Italy's AIFA registry versus Spain's Valtermed system, with transaction costs also lower in Italy. Earlier access to therapies was perceived as a key benefit in Spain, while in Italy views varied across stakeholders. Differences in spillovers and other benefits reflected Spain's relative inexperience with IPMs compared to Italy's longer track record.

The Swedish pilot IPM for novel antibiotics (financial-based risk sharing agreement) involved substantial costs for the payer, mainly administrative and HR-related, as well as medicine-related costs to ensure availability, while manufacturers faced minor to moderate administrative and transaction costs. Costs affected stakeholders across all implementation phases, whereas benefits—earlier access to antibiotics, predictable manufacturer revenue, patient health gains, and broader societal value—were most pronounced during maintenance, sustainment, and wrap-up.

The German cohort model for gene therapy (outcomes-based agreement) involved moderate to significant costs for payers and manufacturers, mainly HR and transaction costs across inception & design, adoption & implementation, and sustainment & maintenance phases, while providers and patients faced minimal costs. The scheme was relatively immature at the time of research, which may have influenced both the

magnitude of costs and the limited capture of health benefits and system cost-savings due to the short duration after implementation. Key benefits included earlier patient access, risk-sharing for high-cost therapies, predictable manufacturer revenue, knowledge gains, and broader societal and scientific spillovers.

The Lithuanian bundling agreement for two oncology medicines (portfolio or bundling agreement) involved minor to moderate costs for all stakeholders. The payer incurred administrative and medicine-related costs across adoption, maintenance, and wrap-up phases, while manufacturers and providers faced limited additional HR and transaction costs within routine operations. Benefits were concentrated in the sustainment & maintenance phases, including faster and more equitable patient access, improved quality of care, reduced patient out-of-pocket expenses, moderate early revenue for manufacturers, and cost savings for the healthcare system. Additional benefits included learning and upskilling opportunities for payer and provider staff.

Discussion

This report presents a comprehensive assessment of the costs and benefits associated with implementing a broad range of innovative payment models (IPMs). The research applies a newly developed evaluation framework that captures implementation impacts across four phases and integrates the perspectives of payers/HTAs, manufacturers, providers, and patients. The framework was applied to four case studies representing different IPM types.

Across all IPMs, implementation introduced additional complexity and costs, particularly human resource and transaction costs for payers, manufacturers, and providers. Outcome-based agreements and instalments and amortisations generally required the greatest effort due to negotiation, monitoring, data collection, and legal and financial requirements associated with contracting and operationalising the schemes. Patients typically incurred minimal direct costs, though indirect costs (e.g., travel, hospitalisation, or adverse events) were noted in some schemes. Despite these costs, IPMs delivered significant benefits. All schemes facilitated timely—and often early—access to innovative therapies, with improved patient outcomes and equity of

care. Payers and providers benefited from risk-sharing, cost offsets, and, in some cases, modest financial savings, while manufacturers gained predictable revenue, earlier market access, and engagement in shaping innovation-friendly policies. Broader system-level gains included knowledge spillovers, upskilling of healthcare professionals, improved infrastructure, and generation of real-world evidence.

The analysis highlights a dynamic trade-off between costs and benefits: while costs are distributed across all implementation phases, benefits tend to concentrate in adoption & implementation, and sustainment & maintenance stages. Stakeholders can manage this trade-off through strategies such as strengthening system readiness, phasing IPMs as transitional tools until standard agreements are feasible or targeting schemes to address specific market failures or clinical uncertainties. Overall, this research demonstrates that IPMs, despite their complexity and implementation costs, can balance financial, clinical, and societal gains, providing flexible solutions to pricing and access challenges across diverse healthcare systems and therapeutic areas.

Conclusion

IPMs provide flexible solutions to improve access to pharmaceutical innovation and address challenges that conventional agreements cannot. They involve trade-offs between costs and benefits, while ongoing learnings are helping streamline implementation, making IPMs increasingly effective and feasible for all stakeholders.

1. Introduction

In the EU and beyond, Member States are struggling to balance sustainability of health innovation with sustainability of health care systems. Central to this challenge and how to address it is the role of pricing and payment models, as they influence affordability, affect access to products, and provide incentives for directing efforts towards areas of the highest societal value. Therefore, it is important that policymakers have a thorough understanding of the key features of pricing and payment models that currently exist in the European Union (EU) and beyond, to facilitate learning from Innovative Pricing and Payment Model (IPM) implementation experiences.

The HI-PRIX consortium Work Package (WP)1 aims to provide policymakers with a comprehensive understanding of the existing pricing and payment models within the Europe, drawing from the collective experiences of European countries. The role of this research is to identify and analyse the characteristics that support the effective real-world implementation of IPMs.

The OHE, within WP1, aims to investigate the costs and benefits, and barriers and enablers of IPMs, focusing on the features that might sustain their effective implementation in real life. This will contribute towards the Hi-PRIX project's ultimate objective of developing a series of tailored policy recommendations that can guide the application of various models to diverse Member States (MS) contexts.

1.1. Context

We conceptualise IPMs departing from the concepts of conventional models. Conventional models describe the typical contracting process in which a uniform price is paid for a single product at the time of purchase, with discounts (if any) applied uniformly or based on volumes to address budget impact concerns.

We therefore define an IPM as a pricing or payment model that differs structurally from conventional pricing and payment models in the means, timing, structure, and/or attached conditions of payments.

1.2. Objectives

This document constitutes the milestone deliverable for task 1.2.2. of the OHE investigation into the costs and benefits, and barriers and enablers (CBBE) of IPM implementation. The objective of task 1.2.2. is to quantify, estimate or document the costs and benefits of IPM implementation.

Task 1.2.2. is part of the broader research under Task 1.2. *Implementation of payment and pricing schemes: costs, benefits, barriers and enablers,* a core component of the HI-PRIX consortium's Work Package 1, *Mapping of payment and pricing schemes for health innovation in the EU: implementation, barriers and enablers*.

The methods, analyses and results in this task aim to capture all costs and benefits the implementation of IPMs entail and to assess them jointly to inform the deliverable *D.1.2. Policy recommendations about successful and flexible implementation of the different schemes to promote access to high-quality affordable innovative technologies* of the WP1 of HI-PRIX project. While some costs (e.g., data collection) and benefits (e.g., access and faster access) are obvious and previously captured in the literature, this research seeks to document and assess all tangible and intangible costs and benefits of IPM implementation from a variety of IPM types, countries and health care systems, and from a variety of perspectives. This is to allow a deeper and detailed analysis of implementation costs and benefits, in general and with country, IPM or system focus that will enable a more nuanced input for generating recommendations in deliverable D.1.2.

2. Methodology

We use a series of four case studies to document the costs and benefits of IPM implementation. Case studies were specific IPMs implemented to either incentivise or enable market access of a particular health technology e.g. gene therapy or a group of medicines e.g., antibiotics. We combine quantitative and qualitative methods to:

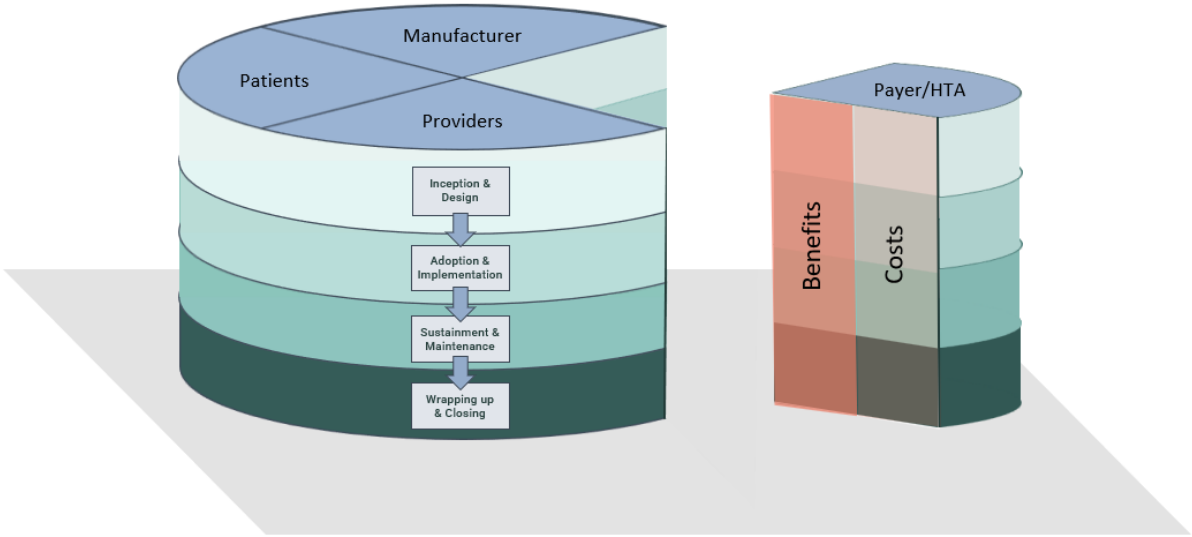
- Document all costs and benefits of IPM implementation.
- Allocate the documented costs and benefits to different phases of

implementation.

- Attribute each documented cost and benefit to the appropriate stakeholder (e.g., payers/HTA, manufacturers, providers, and patients).
- Quantify, estimate or qualitatively determine the size of each cost and benefit.

Relying on implementation science models[1–3] we developed an analytical framework to firstly define the different phases of IPM implementation and, secondly, identify the relevant stakeholder groups involved in the IPM implementation process. Figure 1 summarises the analytical framework.

Figure 1. Analytical framework for cost-benefit analysis



We defined four different phases of implementation. These are:

- Inception and design: this phase involves defining the IPM's objectives for each stakeholder and outlining the scope of relevant costs and benefits. For example, it includes identifying the core issues prompting IPM use, the rationale behind its design, the decision-makers involved, and the costs and benefits they encountered during this stage.
- Adoption and implementation: this phase involves the setup required after an IPM is agreed upon. For example, establishing systems for data collection, reporting, and use; upskilling clinical and non-clinical staff; and accrediting treatment centres.

- Sustainment and maintenance: this phase covers the scheme's operation while the health technology innovation (e.g., innovative therapy) is under the IPM. It includes ongoing costs for data collection on usage or outcomes, payment determination, and administrative expenses.
- Wrapping up and closing: this phase occurs after the health technology innovation is no longer covered under the IPM and may involve finalizing outstanding payments, costs, and investments.

We also identified four main stakeholder groups. These are:

- Payer/HTA: this group comprises public authorities responsible for reimbursement decisions. They lead negotiations during the inception and design stages, hold the authority to approve the IPM proposal, and sign contracts with manufacturers. Additionally, they control the financial resources to fund the health technology innovation and possess the legal power to mandate its adoption by providers. These authorities may operate at the regional or national level.
- Manufacturer: this group comprises the owners of the health technology innovation who hold the legal marketing authorization for its use. They participate in discussions with payers to negotiate the terms and design of the IPM. Upon successful agreement, their innovative health technology is reimbursed (under certain conditions) and integrated into healthcare systems. They also sign the contract that obligate them to supply the innovation under specified conditions, ensuring its availability to healthcare providers.
- Providers: healthcare providers (e.g., NHS, hospital, clinicians) are in charge of implementing or delivering the innovation. While they may contribute clinical and technical expertise during IPM design, their role does not extend to adoption and maintenance. Providers are responsible for providing access to the innovation to patients, clinical data collection, ensuring treatment centres have the necessary resources, and sharing relevant clinical data with payers and/or manufacturers.

- Patients: the end beneficiaries of the innovation. It is the target group for which all other stakeholders work together aiming to provide the earliest access possible to promising therapeutical innovations. It is the only group not subject to legal obligations or responsibilities specific to the IPM, but they also face costs (e.g., travel to accredited treatment centres) and benefits (e.g., earlier access due to IPM).

2.1. Identification and selection of case studies

Case studies of IPM implementation in member states were used as the evidence vehicle for the quantification and assessment of implementation costs and benefits. The use of case studies represents a pragmatic approach for the identification and further quantification, estimation and scaling of costs and benefits associated with IPM implementation. We aimed to cover a sampling of the most implemented schemes spanning 4-5 commonly cited scheme main attributes. We identified potential IPM-attributes using findings in the academic and grey literature including the University of Bocconi taxonomy matrix.[4] We identified the following IPM-types as the most relevant for this task:

1.) Outcome-Based Agreement
2.) Financial-Based Risk Sharing Agreement
3.) Portfolio or Bundling Agreement
4.) Instalment and Amortisation Payments
5.) Indication-based Pricing

Table 1 provides further elaboration of these five IPM types. Table 1 provides further details on these five IPM types. It is important to note that the selected IPM types can in some cases be characterised by overlapping, non-mutually exclusive features. For example, instalment and amortisation payments and outcomes-based agreements

can be combined as for the cases of Luxturna™, Zolgensma™, Yescarta™ and Kymriah™ (Table 1)[1].

[1]Generic names are used for standard medicines, whereas trade names are used for gene and cell therapies, given the complexity of their generic names.

Table 1 Description and examples of IPM-types

	Description	Example
Outcome-Based Agreement	Payment is tied to clinical outcomes achieved in real-world practice. Outcomes for the payment model can be defined at patient level (e.g., payment conditional to survival, cure) or at a population level (e.g., payment determined proportionally to overall population real world effectiveness)	• Genentech and Priority Health agreement for *bevacizumab (Avastin™)*.[5] • AstraZeneca and Catalan Health System agreement for *gefitinib (Iressa™)*.[6] • Spark Therapeutics agreements for *Luxturna*.[7] • AveXis agreements for *Zolgensma™*.[8,9]
Financial-Based Risk Sharing Agreement	The unit price of the product depends on the volume purchased. It can be implemented at the population-level, such as in a price-volume agreement or volume-delinked subscription model, or at the individual patient-level.	• Population-level: o subscription model agreement between Australian government and DAA manufactures for Hep-C patients.[10] o revenue guarantee partially delinked model agreement for antibiotic access between Sweden and four antibiotic manufacturers.[11,12] o agreement between Spark Therapeutics and Italy for *Luxturna™*.[13] • Patient-level dose-capping: o NICE TA for ranibizumab (Lucentis™).[14]
Portfolio or Bundling Agreement	A 'bundle' or 'portfolio' of two or more medicines is purchased at an agreed 'overall' price.	• Vertex portfolio agreements with several EU Member States for Cystic Fibrosis medicines.[15–19] • Arrangements between manufacturers and payers in New Zealand.[20] • Arrangements of multiple vaccine producers.[21]
Instalment and Amortisation Payments	Payments are split into several instalments spread over time. Instalments can be risk-sharing. Split payments may or may not be outcomes-based.	• Novartis agreements for *Kymriah™* in Italy and Spain [22] • Kite (Gilead) agreements for *Yescarta™* in Spain and Italy [22] • Spark Therapeutics agreements for *Luxturna™*.[7]

		• AveXis (Novartis Gene Therapies)agreements for *Zolgensma*™.[8,9]
Indication-based Pricing	The price of the medicine depends on the subgroup (or 'indication') in which it is used.	• Various examples in EU member states, although these are typically implemented with blended prices or separate brands.[23]

The IPM-types selected can all be categorised within the broad typologies of 'financial-based' and 'performance-based' agreements proposed by the OECD for all Market Entry Agreements (MEA).[24]

These five IPM-types are broadly representative of the implemented *innovative* schemes which have been referenced in the literature.[2] To ensure adequate coverage across the spectrum of commonly referenced IPMs, we aimed to include one case study per main IPM IPM-type identified.

We identified feasible case studies for all type of IPM but for indication-based pricing. Table 2 provides detailed information of the four selected case studies.

Table 2. Case studies selection

IPM-type	Case study description
Outcome-Based Agreement	A patient-level outcomes-based prospective cohort payment model for Roctavian™, a gene therapy for haemophilia A in Germany.
Financial-Based Risk Sharing Agreement	Population-level partially delinked revenue guarantee model for access to antibiotics for carbapenem resistant infections. Implemented in Sweden.[12]
Portfolio or Bundling Agreement	Defined patient population level bundling of two medicines for multiple myeloma in Lithuania. Thalomid™ was provided free of charge at a fixed ratio with Revlimid.
Instalment and Amortisation Payments	A patient-level outcomes-based staged payment model implemented in Italy and Spain to introduce the first two CAR-T therapies, Kymriah™ and Yescarta™.[22]

These case studies were chosen based on the availability of quantitative publicly available data on the scheme, and on the willingness of stakeholders to provide cost

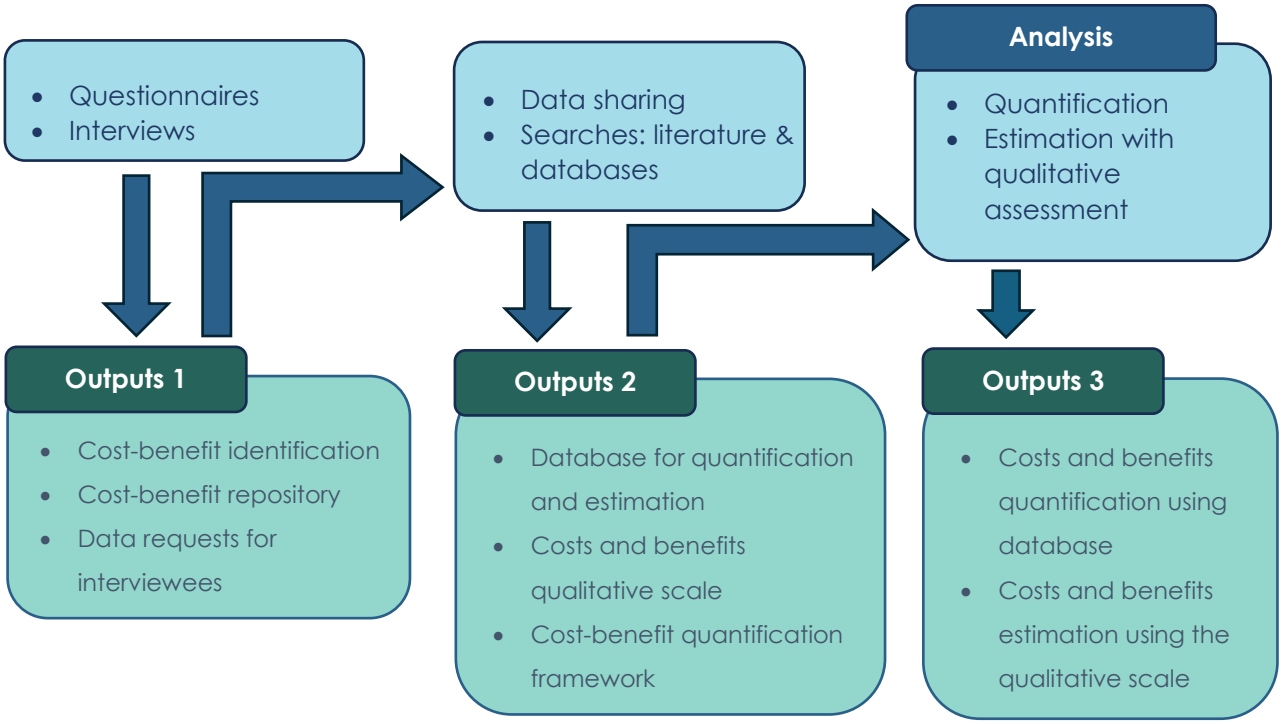
[2] There are payment schemes such as cost-plus pricing, external or internal reference pricing, that are not covered by any of the five categories.

and benefit input for all phases of IPM implementation. Preference was given to case studies from the UK or EU Member States. The implementation framework was applied to each case study for comprehensive analysis. The information was collected through interviews with key stakeholders, followed by quantitative analysis when data were available. This was complemented by a deeper qualitative assessment involving relevant stakeholders to comprehensively analyse the benefits and costs of the IPM's implementation. The case studies thus helped us develop a comprehensive appraisal of all relevant costs and benefits – including those which may not be well characterised in the existing literature – and characterise the extent to which the different costs and benefits are borne by different stakeholders along the different phases of IPM implementation.

2.2. Methodological process

We developed a structured methodological process to document the costs and benefits for stakeholders, allocate them to the appropriate implementation phase and stakeholder group, and finally quantify, estimate, or qualitatively assess them. This process guided us through the various stages of the research. Figure 2 summarises the methodological process followed for the IPM implementation costs and benefits assessment.

Figure 2. Methodological process for the costs and benefits quantification



We used a three-stage process for the quantification of the implementation costs and benefits of IPMs. Stages are qualitative exploration, data collection and analysis. Each stage produced a set of intermediate outputs enabling the process to progress to the next stage. Outputs of stage 3 (analysis) produced the final results of the costs and benefits of IPM implementation.

2.2.1. Qualitative exploration

We used questionnaires and interviews to gather data and information on IPM costs and benefits. We designed a questionnaire to capture all costs and benefits experienced by stakeholders due to the implementation of the IPM (we provide a sample of the questionnaire used for interviews in Appendix 1). We then identified contacts for the relevant stakeholders who had participated in the implementation of the IPM (e.g., payers/HTA, healthcare providers, manufacturers, patients). For each case study, we aimed to conduct interviews with at least one participant per stakeholder group.

Table 3 provides a summary of all interviews conducted for the case studies. At the time of task finalisation, a few perspectives remained uncovered: patients and

providers for the Sweden antibiotic case study. No patient perspective can be captured with interviews for the Swedish revenue guarantee model for antibiotics. This perspective was incorporated based on the evidence reported by the Swedish Public Health agency.[25] We discuss how we have managed these gaps in the discussion section of this report.

Table 3. Interviews conducted per case study by stakeholder group.

	HTAs/ Payers	Manufacturers	Providers	Patients	**Total**
CAR-T outcomes-based instalment model in Italy	1	2	2	1	**6**
CAR-T outcomes-based instalment model in Spain	2	2	1	1	**6**
Revenue guarantee model for novel antibiotics in Sweden	1	2	N/A	N/A	**3**
Portfolio or bundling agreement for multiple myeloma medicines in Lithuania	1	1	1	1	**4**
Outcomes-based agreement for gene therapy for haemophilia in Germany	2	1	1	1	**5**
Total	**7**	**9**	**6**	**4**	**24**

We sent the questionnaire to interviewees in advance and requested that they complete and return it prior to the interview. The questionnaire data were analysed to design the interview structure, which was then used to guide the interviews. All data and information gathered from the questionnaire and the interview were reviewed by interviewees for validation.

The qualitative exploration stage produced a cost-benefit repository that systematically organises all costs and benefits associated with implementing IPMs in the case studies. All specific costs and benefits in the repository are organised into categories and then associated to the relevant affected stakeholder.

2.2.2. Data collection

Based on the qualitative exploration and the cost-benefit repository, requests for relevant data were developed and shared with relevant interviewees. When able, they provided the requested data; otherwise, we explored alternative ways to collect

relevant data and information from publicly available sources. For example, we searched for data in national or supranational statistics offices such as Eurostat and national Ministry of Health databases. We also gathered data from the literature, such as HTA technology appraisals and scientific articles, using targeted search strategies.

Data collection produced three intermediate outputs. These were:

- A database for the quantification and approximation of implementation costs and benefits
- A system based on a qualitative scale for assessing the magnitude of costs and benefits (e.g., moderate, medium, significant)
- A cost-benefit framework detailing all costs and benefits, their phases, affected stakeholders, available data for their quantification or approximation, and their qualitative size scale.

2.2.3. Analysis

Using the cost-benefit framework, we quantified costs and benefits when data allowed direct measurement. When data did not permit this, we approximated values under plausible assumptions. For costs and benefits without reliable data, we estimated their magnitude using the qualitative scaling method.

Outputs of the analysis stage comprise the results of task 1.2.2 of WP1, within-country performance of novel payment/pricing schemes: costs and benefits of implementation. Results were calculated and presented by case study. In addition to quantifying, approximating, and qualitatively assessing the costs and benefits, the results also considered the implementation phases, and the stakeholders involved.

3. Results

3.1. Type of costs and benefits associated with IPMs

We identified a wide range of costs and benefits that were associated with the IPMs in our case studies (see Table 4). IPM schemes involved significant HR and transaction costs for payers, manufacturers, and providers throughout the duration of the scheme from negotiation to wrap-up. Additional transaction costs are associated with clinical monitoring, scheme infrastructure, legal input, IT support and infrastructure, and finance expenses. Despite these costs, IPMs offer numerous benefits: improved efficacy, safety, and quality of life for patients; anticipated revenue and return on investment for manufacturers; cost savings and early access to therapies for payers, providers, and patients; and knowledge spillovers, scientific advancements, and better infrastructure and research-friendly environment.

Table 4: Cost-benefit repository across IPMs for different stakeholders

	Cost/benefit category	Payers	Manufacturers	Providers	Patients
Costs	HR costs	• Negotiation • Set-up of scheme • Maintenance • Payment processing (e.g., re. IPM risk-sharing nature) • Wrap-up • Opportunity costs	• Negotiation • Set-up of scheme • Maintenance • Payment processing (e.g., re. IPM risk-sharing nature) • Wrap-up • Opportunity costs	• Set-up of scheme • Maintenance • Payment processing (e.g., re. IPM risk-sharing nature) • Wrap-up • Upskilling • Opportunity costs	
	Transaction costs (excluding HR)	• Clinical monitoring • Infrastructure for IPM implementation • Legal costs • IT costs • Finance costs	• Clinical monitoring • Infrastructure for IPM implementation • Supply chain, logistics, and storage • Legal costs • IT costs • Finance costs	• Clinical monitoring • Infrastructure for IPM implementation • Supply chain, logistics, and storage • IT costs	
	Medicine cost	• Price*			• Out of pocket costs
	Health-related cost				• Unexpected adverse events
	Other costs				• Hospitalisations • Travel and transport

	Cost/benefit category	Payers	Manufacturers	Providers	Patients
					• Insufficient information on treatment and training
Benefits	Health-related benefits	• Efficacy/Safety • QoL		• Efficacy/Safety • QoL	• Efficacy/Safety • QoL
	Revenue		• Earlier Revenue and return on investment		
	Cost savings	• Risk-sharing with reduced costs to asset • Cost-offset		• Cost-offset	
	Early access	• Early access	• Earlier access to market or market launch	• Early access	• Early access
	Spillovers and other positive externalities	• Knowledge spillover to other schemes • Infrastructure spillovers • Innovativeness and preparedness to absorb	• Knowledge spillover to other schemes or countries • Knowledge spillover to better product value understanding	• Scientific spillover • Infrastructure spillover • Upskilling HR • Innovation environnent e.g. Clinical trials • Provider accreditation	
	Other benefits	• Political win	• Risk sharing and generation of RWE • Predictability of revenue		• Quicker and more optimal adoption

* This cost was not mentioned in the interviews but was inferred from the evidence, which suggested that earlier access led to earlier revenue for the manufacturer and, consequently, an earlier price cost for payers.

3.2. Instalment and amortisation payments: CAR-T therapies in Italy and Spain

CAR-T cells therapies are engineered to direct T cells to specific antigens on tumour cells, triggering an antitumor response.[26] The FDA and EMA approved tisagenlecleucel (Kymriah™) and axicabtagene ciloleucel (Yescarta™) in 2017 and 2018 for use in specific types of leukaemia and lymphoma. However, CAR-T cell therapies were considered to impose significant financial burdens due to high treatment costs and associated expenses like hospitalization and ICU stays

and hence there were concerns about patient access and healthcare sustainability.[27] The published list prices of CAR-T cell therapies are approximately EUR320,000 across European countries including Italy and Spain.[28,29]

3.2.1. Spain

In Spain, the reimbursement of Kymriah™ and Yescarta™ is managed through the Inter-ministerial Pricing Committee.[29,30] The Ministry of Health and the Spanish Medicine Agency negotiated the staged outcomes-based payment schemes for these therapies. Payments, adjusted for a confidential discount on the list price, are made in instalments that are contingent upon patients reaching certain outcomes. The use of instalments-based outcomes-based agreements marks a shift from traditional pricing methods. Kymriah™ is reimbursed in the Spanish NHS in two instalments if patient achieves a sustained complete remission at two separate time points. A first instalment, at the time of infusion, covers 52% of the price. The second instalment, at 18 months after infusion, covers the remaining 48%. Yescarta™ is also reimbursed in two instalments, linked to survival data. The first instalment is at the time of infusion and covers 36%, while the second, 18 months after infusion, covers the remaining 64%.

Both therapies have designated reference centres across Spain to ensure equitable access for patients. Data collection was facilitated through Valtermed, a registry designed to collect real world clinical data through a web-based tool introduced by the Ministry of Health in 2019. Both therapies were used to pilot this system.[29,30]

The interviews revealed that the main motivation for implementing these IPMs in Spain was the high upfront costs and the uncertainty level surrounding its long-term effectiveness, which made investing in the therapy a risky proposition. The payment model enabled contracting parties to share this risk in the short and long term.

The interviews revealed significant administrative and HR costs throughout the IPM design and maintenance phases. While payers and manufacturers were involved from

the start, providers faced the main costs during maintenance. These costs were seen as opportunity costs for existing staff rather than requiring additional resources.

Providers faced mainly administrative costs associated with purchasing the product and paying for it according to patient outcomes. They also incurred a significant cost and burden to collect data on relevant outcomes and incorporate them to the registry. The payer/HTA interview estimated the total human resource use to be about 4.5 full-time equivalents (FTEs) for one region with six treatment centres, including roles for case management, data exploitation, user registration, formulary development, and administrative tasks. This figure might differ depending on the size of the region and number of treatment centres. When contextualising this figure with the annual average salary in Spain as reported by the OECD (€ 31,945) this corresponds to €143,753 per year.[31] However, this is likely an underestimate, as the sector-specific average wage is expected to be higher than the national cross-sector average.

Manufacturers noted high resource use for patient follow-up at individual treatment centres in the context of a devolved and complex health system, equating to one FTE (i.e., € 31,945) for this task. [31] When contextualising these additional human resource costs with average salaries, this can be seen as an underestimate for the pharmaceutical industry, where salaries are typically higher. Additional costs included legal and contracting expenses for providers and finance costs for manufacturers, particularly regarding VAT timing and deferred payments. Manufacturers also faced revenue loss risks if clinical milestones were not met, due to the risk-sharing nature of the payment scheme.

The patient interview reported that patients are more likely to experience unexpected adverse events when receiving highly innovative treatments; therefore, early access and monitoring facilitated by IPMs can improve the chances of detecting them. The CAR-T IPM implemented in Spain addressed concerns about long-term uncertainty regarding effectiveness, while the full scope of adverse effects also remained unclear. The IPM also helped identify unexpected adverse events that may not have been captured in clinical trials, ultimately impacting patients' quality of life.[32]

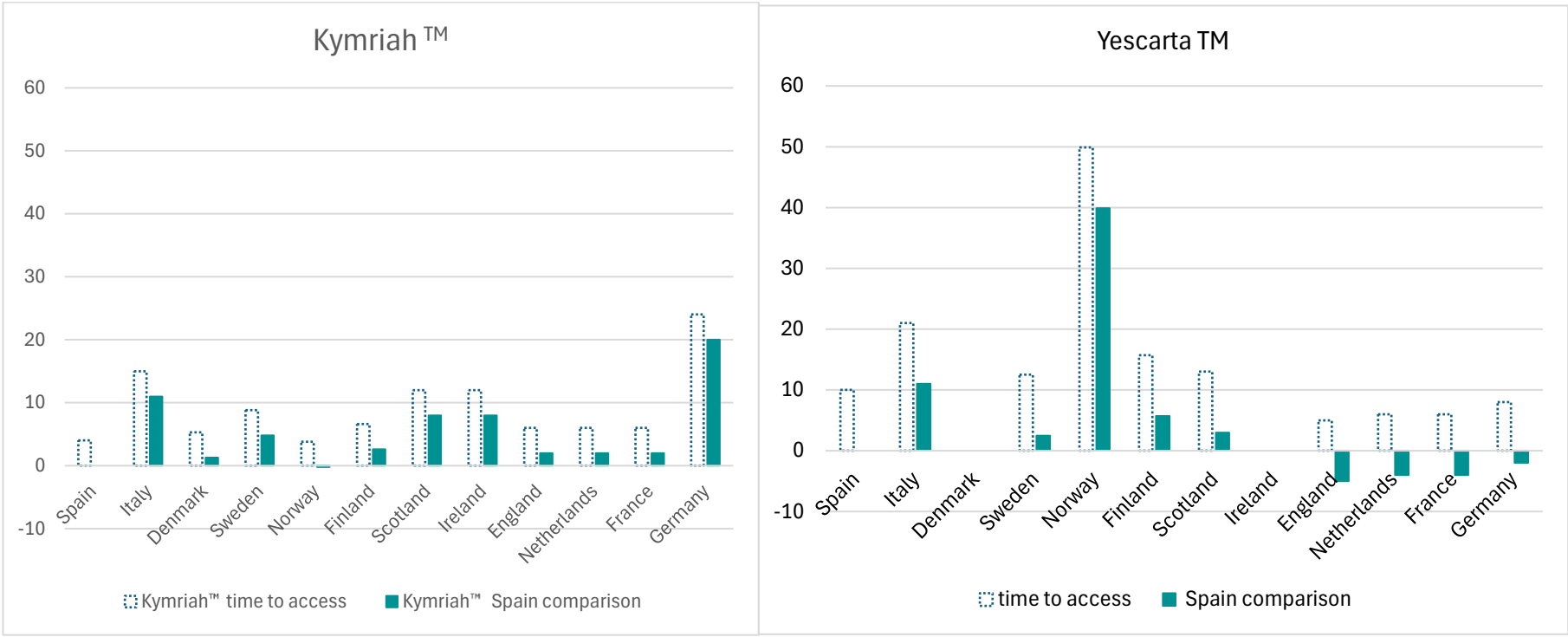
Patients also had to undergo training to understand the new therapies and their potential effects. Clinical staff did not always explain these effectively, leaving patients to invest time in gathering information or facing unexpected costs, such as prolonged work absences due to unanticipated requirements for treatment and/or side effects. Additionally, the CAR-T IPM required patients to travel to accredited treatment centers, as not all regions in Spain have one—forcing some to seek care outside their home region, with added financial and time burdens.

All interviewees agreed that the primary benefit of the IPM is its risk-sharing nature as the long-term treatment effect of the two CAR-Ts was uncertain given the available evidence on efficacy and safety. The IPM was designed to address that uncertainty and the budget impact, allowing earlier patient access to the two therapies and enabling payers to save costs if milestones were not achieved. We conducted an analysis of time to access—defined as the elapsed time between regulatory approval and a positive reimbursement decision—for Kymriah™ and Yescarta™ in Spain. We compared this to access times in other European countries[33,34], as well as to benchmark data from the WAIT indicator for all medicines, oncological medicines, and orphan medicines in Spain. [35] Kymriah™ and Yescarta™ were accessible within 4 months and 10 months from EU marketing authorisation, respectively. This was faster than in most comparator countries — except for Yescarta™ access in England, the Netherlands, Germany, and France — and faster than Spanish benchmark data. All these data are represented in Figure 3 and Figure 4. All data used in the figure are available in Appendix 2 of the report.

Manufacturers reported that the IPM facilitated earlier market access for the two therapies in Spain, as also reflected in the WAIT indicator (Figures 3 and 4).[35] This resulted in access months ahead of the usual timeline, enabling earlier revenue generation and returns on investment. The IPM also contributed to scientific and knowledge spillovers, supporting future negotiations and fostering a more innovative and research-friendly environment. Both payers and manufacturers highlighted the value of generating real-world evidence to inform future decisions—such as transitioning to standard agreements with lower implementation costs and burdens.

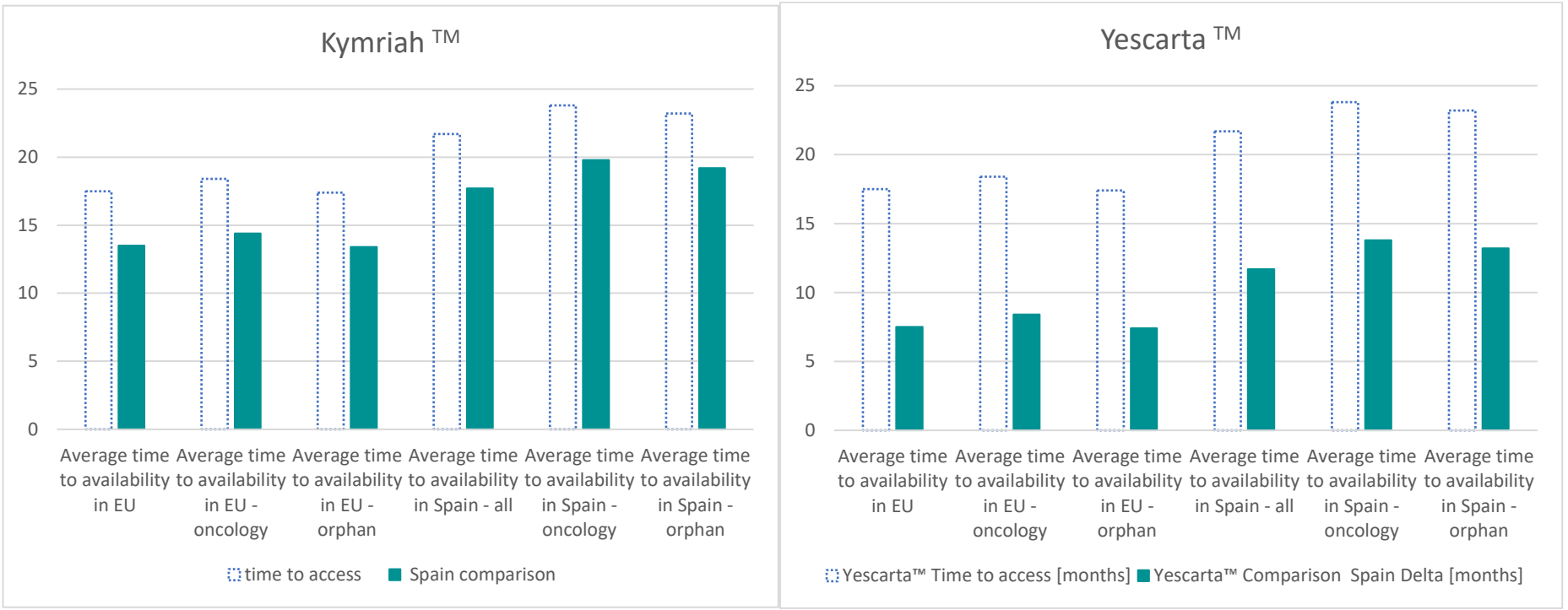
From the patient perspective, IPMs can accelerate access to innovative but costly treatments that offer promising outcome improvements, particularly for those with limited therapeutic options. They also incentivise treatment efficiency and improve the likelihood of better outcomes. In the case of CAR-Ts in Spain, patients reported that the IPM ensured access to these advanced therapies and delivered significant health benefits, although they could not confirm whether it enabled earlier access.

Figure 3: **Time (in months) to access of Kymriah™ and Yescarta™ in Spain compared to other European countries** [33–35]



Note: Positive values of green bars measure, in months, the earlier access in Spain compared to other countries. Negative values of green bars measure, in months, the delay in access in Spain compared to other countries.

Figure 4: **Time (in months) to access of Kymriah™ and Yescarta™ in Spain compared to average time to access to all medicines, oncology medicines and orphan medicines in the EU and Spain** [33–35]



Note: Positive values of green bars measure, in months, the earlier access in Spain compared to average time to access to all medicines, oncology medicines and orphan medicines in both, the EU and Spain.

To explore the broader impact of IPM implementation, we conducted several analyses focused on early access, which nearly all interviewed stakeholders identified as its primary benefit. These analyses considered a range of associated costs and benefits, including health gains, unexpected adverse events, early revenue, cost savings, and the costs of early access to medicines. We focused on the health and financial benefits of early access, based on the assumption that both CAR-T therapies would likely have been accessed eventually, but only after a delay while a discount and net price were negotiated between the manufacturer and the payer.

We began by estimating the duration of early access to Kymriah™ and Yescarta™ in Spain based on our previous analysis comparing time to access of CAR-T therapies with Spain benchmarks for all, oncology and orphan medicines in Spain (Figure 4). This estimate served as the core assumption for assessing the costs and benefits associated with early access in Spain. Table 5 presents the estimated early access durations for Kymriah™ and Yescarta™ in Spain.

Table 5: Months of earlier access of CAR-Ts in Spain

	Kymriah™	Yescarta™
Earlier access versus orphan medicines	19.2	13.2
Earlier access versus oncology medicines	19.8	13.8
Earlier access versus all medicines	17.7	11.7

Source: EFPIA Patients W.A.I.T. Indicator 2023 Survey[35]

We calculated the difference in months between the time to access for the two CAR-T therapies in Spain and the average access time for orphan drugs in the country. The resulting differences were 19.2 months for Kymriah™ and 13.2 months for Yescarta™, which we assumed represent the impact of the IPM on early access to CAR-T therapies in Spain.

We collected data from official sources[32] on patients treated with the two CAR-T therapies in Spain to estimate how many gained earlier access and how many responded to treatment. The data were not sufficiently granular and had certain limitations, requiring several assumptions to support the estimation. For example, data on the specific use of each CAR-T therapy were unavailable, making it impossible to attribute treated patients to one product or the other. We therefore assumed an even market share during the period when both options were available for the DLBCL

indication. These assumptions, along with further details on the estimation approach, are provided in Appendix 3.

Table 6 presents our estimates of the total number of patients who accessed treatment earlier with the two CAR-T therapies in Spain, as well as the number who benefited from earlier access to each CAR-T option individually. It also includes a breakdown by indication.[32]

Table 6: Number of patients in Spain who accessed CAR-T therapies earlier than the average access time for orphan medicines.

	DLBCL*	PMBCL**	ALL***	Total
Kymriah™	89	N/A	42	131
Yescarta™	66	14	N/A	80
Total	155	14	42	211

Abbreviations: DLBCL: Diffuse Large B-Cell Lymphoma; PMBCL: Primary Mediastinal B-Cell Lymphoma; ALL: Acute Lymphoblastic Leukaemia.
Source: Informe de Seguimiento Terapias Avanzadas (2022)[32]; Authors' calculations.
Analysis is limited to patients with outcome data collected between 2019 and 2022.[32]
*DLCBL patients were treated with both therapies during a certain period when equal market share was assumed in absence of therapy specific use data.
** PMBCL patients were only treated with Yescarta™.
***ALL patients were only treated with Kymriah™.

In total, we estimated that 211 patients accessed CAR-T therapies earlier due to the implementation of the IPM in Spain when comparing to the average time to access of orphan medicines. In detail, this included 155 treated for diffuse large B-cell lymphoma (DLBCL), 14 for primary mediastinal B-cell lymphoma (PMBCL), and 42 for acute lymphoblastic leukaemia (ALL). All PMBCL patients were treated with Yescarta™, and all ALL patients with Kymriah™. Using simplifying assumptions, we estimated that 89 DLBCL patients were treated with Kymriah™ and 66 with Yescarta™ (details of the estimation are provided in Appendix 3).

We then estimated the number of positive treatment responses, deaths, and cases of disease progression among patients who gained earlier access to CAR-T therapies in Spain. As therapy-specific patient response data were not available in published reports, we assumed uniform response rates across all patients treated with either CAR-T therapy, based on the follow-up report by the Spanish Ministry of Health.[32] Figure 7 presents our estimates of patient responses by indication and therapy option.

Table 7: Treatment response data for patients who accessed CAR-T therapy earlier than the average access time to orphan medicines in Spain.

	Kymriah™				Yescarta™				Total			
	Total	Resp.	Death	Progr.	Total	Resp.	Death	Progr.	Total	Resp.	Death	Progr.
DLBCL	89	25*	42	22	66	19	31	16	155	44	73	38
PMBCL	N/A	N/A	N/A	N/A	14	7	3	4	14	7	3	4
ALL	42	20	17	5	N/A	N/A	N/A	N/A	42	20	17	5
Total**	131	45* (34%)	59 (45%)	27 (21%)	80	26 (33%)	34 (42%)	20 (25%)	211	71 (34%)	93 (45%)	47 (21%)

*Assumes all responses are sustained.
**Overall calculation, including all indications.
Abbreviations: DLBCL: Diffuse Large B-Cell Lymphoma; PMBCL: Primary Mediastinal B-Cell Lymphoma; ALL: Acute Lymphoblastic Leukaemia; Prog.: Progression; Resp.: positive response.
Source: Informe de Seguimiento Terapias Avanzadas (2022)[32]; Authors' calculations.
Notes: Deaths include only those occurred before 18 months after receiving treatment. Our analysis is limited to patients with outcome data collected between 2019 and 2022. [32] LLA patients were only treated with Kymriah™. PMBCL patients were only treated with Yescarta™.

Estimates of treatment response show an average positive response rate of 34%, a death rate before 18 months of 45%, and a disease progression rate before 18 months of 21% (details of the estimation are provided in Appendix 3).

For Kymriah, the second-stage payment—48% of the total price—was agreed to be paid 18 months later, conditional on the patient achieving and sustaining a complete response. [29] For Yescarta™, the agreed reimbursement criteria differed: 64% of the total price was to be paid 18 months later, conditional on patient survival.[29] Using the treatment response data in table 7, published list price information,[22] details of agreed instalment payments and data of treated patients since market access of both CAR-Ts,[32] we produced illustrative estimates of early revenue from manufacturer's perspective, as well as outcome-based adjusted medicine costs and potential cost savings from IPM-related risk-sharing from payer's perspective.

Table 8 presents estimates of the early actual medicine costs and associated revenues, as well as the cost savings to the health system resulting from the implementation of the IPM. It also shows the total potential costs (i.e. maximum medicine cost) in the absence of the IPM. Our illustrative figures in Table 8 suggest that the total cost to the health system (and corresponding manufacturer revenue) for earlier access to CAR-T therapy may have been reduced by approximately 30%.

It is important to note that the illustrative estimates presented in Table 8 are based on list prices and may differ significantly from actual values based on net prices. However, they serve to illustrate the potential magnitude of IPM implementation impacts—highlighting early revenue and return for manufacturers, as well as potential cost savings for payers through risk-sharing arrangements. Further details on the estimation approach are provided in Appendix 3.

Table 8: Estimated total medicine cost and cost savings from risk-sharing under the CAR-T IPM in Spain for the earlier access period.

	List Price
Maximum medicine cost*	€68.1 millions
Early actual cost/revenue	€47.7 millions
Cost saving	€20.4 millions

* Maximum medicine cost assumes the full price is paid for all treated patients.

To estimate the health gains from early access to CAR-T therapies in Spain, we first searched for cost-effectiveness studies reporting life-years (LYs) and quality-adjusted life-years (QALYs) gained with Yescarta™ and Kymriah™ in the three relevant indications—DLBCL, PMBCL, and ALL—compared to the standard of care. We prioritised studies conducted in Spain where available.

We identified and selected one study for DLBCL with Yescarta™ and one study for ALL with Kymriah™ in Spain.[36,37] We also included one study from Italy for Kymriah™ in DLBCL[38] as we did not identify a Spain-specific study that met the selection criteria (e.g., CAR-T versus standard of care). Table 9 shows LY and QALY gains for the two CAR-Ts and indications. It also provides information about the study used and the comparator used in the study.

Table 9: QALY and LY gains by indication and CAR-T therapy.

Therapy/indication	LY gain	QALY gain	Comparator	Study
Kymriah™ ALL	10.1	8.3	Hematopoietic stem-cell transplantation	Santasusana et al. (2020)[37]
Kymriah™ DLBCL	2.22	2.1	Salvage chemotherapy (chemotherapy regimens from the SCHOLAR-1 study)	AIFA. Kymriah Report Tecnico.; 2021[38]
Yescarta™ DLBCL	1.72	1.81	Autologous stem-cell transplantation	Martin Garcia-Sancho et al. (2024)[36]

We estimated the additional life-years (LYs), and quality-adjusted life-years (QALYs) gained from earlier access to CAR-T therapies in Spain, based on the incremental LYs and QALYs reported in

Table 9 and the estimated number of patients who received early access. The results are shown in Table 10, with details of the estimation approach provided in Appendix 3.

Table 10: Total LY and QALY gains from early access to CAR-T in Spain.

	DLBCL	ALL	Total
LY gain	101.68	27.67	129.34
QALY gain	100.04	22.74	122.77

Note: LY and QALY gains for PMBCL have not been estimated due to the lack of indication specific cost-effectiveness studies

3.2.2. Italy

In Italy, the reimbursement of Kymriah™ and Yescarta™ involved an outcomes-based staged payment scheme introduced by AIFA.[29,38,39] Both therapies are considered innovative by AIFA, included in regional formularies, and funded through the national innovation fund. Data collection is managed through AIFA's national registry and web-based tools. Payments are made in instalments based on patient outcomes, with confidential discounts applied to the list prices in the case of Yescarta™.

Yescarta™ was reimbursed according to the payment scheme for diffuse large B-cell lymphoma (DLBCL). An indication specific payment scheme was used for Kymriah™: The use in diffuse large B-cell lymphoma (DLBCL) patients involved a confidential discount to the list price in addition to the staged payment, while the use for acute lymphoblastic leukaemia (ALL) indication does not include the confidential discount.

Prescribing centres are regionally identified and must use a web-based patient monitoring registry.[29,38,39] Differently to the Spanish two-instalment scheme, the Italian scheme involved three instalments to be paid if the patient sustains the agreed benefit (e.g., survival or progression free survival). In the case of Kymriah™, the three instalments were 45 days post-infusion, after six months and after 12 months.[40,41] For Yescarta™, the main difference was that the first instalment was agreed at 180 days after infusion with second and third instalments at 270 and 365 days respectively.[30]

As in the Spanish case study, interviews revealed that the main motivation for implementing the IPM in Italy was the high upfront cost and uncertainty around its long-term effectiveness, which made investing in the therapy a high-risk decision. The payment model helped share this long-term risk, enabling access to CAR-Ts in Italy.

All interviews highlighted significant administrative and HR costs throughout the IPM design and maintenance phases. Again, these costs were seen as opportunity costs for existing staff rather than requiring additional resources. Additional transaction costs included legal and IT expenses for payers and providers. Unlike the Spanish case, data collection for clinical follow-up in Italy is managed more centrally, leading to higher transaction costs for payers to facilitate and process data. This central management reduces manufacturers' resource spending on patient follow-up but requires them to financially contribute to the registry system through registry fees,[42] adding to their transaction costs.

Providers emphasized the need for staff upskilling and the high efforts and costs associated with clinical monitoring. For wrap-up and closing, the Italian payer noted that a report for auditing, outcome assessment, and reporting on the effectiveness of the IPM model needed to be synthesised. In Italy, the technical reports on cost-effectiveness have been published by AIFA.[38,39] They evidenced the additional incremental health costs compared to the costs of standard of care for payers were €127.399,95 in DLBCL and €274.137,93 in ALL for Kymriah™, and €183,243 for both DLBCL. The estimation of the incremental health cost in the cost-effectiveness analysis includes confidential discounts and the impact of the outcomes-based staged payment (Table 11).

All interviewees agreed that the primary benefit of the IPM is its risk-sharing nature, providing early access for patients, potential cost savings for payers, and return on investment for manufacturers. We analysed the time to access for Kymriah™ and Yescarta™ in Italy and compared it with that in other European countries,[33,34] and to WAIT indicator benchmarks for all, oncological, and orphan medicines in Italy.[35] Kymriah™ and Yescarta™ were accessible within 15 months and 24 months from EU marketing authorisation, respectively. This was however not significantly faster compared to most comparator countries or against Italian benchmark data (Figures 5 and 6).

Figure 5 compares time to access to Kymriah™ and Yescarta™ in Italy with comparable time to access data of other eleven European countries.[33–35] In general, access to Kymriah™ happened later in Italy than in other European countries. This is the case for 9 out of 11 countries, with only Ireland and Scotland having longer times to access than Italy. Access to Yescarta™ was faster in all European countries except Finland and Norway. In Ireland and Denmark, the therapy had not yet been accessed at the time of this research.

Figure 6 compare the time to access both CAR-T therapies in Italy with benchmark data from the WAIT indicator for all medicines, oncological medicines, and orphan medicines.[35] Access to Kymriah™ was consistently faster than all benchmark categories. In contrast, access to Yescarta™ was slightly quicker than the EU averages but broadly in line with Italian averages for all, oncology, and orphan medicines. This suggests significantly faster access to Kymriah™ in Italy, while Yescarta™ followed typical national patterns. All data used in Figure 6 are available in Appendix 2 of the report.

In Italy, providers recognised the health benefits for patients and the healthcare system. AIFA's technical reports on cost-effectiveness[38,39] quantify the additional health-related benefits for patients, estimating gains of 2.1 to 8.42 quality adjusted life years (QALY) (**Error! Reference source not found.**11). Interviews also highlighted the model's potential to foster knowledge and scientific spillovers—shaping future negotiations, informing clinical practice, and supporting value-based pricing for the follow-up scheme.

Table 11: Cost-effectiveness as determined by AIFA [38,39]

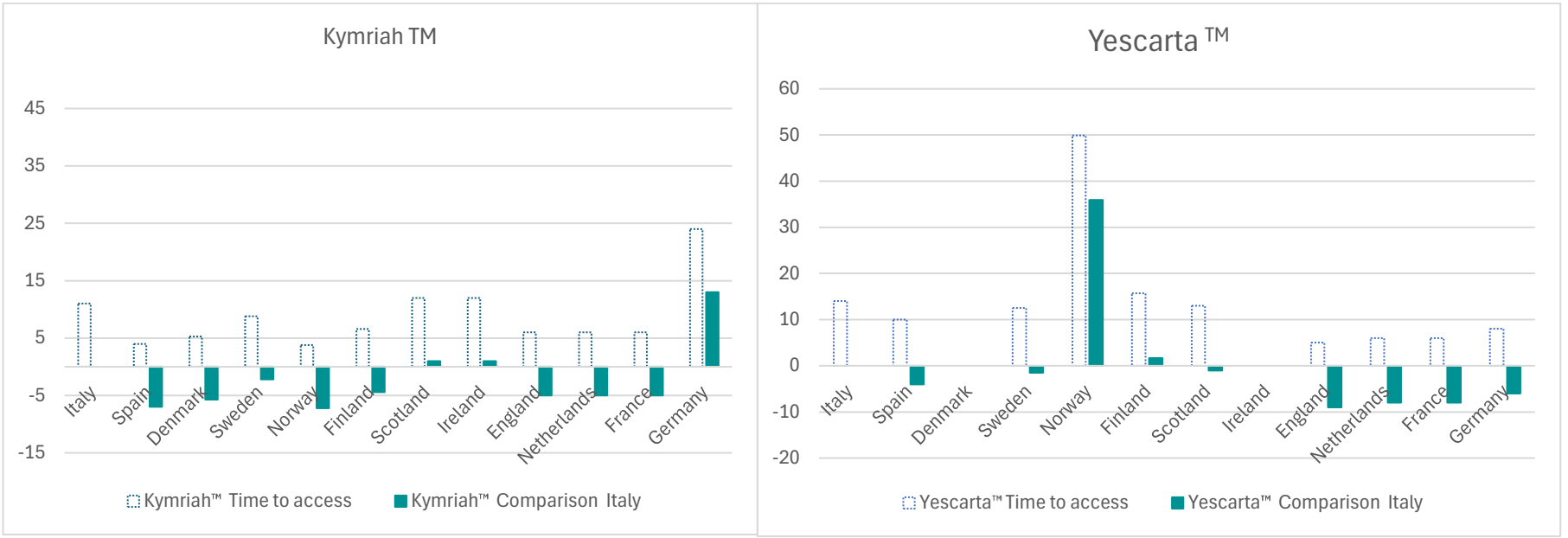
	Kymriah™	Yescarta™
Indication 1	**Diffuse Large B-Cell Lymphoma (DLBCL)**	
Total Costs Differences	€127.399,95	€ 183.243 *
Years of Life Differences (chemotherapy rescue versus intervention)	2.22 (3.12 vs 5.34)	4.16 (2.88 vs 7.04)
QALY Differences (chemotherapy rescue versus intervention)	2.1 (2.26 vs 4.35)	3.35 (2.33 vs 5.58)
ICER (per Years of Life)	€57.491,65	€ 44.049 *
ICER (per QALY)	€60.680,63	€ 54.699 *
Indication 2	**Acute Lymphoblastic Leukemia (ALL)**	

Total Costs Differences	€274.137,93 *	
Years of Life Differences (chemotherapy rescue versus intervention)	9.59 (0.84 vs 10.43)	
QALY Differences (chemotherapy rescue versus intervention)	8.42 (0.44 vs 8.86))	
ICER (per Years of Life)	€28.587,96 *	
ICER (per QALY)	€32.543,80 *	

*VAT included

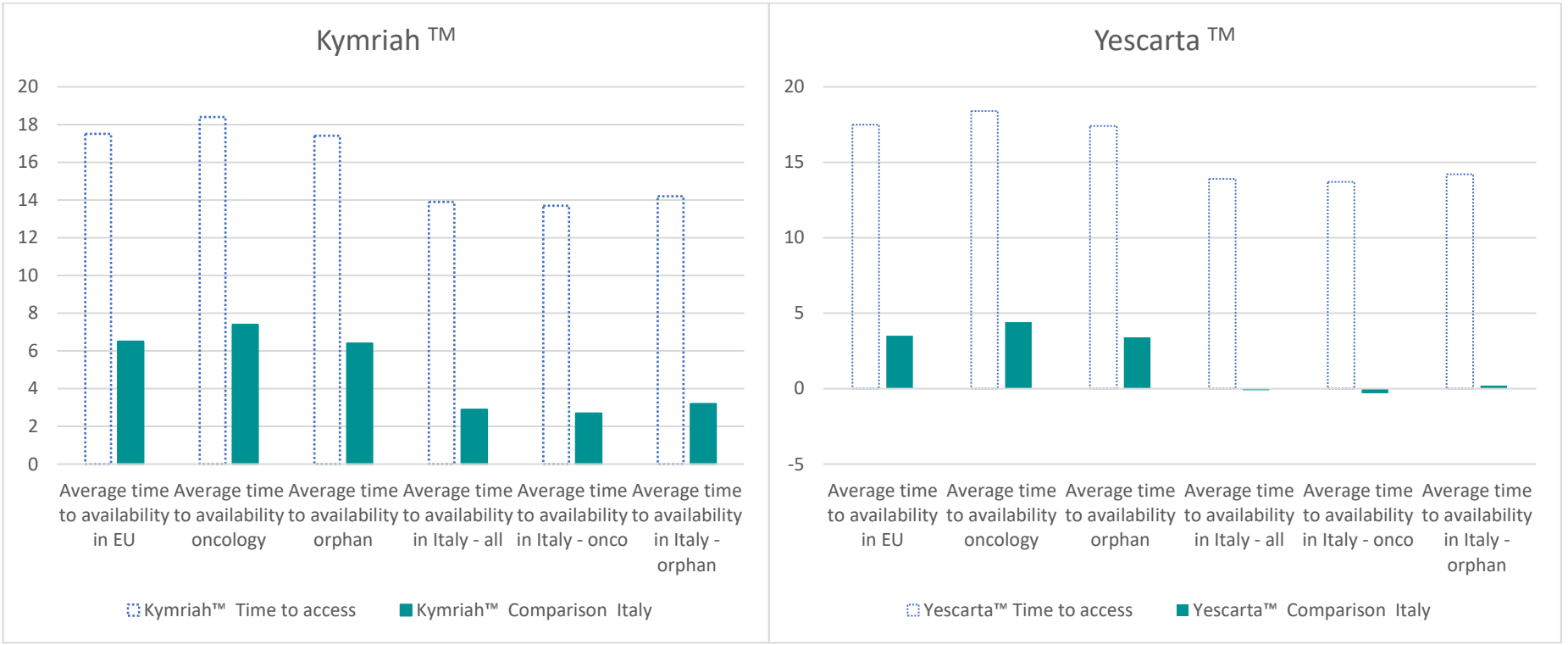
Our interviews confirmed that patients primarily benefit from access to therapies and associated health improvements. Patient representatives noted that patients generally have limited understanding of how medicines are funded, as treatments are typically provided through publicly funded healthcare systems. They also emphasized that patients are rarely included in discussions about drug value and pricing unless healthcare professionals actively involve them. This limits their ability to influence decisions and to understand the specific contract terms and payment conditions that govern access to innovative therapies.

Figure 5: Time (in months) to access of Kymriah™ and Yescarta™ in Italy compared to other European countries [33–35]



Note: Positive values of green bars measure, in months, the earlier access in Italy compared to other countries. Negative values of green bars measure, in months, the delay in access in Italy compared to other countries.

Figure 6: Time (in months)to access of Kymriah™ and Yescarta™ in Italy compared to average time to access to all medicines, oncology medicines and orphan medicines in the EU and Italy [33–35]



Note: Positive values of green bars measure, in months, the earlier access in Italy compared to other countries. Negative values of green bars measure, in months, the delay in access in Italy compared to other countries.

To assess the wider effects of IPM implementation, we also conducted complementary analyses centered on early access—consistently highlighted by interviewees as its key advantage. These analyses examined various related factors, including health outcomes, early revenue generation, cost savings, and the financial implications of accelerated access to medicines. Again, we focused on the benefits of early access, assuming that both CAR-T therapies would eventually have been accessed under a negotiated discount and net price agreement.

The analyses were based on the core assumption that both CAR-T therapies became available earlier than average in Italy. Specifically, we used the difference between the time to access each CAR-T and the average time to access orphan medicines in Italy.

For Yescarta™, the time to access did not differ significantly from the average access times for orphan medicines, oncology medicines, or all medicines. In contrast, access to Kymriah™ was approximately three months earlier across all benchmark categories. When compared specifically to the average time to access orphan medicines, we estimated an earlier access period of 2.9 months.

Table 12 presents these differences, measured in months, for Kymriah™ and Yescarta™ compared with all medicines, orphan medicines, and oncology medicines in Italy.

Table 12: Months of earlier access of CAR-Ts in Italy

	Kymriah™	Yescarta™
Earlier access versus orphan medicines	2.9	-0.1
Earlier access versus oncology medicines	2.7	-0.3
Earlier access versus all medicines	3.2	0.2

Source: EFPIA Patients W.A.I.T. Indicator 2023 Survey[35]

We accessed medicine use data from AIFA's annual medicine use reports.[43,44] These publish data of total annual cost per medicine and defined daily doses (DDD) used per annum. Both CAR-Ts are single-administration and dose therapies which enabled us to identify DDDs with the number of patients treated. For Kymriah™, a total use of 16 DDDs (patients) were reported in 2019 at a total cost of €1.19 million.

Italy accessed Kymriah™ in August 2019,[29] meaning the 16 patients were treated within four months and a half until end of year. Assuming a uniform distribution of patients, this means around 11 patients accessed the therapy earlier at a proportional total cost of €770 million.

Unlike in Spain, there is no available information on the breakdown of Kymriah™ use by indication in Italy. In addition, the number of instalments and payment periods differs from the Spanish arrangement. As a result, we were unable to generate an illustrative estimate of potential cost savings or early revenue for the Italian case based on assumptions drawn from the Spanish data.

For health gains, LY gains compared to standard of care exceeded one in both indications—PMBCL and ALL (Table 11). We estimated the portion of one LY corresponding to 2.9 months and multiplied this by 11 patients to calculate a total LY gain of 2.66 attributable to early access.

Tables 13 and 14 summarize the implementation costs and benefits of the CAR-T IPM in Spain and Italy, respectively. The tables present cost and benefit information by implementation phases and stakeholders, using a colour-coded heat map to indicate the size and intensity at a high level.

No significant differences were observed in the distribution of the main costs of IPM implementation when comparing Spain and Italy. The most substantial costs faced by payers, manufacturers, and providers were HR-related, including additional resource use such as additional FTEs and opportunity costs due to increased staff utilization. While payers and manufacturers experienced these costs during the design, adoption, and maintenance phases in both countries, providers did not report HR costs in the design phase in either country, reflecting their limited involvement in contract design and agreement.

A common feature in both countries was that providers reported significant IPM-related costs during the 'adoption and implementation' and 'maintenance and sustainment' phases. However, there are differences when comparing payers and manufacturers. HR costs were reported as moderate in Italy by both stakeholder groups, while in Spain, they were reported as significant. Our interpretation is that the AIFA registry, managed by the Italian Medicines Agency and used for tracking patients in this CAR-T payment model, was more mature and efficient than the Spanish registry, Valtermed, leading to better outcomes in Italy. This is also likely the reason for the shorter—or even absent—early access to CAR-Ts in Italy, compared to

benchmark data for orphan medicines (Figure 6). If this interpretation of the results is correct, access—and particularly early access—to innovation remains the main benefit of IPMs. However, measuring and attributing the associated benefits is unfeasible due to the lack of a well-defined benchmark.

Unlike in Spain, payers in Italy experienced moderate transaction costs during both the design and maintenance phases—a difference that may be attributed to the more effective functioning of the Italian registry and its central management by AIFA.

Another key finding from the cross-country comparison is how stakeholders perceive earlier access as a benefit. In Spain, payers, providers, and manufacturers reported this benefit. In Italy, manufacturers and patients also acknowledged it, but payers and providers did not report a significant advantage. While the perception among Spanish stakeholders aligns with the data (Figures X1 and X2), the Italian data (Figures 5 and 6) do not fully support views of manufacturers and patients—only Kymriah™ showed a shorter time-to-access period.

There are also substantial differences between the two countries in the categories of spillovers and other benefits. We interpret these differences as reflecting the relative novelty of implementing this type of agreement in Spain—using a new registry—compared to Italy, where outcome-based payments and the use of the AIFA registry have a longer track record.

Table 13: Heatmap of costs and benefit summary for the staged Outcome-based payment model for CAR-T in Spain

	Inception & design				Adoption & implementation				Sustainment & maintenance				Wrap-up & closing			
	PH	M	Pr	Pa	PH	M	Pr	Pa	PH	M	Pr	Pa	PH	M	Pr	Pa
Human Resource cost	3	3	3	0	3	3	3	0	3	3	3	0	2	0	0	0
Transaction cost	0	1	0	0	0	1	1	0	0	1	1	0	0	0	0	0
Health-related costs	0	0	0	0	0	0	0	3	0	0	0	3	0	0	0	3
Medicine-related cost	3	0	0	0	3	0	0	0	3	0	0	0	3	0	0	0
Other costs	0	0	0	0	0	0	0	0	0	0	0	3	0	0	0	3
Health related benefits	0	0	0	0	0	0	0	0	0	0	3	3	0	0	3	3
Revenue	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
Cost savings	0	0	0	0	0	0	0	0	3	0	3	0	3	0	3	0
Early access	0	0	0	0	0	0	0	0	3	3	3	0	3	3	3	0
Spillovers/ pos. externalities	1	1	0	0	1	1	0	0	1	1	2	0	1	1	2	0
Other benefits	3	3	0	0	3	0	0	0	0	0	0	0	3	3	0	0

Abbreviations: PH: Payer/HTA, M: Manufacturer, Pr: Provider, Pa: Patients.
Scoring: 3- Significant, 2- Moderate, 1- Minor, 0 – not reported

Table 14: Heatmap of costs and benefit summary for the staged Outcome-based payment model for CAR-T in Italy

	Inception & design				Adoption & implementation				Sustainment & maintenance				Wrap-up & closing			
	PH	M	Pr	Pa	PH	M	Pr	Pa	PH	M	Pr	Pa	PH	M	Pr	Pa
Human Resource cost	2	2	3	0	2	2	3	0	2	2	3	0	1	0	0	0
Transaction cost	2	2	0	0	2	2	1	0	2	2	2	0	0	0	0	0
Health-related costs	0	0	0	0	0	0	0	3	0	0	0	3	0	0	0	3

Medicine -related cost	3	0	0	0	3	0	0	0	3	0	0	0	3	0	0	0
Other costs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Health related benefits	0	0	0	0	0	0	0	0	0	0	3	3	0	0	3	3
Revenue	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
Cost savings	0	0	0	0	0	0	0	0	3	0	0	0	3	0	0	0
Early access	0	0	0	0	0	0	0	0	0	3	0	3	0	3	0	3
Spillovers / pos. externalities	3	1	0	0	3	1	0	0	3	1	2	0	1	1	2	0
Other benefits	0	0	0	0	0	0	0	0	0	0	0	0	3	3	0	0

Abbreviations: PH: Payer/HTA, M: Manufacturer, Pr: Provider, Pa: Patients.
Scoring: 3- Significant, 2- Moderate, 1- Minor, 0 – not reported

3.3. Financial risk-sharing agreement: revenue guarantee model for antibiotics in Sweden

The Public Health Agency (PHA) of Sweden conducted a pilot project to test a reimbursement model aimed at improving access to critical antibiotics. The initiative was driven by the Swedish government's concern that companies lacked sufficient incentives to launch antibiotics effective against resistant bacteria. The project was commissioned to PAH in 2018 and sought to ensure the availability of critical hospital-use antibiotics for treating infections caused by carbapenem multi-resistant bacteria.[45]

The reimbursement model tested in the pilot was a financial risk-sharing mechanism that partially delinked revenue from sales volume, guaranteeing pharmaceutical companies a minimum level of revenue. By using the partially delinked model, PAH aimed to address the commercial uncertainty faced by manufacturers when launching low-usage antibiotics—driven by antimicrobial stewardship—in a small market like Sweden.

The model calculated the delinked income by multiplying the volume of stock set aside for Sweden by the template price per pack and then multiplying the result by 1.5 to provide an additional incentive for companies to participate in the pilot. The stock volume is based on estimated medical needs in a worst-case scenario to handle global delivery issues. An inventory incentive, set at 10% of the annual guaranteed minimum revenue, was also offered as an addition and on top of the revenue guarantee to cover costs for maintaining product availability, even if sales exceed the reimbursement level during the contract period.[45]

In the pilot study, Sweden signed agreements with pharmaceutical companies to supply five different antibiotics: imipenem/relebactam (Recarbrio, MSD), ceftolozane/trazobactam (Zerbaxa, MSD), meropenem/vaborbactam (Vaborem, Pharmaprim), fosfomycin (Fosfomycin Infectopharm, Unimedic Pharma), and cefiderocol (Fetcroja, Shionogi). Regions paid for the drugs as usual, but if revenues fell below the guaranteed amount, the state covered the difference. Each company was guaranteed at least SEK 4,000,000 (approximately €400,000) per product annually for maintaining stock and ensuring delivery within 24 hours. Companies with higher sales received an additional SEK 400,000 (approximately €40,000) yearly.

The pilot ran from July 15, 2020, to December 31, 2022, and allowed Sweden to access new antibiotics earlier than other European countries.[45] The program was structured so that costs were shared between the regions and the state, with the regions covering the majority. Under this model, the state contributed just over SEK 2 million per product annually, ensuring access to treatment for critically ill patients with limited alternatives.[45] The interviews revealed that the primary motivation for implementing the IPM in Sweden was the risk that novel antibiotics effective against resistant bacteria might not be launched in Sweden due to its small pharmaceutical market. The revenue guarantee model was designed to create a market of sufficient and predictable size to incentivize antibiotic manufacturers to launch and guarantee the supply of their products. This was achieved by sharing the financial risk through the partial delinking of revenue from sales.

The Public Health Agency, acting as the payer, reported significant administrative and human resource costs, including stakeholder meetings during the design phase and contracting, operating, and monitoring costs in later phases. They reported that they required a dedicated project team equivalent to 3-4 full-time employees (FTEs) throughout the pilot. A published

report confirms this figure and indicates that a total of 6,056 hours of work-time was required for all phases.[46] They found that preparing and executing the procurement took nearly as long as validating and managing contracts, requiring almost one full-time position per year (3.7 full-time positions over 4.5 years). [46] When contextualising this figure with the annual average salary in Sweden per OECD (Swedish Kronor SEK 506,967) this corresponds to additional costs between SEK 1,520,901 (3FTE) (approximately €150,000) and SEK 2,281,351.50 (4.5 FTE) (approximately €220,000) per year.[31]

In addition, the payer in this agreement had to bear medicine-related costs when sales and payments by local providers do not reach the revenue guarantee threshold. Published reports from the Public Health agency confirm that prices for the five novel antibiotics in Sweden were overall in line with other European counterparts and from 15 July 2020 to 31 December 2022, the pilot model incurred an additional payer expenditure of SEK 25,535,453 —averaging approximately SEK 10 million per year or SEK 2 million per product—to ensure product availability (

Table). [25] This means that the payer covered approximately 56% of the total medicine- related costs in this IPM scheme (

Table).

Table 15: Medicine-related costs per product and year

Product	Year	Revenue guarantee amount (SEK)	Regional provider costs (SEK)	PAH/payer costs (SEK)	PHA/payer contribution (%)
These Vaborem	2020	338,798	0	338,798	100%
	2021	4,000,000	548,856	3,451,144	86%
	2022	4,000,000	141,372	3,822,721	96%
Recarbrio	2020	1,846,994	81,300	1,765,694	96%
	2021	4,000,000	1,097,550	2,861,800	72%
	2022	4,000,000	894,300	3,105,700	78%
Fetcroja	2020	0	0	0	N/A
	2021	4,000,000	>4,000,000	400,000	4%
	2022	4,000,000	>4,000,000	400,000	5%
Zerbaxa	2020	1,846,994	2,344,907	151,453	6%
	2021	4,000,000	Global shortage		N/A
	2022	4,000,000	3,004,090	321,096	10%
Fosfomycin Infectopharm	2020	1,420,765	13,200	1,407,565	99%
	2021	4,000,000	46,200	3,886,150	99%
	2022	4,000,000	221,100	3,623,332	94%
Total		**45,453,551**	**16,392,875 ***	**25,535,453**	**56% ****

Unless otherwise specified all figures are captured as per the Swedish Public Health Agency in their report. [25]

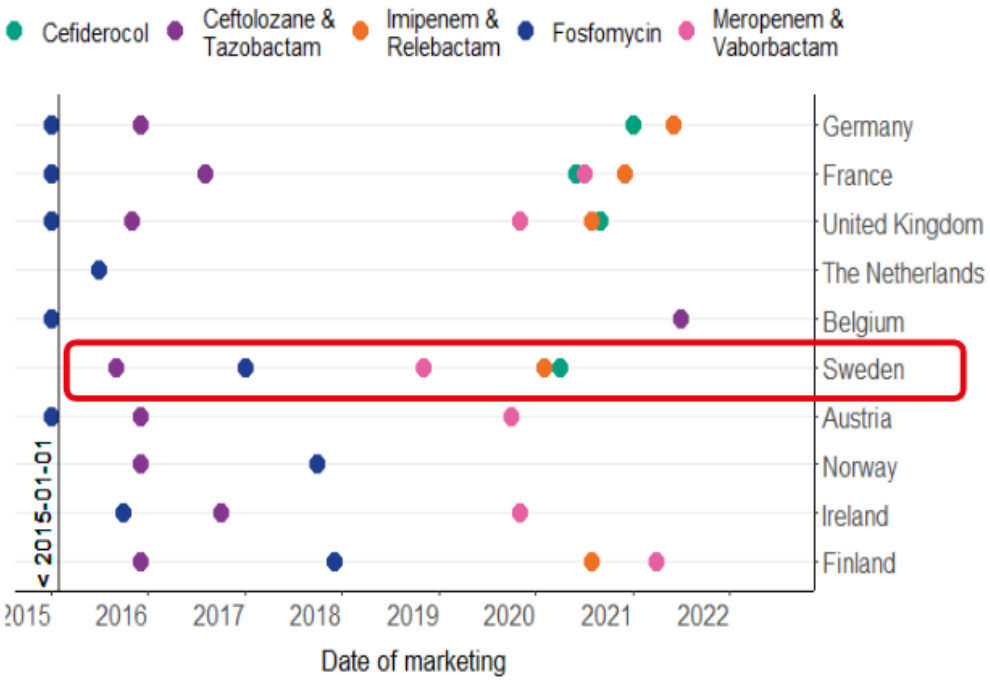
* Authors calculation of the Swedish Public Health Agency data

** This number differs from the figure provided by the Swedish Public Health Agency and represents an author calculation of the of the proportion of total PHA/payer costs (SEK 25,535,453) relative to the total revenue guarantee (SEK 45,453,551).

Manufacturers. experienced minor to moderate administrative and HR costs for tendering and participating in the pilot, but not significantly higher when compared to standard agreements. They also faced additional transaction costs, including strengthening supply chains and logistics to meet contractual supply guarantees, penalty fees, and regulatory costs for Swedish packaging and labelling.

The benefits of the system varied by perspective. For the payer, the main benefit was securing access to novel antibiotics in Sweden. Published reports concluded that the scheme led to the introduction of five products to the relatively small Swedish market.[46] Between 2015 to 2022, only three European countries—Sweden, UK, and France—managed to launch all five of the pilot drugs (Figure 7). In the years leading up to the pilot, Sweden showed great improvements in escalating the access of the pilot drugs. While it was initially one of the later countries to launch Fosfomycin, it brought ceftolozane/tazobactam to market around the same time as most other countries and was the first to launch meropenem/vaborbactam. The introduction of the reimbursement model during pilot further enabled Sweden to achieve early access to imipenem/relebactam and cefiderocol. For these two medicines, Sweden was the quickest to market among the ten European countries included in published reports.[25,45,46] These data show that Sweden improved access to novel antibiotics not only compared to other Nordic countries, such as Norway and Finland, but also to larger or more commercially attractive markets like Germany, the Netherlands and Belgium.[25,46]

Figure 7: Timing of the launch of the five drugs included in the Swedish pilot study, in ten European countries, sorted by size [25,46]



Manufacturers benefited from a predictable revenue stream and achieved a guaranteed return on investment of at least SEK 4,000,000 (approximately €400,000) per product annually. Results showed that the demand varied significantly between products, influencing their sales volumes.[25] High-demand products like cefiderocol generate minimal additional revenue from the pilot model, while low-demand products such as Fosfomycin, meropenem/vaborbactam, and imipenem/relebactam rely heavily on the pilot model for revenue. [25] In case of cefiderocol, revenue from sales also exceeded the revenue guarantee, which is possible in this partially delinked payment scheme. The manufacturer of cefiderocol still received a 10% of the annual guaranteed minimum revenue on top of sales revenue as stock incentive to cover costs for maintaining product availability.

More importantly, manufacturers reported that they valued participating in a scheme that could help shape global pull incentive models for antimicrobial resistance (AMR). Their participation signalled willingness to engage and fostered stronger relationships with decision-makers working to address the failing antibiotic market in Sweden—and potentially beyond. Published reports by the Swedish Public Health Agency confirm, that overall, companies viewed model positively, appreciating its simplicity and transparency. However, they also identified several challenges, including the requirement for large physical warehouses, difficulty in determining stock levels for new products, and non-value-based compensation amounts. Companies also recommended longer contract periods and value-based compensation.[46]

There is no patient perspective that could be captured for this case study, but the main benefit from patient perspective is the gained health benefits without any additional out-of-pocket costs. The reports by the Public Health Agency in Sweden demonstrate that during the scheme a total of 2,110 packages of novel antibiotics were purchased and used. We estimated that this results in a total of 3,640 treatment days and approximately 331 patients being treated when assuming an average treatment duration of 11 days (Table 16).

Table 16: Number of packages sold, treatment days and patients treated

Product	Year	Sold packages *	Estimated treatment days *	Estimated number of treated patients **
Vaborem	2020	0	0	0
Vaborem	2021	132	132	12
Vaborem	2022	34	34	3
Recarbrio	2020	2	13	1
Recarbrio	2021	27	169	15
Recarbrio	2022	22	138	13
Fetcroja	2020	0	0	0
Fetcroja	2021	657	1,095	100
Fetcroja	2022	535	892	81
Zerbaxa	2020	270	450	41
Zerbaxa	2021	0	0	0
Zerbaxa	2022	346	575	52
Fosfomycin Infectopharm	2020	4	7	1
Fosfomycin Infectopharm	2021	14	23	2
Fosfomycin Infectopharm	2022	67	112	10
Total		**2,110**	**3,640**	**331 (228 – 607, IQR)**

* Derived from the report of the Swedish Public Health Agency. ** Estimated by assuming treatment duration of 11 days. This assumption was derived from the small observational patient study by Uppsala University that was conducted as part of the scheme and reported by the Swedish Public Health Agency. The study reported a median treatment duration of 11 days (6-16 days, IQR). [25(p2)]

The published report by Public Health Sweden highlights a prospective observational study of 33 patients at all university hospitals in Sweden.[47] The study showed that the patient population that benefitted most were elderly individuals treated for carbapenem-resistant *Pseudomonas aeruginosa,* many of whom had kidney failure requiring dialysis and were cared for in the ICU. The group also showed a moderately high short-term mortality.[25]

While the scientific literature includes efforts to quantify the comparative and incremental health benefits of novel antibiotics—particularly in terms of mortality reduction and cure rates—there remains limited robust evidence on their specific impact within the target population.[48] Given the relatively short duration of treatment and the prognosis of infections in the affected population, improved availability and earlier access to effective antibiotics is likely to have resulted in significant health gains for patients, in particular those with resistant infections and co-morbidities, as described in the pilot observational study conducted during the scheme's implementation. [25(p2)] Beyond direct patient health outcomes, novel antibiotics offer broader

societal benefits. These are captured in the so called STEDI framework and include access to more diverse and targeted (narrow spectrum) antibiotic interventions, reduced transmission of resistant pathogens, enablement of other medical interventions (e.g., surgeries, chemotherapy), and an "insurance value" for scenarios where all other treatment options fail.[49]

There is no health provider perspective that could be captured for this case study. The interviews with payer and manufacturer confirmed that health providers would benefit from access to novel antibiotics. They would also likely benefit from avoiding the additional costs associated with treating patients using antibiotics to which the infecting pathogens were resistant, such as longer hospital stays. In terms of costs, they would bear the full treatment-related costs, and the payer contribution would only be applicable if the revenue guarantee was not achieved by sales alone. Published reports by the Swedish Public Health Agency confirm that the cost of treatment per day using the included products ranges from approximately SEK 2,000 to 9,500. In total, from 15 July 2020 to 31 December 2022, the pilot model incurred an aggregated sum of provider expenditure of SEK 16,392,875 (Table 15).[25(p2)] This represents 44% of the total revenue guarantee payment to manufacturers (Table 15).

Table 17 summarises the implementation costs and benefits of the partially delinked revenue guarantee model for novel antibiotics in Sweden. The table presents cost and benefit information by implementation phases and stakeholders, using a colour-coded heat map to indicate the size and intensity at a high level. Patient perspective was not covered with interviews in this case study as no IPM implementation cost is expected to be borne by patients treated with antibiotics in hospital settings. However, we included earlier access and health gains as benefits to patients, even though they were not explicitly reported by patients as these are evident consequences of the scheme for patients. Benefits to patients beyond earlier access and health gains were not expected.

Table 17: Heatmap of costs and benefit summary for Abx revenue guarantee Sweden

	Inception & design				Adoption & implementation				Sustainment & maintenance				Wrap-up & closing			
	PH	M	Pr	Pa	PH	M	Pr	Pa	PH	M	Pr	Pa	PH	M	Pr	Pa
Human Resource cost	3	2	0	0	3	2	0	0	3	2	0	0	2	2	0	0
Transaction cost	0	2	0	0	0	2	0	0	0	2	0	0	0	0	0	0

Health-related costs	0	0	0	0	0	0	0	3	0	0	0	3	0	0	0	3
Medicine-related cost	3	0	3	0	3	0	3	0	3	0	3	0	3	0	3	0
Other costs	0	0	0	0	0	0	0	0	0	2	0	0	0	2	0	0
Health related benefits	0	0	0	0	0	0	0	0	0	0	3	3	0	0	3	3
Revenue	0	0	0	0	0	0	0	0	0	2	0	0	0	2	0	0
Cost savings	0	0	0	0	0	0	0	0	2	0	2	0	2	0	2	0
Early access	0	0	0	0	0	0	0	0	3	0	0	0	3	0	0	0
Spillovers/ pos. externalities	0	2	0	0	0	2	0	0	0	2	0	0	0	2	0	0
Other benefits	0	3	0	0	0	3	0	0	0	2	0	0	0	2	0	0

Abbreviations: PH: Payer/HTA, M: Manufacturer, Pr: Provider, Pa: Patients.

Scoring: 3- Significant, 2- Moderate, 1- Minor, 0 – not reported

No interviews were yet conducted with providers or patients in Sweden. Data imputed from insights from other stakeholder interviews.

3.4. Outcomes-based agreement: gene therapy in Germany

Roctavian™ is a gene therapy designed to treat hemophilia A. In Germany, it became the first gene therapy to treat haemophilia A to be reimbursed by the statutory health insurance through a prospective, outcome-based cohort model. This agreement was negotiated under the German AMNOG system, which allows manufacturers full market access during the first year before HTA assessment begins, followed by price negotiations with health insurance organisations.[50,51] Germany has a decentralized healthcare system and the agreement was between the manufacturer, BioMarin Pharmaceutical Inc., and the German National Statutory Health Insurance Funds (GKV-SV), which is an umbrella organization for federal health insurance companies and covers approximately 90% of the German population.[51]

The outcomes-based model enables regular adjustments to the reimbursement price—upward or downward—based on outcomes data from the German haemophilia registry.[50] The initially proposed price discount is around 50%, based on an initial manufacturer proposal of €1.6 million,

resulting in a final reimbursement amount approximately in $900,000 per patient.[51] The price is regularly adjusted based on the therapy's performance, as monitored through the registry. The contract is legally binding and the individual insurance funds will use this agreement, but decisions on patient inclusion will be made on a case-by-case basis. The agreement has a minimum term of three years and guarantees the access and reimbursement for eligible patients (approximately 2,000).[51] The contract was finalized at the end of 2023, so only the design and implementation phases can be reported at this time.

Interviewees agreed that the primary motivation for implementing the IPM in Germany was the therapy's high upfront costs and the significant uncertainty surrounding its long-term effectiveness. The payment model helped mitigate this risk over time.

The payers did not agree on the extent of additional human resources or transaction costs compared to a standard agreement but indicated minor to moderate additional costs for negotiation and implementation.

Given the uncertainty surrounding the treatment's effectiveness, the payers noted that the primary benefit was providing earlier and continuous access to patients while sharing the treatment risks with the manufacturer. They believed that a standard agreement would not have been feasible in this context.

The payers also did not agree on the extent of potential cost savings through risk-sharing, but emphasised that, especially for smaller sickness funds, the full coverage of such therapies can be a bigger risk that can be mitigated through outcome-based agreements where treatment failure is possible.

Furthermore, they highlighted knowledge gains useful for future negotiations and agreements.

The industry perspective emphasized significant human resource and legal costs in negotiations. Their main benefit from the agreement was access to the German market and return on investment.

Providers were not involved in negotiations and do not bear specific costs related to the agreement, as these are covered by sickness funds. However, they noted additional benefits beyond patient access and health-related outcomes. Their clinical monitoring activities are financially compensated, and they believe there is a scientific spillover to other therapies and patient groups, such as paediatric patients, associated with adopting new innovative therapies.

The patient representative highlighted the benefit of the IPM in allowing access to patients and the health-related benefits associated with the technology for patients. They stressed that patients do not face any additional costs when participating in the IPM.

Key enablers included the haemophilia registry for tracking cohort-level outcomes data. The interviewees confirmed that the German haemophilia registry was chosen for its comprehensive cohort-level data, which is crucial for initial and future price negotiations. Other data sources, like claims-based data, lacked the necessary detail, particularly for patient follow-up after diagnosis. The existence of the haemophilia registry may have reduced the transaction and HR costs of implementing the model.

The main barrier was the high price expectations from manufacturers, which were not always supported by real-world evidence on efficacy and cost savings. These factors might have impacted the cost of negotiations and the design of the model, especially when details such as the price discount and the scheme's outcome were being negotiated.

Table 18 summarises the implementation costs and benefits of the prospective, outcome-based cohort model implemented by the German National Statutory Health Insurance Funds (GKV-SV) to introduce the first haemophilia-A gene therapy in Germany. The table presents cost and benefit information by implementation phase and stakeholder group, using a colour-coded heat map to indicate the relative size and intensity at a high level. The heat map highlights significant health-related benefits for providers and patients, as well as notable early access benefits for all stakeholders. These benefits are primarily concentrated in the sustainment & maintenance and wrap-up & closing phases. Payers/HTA bodies and manufacturers bore most of the costs, primarily moderate to significant human resource and transaction costs, distributed across all phases except wrap-up & closing. Patients also reported expected significant costs related to unexpected adverse events, occurring in all phases except inception & design.

Table 18: Heatmap of costs and benefit summary for Roctavian™ outcome-based agreement in Germany

	Inception & design				Adoption & implementation				Sustainment & maintenance				Wrap-up & closing			
	PH	M	Pr	Pa	PH	M	Pr	Pa	PH	M	Pr	Pa	PH	M	Pr	Pa
Human Resource cost	2	3	0	0	2	3	0	0	2	1	0	0	0	0	0	0
Transaction cost	0	2	0	0	0	2	0	0	0	2	0	0	0	0	0	0
Health-related costs	0	0	0	0	0	0	0	3	0	0	0	3	0	0	0	3
Medicine-related cost	3	0	0	0	3	0	0	0	3	0	0	0	3	0	0	0
Other costs	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Health related benefits	0	0	0	0	0	0	0	0	0	0	3	3	0	0	3	3
Revenue	0	0	0	0	0	0	0	0	0	3	0	0	0	0	0	0
Cost savings	0	0	0	0	0	0	0	0	2	0	2	0	2	0	2	0
Early access	0	0	0	0	0	0	0	0	3	3	3	3	3	3	3	3
Spillovers/ pos. externalities	1	0	0	0	1	0	0	0	1	0	1	0	1	0	1	0
Other benefits	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0

Abbreviations: PH: Payer/HTA, M: Manufacturer, Pr: Provider, Pa: Patients.
Scoring: 3- Significant, 2- Moderate, 1- Minor, 0 – not reported

3.5. Portfolio or bundling agreement: multiple myeloma therapies in Lithuania

The European Medicines Agency (EMA) approved thalidomide (Thalomid™) for the treatment of multiple myeloma, a rare cancer of the bone marrow in 2008.[52] Thalidomide is currently used in multiple myeloma as a first line treatment in combination with dexamethasone. EMA approved lenalidomide (Revlimid™) in 2007 for the treatment of multiple myeloma and it is currently the most frequently used second-line treatment.[53] Both medicines, thalidomide and lenalidomide were made available in Lithuania in 2016, almost ten years after their approval by the EMA.

In 2015, the manufacturer of lenalidomide submitted a request for reimbursement in Lithuania. After a prolonged negotiation of approximately 12 months, an agreement was reached and lenalidomide was included in the Positive List in April 2016, obtaining the reimbursement status in Lithuania.

The Minister of Health approved the reimbursement of lenalidomide subject to prescribing restrictions. It was reimbursed as second-line treatment for patients with multiple myeloma "*who have relapsed or have resistance to the drug bortezomib, and who have been diagnosed with grade 2, 3 or 4 neuropathy*".[54] According to the signed agreement, the manufacturer also agreed a portfolio or bundling-type IPM, providing thalidomide free of charge in a fixed ratio to lenalidomide at three designated hospitals. Both treatments — thalidomide and lenalidomide — were owned by the same manufacturer that signed the portfolio agreement. Patient access to both medicines was significantly improved, with a reduced total budget impact.

This was the first time a portfolio or bundling agreement mechanism was used in Lithuania. In this example the IPM enabled access not only to the innovative medicine, lenalidomide, but also to thalidomide, the first-line therapy in multiple myeloma. At the time the manufacturer submitted the reimbursement request for lenalidomide in 2016, thalidomide was not reimbursed in Lithuania either. However, lenalidomide was licensed as a second-line treatment, requiring that thalidomide, the first-line treatment, be reimbursed and in use. The portfolio agreement — which provided thalidomide free of charge at a fixed ratio with lenalidomide — addressed this issue, enabling access to the innovation in Lithuania and offering patients access to both medicines at once.

At the time of its implementation the IPM represented an innovative solution as it was the first time such a model had been used in Lithuania. Since then, this type of payment model has been widely used in Lithuania. In 2023, the National Health Insurance Fund (NHIF) had five agreements with manufacturers on individual or average patient treatment prices, using this type of IPM.[55]

In August 2019, following the expiration of lenalidomide's patent, generic alternatives entered the reimbursement system. This led to the termination of the agreement and the subsequent inclusion of thalidomide in the reimbursement system, which until that point had only been available in Lithuania under the conditions of the agreement and was not reimbursed on its

own.[56]

Access to lenalidomide expanded markedly after October 2020, when prescribing restrictions were lifted as a result of a price reduction following patent expiry, resulting in increased patient uptake. Lenalidomide transitioned from second-line treatment under previously mentioned criteria, to a broader use in combination with dexamethasone for adults with multiple myeloma who had undergone at least one prior course of treatment. The removal of prescribing restrictions led to a rapid increase in the number of patients treated — from 114 in 2019 to 346 in 2021. Table 19 shows the historic uptake data for Lenalidomide.

Table 19. Patients treated with lenalidomide in Lithuania 2016-2023

	2016	2017	2018	2019	2020	2021	2022	2023
Lenalidomide	32	70	100	114	164	346	268	287
Thalidomide	n/a	n/a	n/a	n/a	38	121	152	130

Note: n/a, non-available data about publicly funded medicines
Source: Calculated upon National Health Insurance Fund (NHIF) statistics (https://ligoniukasa.lrv.lt/lt/veiklos-sritys/gydymo-istaigoms-ir-partneriams/kompensuojamieji-vaistai-ir-medicinos-pagalbos-priemones-2/statistika-1/)

In the absence of research papers, the costs and benefits of implementing the discussed agreement are based on insights from the stakeholders interviewed. The evidence presented in this section capture the perspectives of key informants, including the single public payer, manufacturers, providers, and patients.

The National Health Insurance Fund (NHIF), as the payer, did not incur substantial administrative and human resource expenditures that required the involvement of additional personnel at any phase of establishing and managing the IPM. Consequently, no supplementary FTE positions or significant time commitments were noted. The highest resource mobilization occurred for the adoption of the IPM when the internal legal unit was required to produce the final legal documents. The responsible NHIF division, primarily utilized available human resources to maintain the IPM, focusing mainly on verifying and reconciling the use of thalidomide and lenalidomide in the annual accounting reports.

The manufacturer did not employ additional staff in any phase of IPM implementation. The costs of IPM preparation were considered moderate: interviewees representing the manufacturer perspective identified moderate opportunity costs associated with the initial stages of designing and negotiating the IPM, which lasted approximately one year. During this time, the manufacturer played a pivotal role in developing and modifying the IPM design and contract

options to meet the payer's requirements. The maintenance & sustainment phase required additional logistical efforts to deliver medications to three partnering hospitals; however, these were integrated with standard logistical procedures, keeping transaction costs low. Although the agreement automatically terminated when the patented pharmaceutical became generic, the final reconciliations for accounting reports required additional minimal work during the wrap-up & closing phase.

The same applies to the involvement of the providers' staff (e.g., hospitals) during the final wrap-up & closing phase of the IPM. Senior nurses in pertinent hospital departments took on significant responsibility in collecting physicians' prescriptions, managing inventory, and dispensing medications. The adoption & implementation phase required additional effort and time from hospital personnel to establish necessary processes, including reporting.

The estimated costs incurred by members of the external committees involved in the medicine reimbursement decision-making — including clinicians and patient organization representatives — were calculated using a simplified approach. This involved multiplying the country's average hourly wage (€7.40 per hour, based on an average monthly wage of €1,226 for specialists with higher education or in 2018)[57] by the approximate monthly hours of their work. Calculations resulted in an estimated annual total cost of €370 per person (€7.4 * 5 hours *10 meetings).

The parties derived different benefits from the IPM. The primary benefit for the healthcare system, patients and providers, was faster access to therapy and improved quality of care for individuals with multiple myeloma. Notably, the agreement significantly enhanced geographical equity nationwide by ensuring the medications were distributed across three hospitals in different cities. This approach not only reduced travel costs for patients but also helped lower treatment-related expenses for the healthcare system. Additionally, patients who previously purchased medications out-of-pocket experienced significant private savings. It is estimated that 300 patients, each purchasing for six months at a cost of €150 per month, results in annual savings of €270,000.

The manufacturer received additional revenue by keeping the reimbursement price of lenalidomide constant while offering a rebate to the payer through free delivery of thalidomide at the agreed fixed rate. The payer saved money by receiving thalidomide free of charge while a positive reimbursement decision for lenalidomide was being made, thereby improving access

and availability.

Additional benefits include learning and upskilling opportunities for both the payer (NHIF employees) and the staff of the three hospitals in the agreement.

Table 20 summarises the implementation costs and benefits of the portfolio or bundling model for lenalidomide and thalidomide in Lithuania. The table presents cost and benefit information by implementation phases and stakeholders, using a colour-coded heatmap to indicate the size and intensity at a high level. Implementation benefits were concentrated in the sustainment & maintenance phase and were primarily related to access and early access to innovation. Manufacturers gained moderate benefits in terms of early revenue, while patients experienced significant health benefits. Patients, providers, and payers also achieved minor to moderate cost savings as a result of IPM implementation.

In contrast to benefits, costs were distributed across all phases. All stakeholders incurred minor to moderate costs throughout. The payer faced significant medicine costs due to increased access in all phases except inception and design. Patients experienced minor costs related to unexpected adverse events, also across all phases except inception and design.

Table 20: Heatmap of costs and benefit summary for Portfolio or bundling agreement in Lithuania.

	Inception & design				Adoption & implementation				Sustainment & maintenance				Wrap-up & closing			
	PH	M	Pr	Pa	PH	M	Pr	Pa	PH	M	Pr	Pa	PH	M	Pr	Pa
Human Resource cost	1	2	0	0	1	2	0	0	1	0	1	0	1	2	1	0
Transaction cost	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
Health-related costs	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0
Medicine-related cost	0	0	0	0	3	0	0	0	3	0	0	0	3	0	0	0
Other costs	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Health related benefits	0	0	0	0	0	0	0	0	1	0	1	3	0	0	0	0
Revenue	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
Cost savings	0	0	0	0	0	0	0	0	1	0	2	2	0	0	0	0

Early access	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0
Spillovers/ pos. externalities	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0
Other benefits	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Abbreviations: PH: Payer/HTA, M: Manufacturer, Pr: Provider, Pa: Patients.

Scoring: 3- Significant, 2- Moderate, 1- Minor, 0 – not reported

We conducted several analyses focused on the impact of the IPM on early access, which all stakeholders identified as a key implementation benefit. We combined the data we were able to gather on earlier access to lenalidomide with cost-effectiveness data to provide illustrative estimates of the broader benefits associated with early access—such as health gains, cost savings, and net monetary benefit to the system.

We assumed that all patients treated between 2016 and 2019—totaling 316—accessed lenalidomide earlier due to the IPM. The IPM concluded in 2020, when generic lenalidomide became available to patients in Lithuania through the routine outpatient medicine reimbursement mechanism, following the expiration of its patent.

We collected data from the literature on drug costs and life years (LY) gained. We used an estimate of mean incremental LY per patient of 4.39[58] based on a comparison to dexamethasone alone—the treatment available for multiple myeloma in Lithuania at the time of the agreement. The research evidence appears relevant to the Lithuanian case because the agreement provided access to both thalidomide (as first-line treatment) and lenalidomide (as second-line treatment), which were not reimbursed in Lithuania at the time.

We assumed that, for the first year of treatment, the number of LYs gained would equal half the number of treated patients, since treatment may begin at any point during the year. We used official estimates of the value of a LY in Lithuania, as provided by the Central Project Management Agency, which operates under the Ministry of Finance. This value increased steadily from €17,741 in 2016 to €25,330 in 2019, based on estimates of expected lifetime earnings adjusted for real GDP growth (using International Monetary Fund forecasts) and discounted over time.

We combined these data to estimate the value of additional LYs, the cost of the medicine, and the net benefit of treatment during the period of earlier access (2016–2019), as shown in the Table 20 below:

- Spending data from the National Health Insurance Fund's 2019 budget impact reports were used to calculate the average per-patient cost of lenalidomide and dexamethasone.
- We assumed that the average cost (€15,084) remained constant in previous years to estimate total public expenditure on the therapy.
- We estimated the net benefit of lenalidomide under early access and IPM by calculating the difference between the value of life years saved and public expenditure from 2016 to 2019, which totalled €7,366,266.

Table 20 summarises all illustrative net benefit and cost-effectiveness calculations.

Table 20: Costs-effectiveness calculations for the portfolio agreement in Lithuania

		2016	2017	2018	2019
	N patients	32	70	100	114
Benefit	LY/patient	4.39			
	LY saved	16	32	32	32
			35	70	70
				50	100
					57
	Total LY saved	16	67	152	259
	Value of LY, €	17,741	23,713	24,340	25,331
	Total gain	283,854	1,588,774	3,699,609	6,560,651
Cost	Cost of lenalidomide plus dexamethasone	€15,084			
	NHIF expenditure, €	482,696	1,055,897	1,508,425	1,719,604
Net benefit		-198,842	532,877	2,191,184	4,841,047
Total net benefit					7,366,266

4. Discussion

The methods, analyses, and results presented in this report aim to capture the full range of costs and benefits associated with implementing a broad range of IPMs. They also seek to inform Deliverable D.1.2 of HI-PRIX Work Package 1: *Stakeholders' Judgement on Barriers and Enablers of Novel Payment/Pricing Schemes*.

While some costs (e.g., data collection) and benefits (e.g., access to innovation) are documented in the literature, this research goes further by systematically identifying and assessing both tangible and intangible implementation impacts across various IPM types, countries, healthcare systems, and stakeholder perspectives. To our knowledge, this is the first time a comprehensive evaluation framework has been developed and applied to assess implementation costs and benefits of IPMs across different types and phases. It is also the first time that implementation costs and benefits have been systematically documented across a broad range of IPM types.

To support this, we examined four case studies covering different types of IPMs: instalments and amortisations, financial-based risk-sharing agreements, outcomes-based payments, and portfolio or bundling agreements. These were implemented across five countries—Italy, Spain, Sweden, Germany, and Lithuania.

The remainder of the section discusses the evaluation framework applied, the main findings, and the associated limitations and caveats.

4.1. Framework and utility

We developed an IPM cost-benefit evaluation framework by adapting implementation assessment models from the implementation science literature. The framework is comprehensive, dividing the implementation process into four key stages: inception & design; adoption & implementation; sustainment & maintenance; and wrapping up & closing. It integrates the perspectives of all major stakeholders, including payers/HTAs, manufacturers, healthcare providers, and patients. The framework is designed to be flexible and applicable across all types of IPMs, enabling the identification and assessment of a wide range of costs and benefits. To support this, we developed a cost/benefit inventory that captures both

generalisable impacts—relevant across IPM types and healthcare systems—and context-specific impacts, which vary depending on the IPM model, therapeutic area, or national context.

We demonstrated the utility of the framework and inventory through four case studies, each representing a distinct IPM type:

1. **Financial-based risk-sharing agreement:** Swedish antibiotic pilot scheme
2. **Instalment and amortisation payments**: CAR-T cell therapies in Italy and Spain
3. **Outcomes-based agreement**: Roctavian™ in Germany
4. **Portfolio or bundling agreement**: Lenalidomide and thalidomide in Lithuania

Depending on the data available and the evaluation objectives, the framework and cost/benefit inventory support both semi-quantitative and fully quantitative approaches to comprehensively assessing costs and benefits. For our case study validation, we conducted semi-structured interviews with all stakeholders in the framework and involved in the implementation of IPMs.

The research faced limitations due to the number of interviews conducted, often only one per perspective. However, we discussed alternative perspectives with interviewees to enhance our understanding and validate findings across all viewpoints. The use of this approach enabled the identification, or approximation, of implementation costs and benefits from all perspectives and for all stakeholders.

Not all interviewees were able to provide data and monetary estimates for the documented costs and benefits. As a result, we adopted a semi-quantitative approach to estimate their magnitude in the absence of precise financial data. This method enabled us to consistently capture a wide range of implementation impacts across all case studies. However, it has inherent limitations —particularly in comparing the relative size of different costs and benefits within and across case studies. That said, it does allow for an insightful case-by-case assessment of the nature and magnitude of implementation costs and benefits affecting an IPM, including when (e.g., phases) and to whom (e.g., stakeholder group) they occurred.

4.2. IPM Motivation

When discussing the IPM motivation with the interviewees it became apparent that in all case

studies, IPMs were considered as solutions to specific issues that otherwise cannot be addressed with simple discounts in 'a conventional' contract.

- CAR-T cell therapies in Italy and Spain and the gene therapy for the treatment of haemophilia in Germany were seen as a highly expensive innovations with significant expected budget impacts and uncertain value for money, due to long-term uncertainty around effectiveness and limited supporting clinical evidence. Outcome-based payments and instalments offered a solution by enabling patient access while addressing the high costs and long-term uncertainty through risk-sharing between the manufacturer and the payer.
- In Sweden, government identified the issue of commercial sustainability for novel antibiotics in its the relatively small pharmaceutical market. A revenue guarantee model, partially delinked from sales, provided access for patients while offering manufacturers predictable, encouraging both product launch and sufficient availability in the Swedish market.
- In Lithuania, the portfolio or bundling payment model enabled access to two multiple myeloma treatments for patients that would otherwise go untreated or face out-of-pocket costs. It also allowed manufacturers to launch the innovative second line therapy, lenalidomide, and generate revenue.

This demonstrates the wide range of IPM options, each offering potential solutions to specific pricing and access challenges—from market failures to high upstream costs and clinical uncertainty.

4.3. IPM Implementation Costs

While IPMs serve different objectives and offer varied solutions, our analysis found that all examined models introduced increased complexity and incurred a range of costs across stakeholders compared to standard agreements.

Payers, manufacturers, and healthcare providers often face high HR and transactional costs. These costs were generally significant across IPMs and spread over all four phases of our framework: inception and design, adoption and implementation, maintenance and

sustainment and wrap-up and closing HR and transaction costs were particularly pronounced in outcome-based agreements—especially during inception and design, adoption and implementation and maintenance and sustainment—which required more effort and resources compared to revenue guarantee and portfolio agreements. This is largely due to the need for case-by-case negotiation of relevant outcomes, agreement on how these outcomes are measured, and the establishment and use of a supporting infrastructure to monitor and evaluate the scheme. As a result, the burden on payers/HTAs, manufacturers, and healthcare providers is significantly higher.

While patients in Europe typically do not face substantial out-of-pocket expenses, they may still incur indirect costs, such as those related to transportation, hospitalisation, or training. These can be particularly significant when treatments involve specialised administration or follow-up care. In the case of outcome-based agreements, there may also be health-related costs arising from unrelated adverse events, especially when the treatment safety profile is uncertain.

In addition, context-specific costs can arise. For instance, in revenue guarantee schemes—such as the Swedish case for antibiotic availability—a breach of contract may lead to penalty payments or revenue losses for manufacturers.

4.4. IPM Implementation Benefits

Despite the complexity and associated costs, IPMs offer significant benefits across stakeholder groups. There is broad consensus that the primary advantage of IPMs lies in enabling access—and especially early access—to innovation, which is particularly valuable in areas with high unmet medical need.

For patients and healthcare providers, IPMs can deliver substantial health-related benefits, including earlier access to cutting-edge therapies and improved treatment outcomes across all schemes.

Payers and providers may benefit from cost savings, particularly through outcomes-based risk-sharing agreements and bundled payments. They may also see cost offsets resulting from improved health outcomes and reduced downstream healthcare utilisation. However, such savings were generally described as minor to moderate. The greatest cost savings were observed in outcome-based agreements, where initial medicine-related payments could be

significantly reduced based on the patients' responses to treatment. This was particularly relevant in the Italian and Spanish CAR-T outcomes-based instalment models.

For manufacturers, IPMs can enhance revenue generation and return on investment across various schemes—particularly through mechanisms that facilitate and accelerate market entry and uptake while sharing financial risk.

Beyond direct financial and clinical gains, IPMs may also generate broader system-level value for stakeholders. These include knowledge spillovers, such as scientific advancements, upskilling of healthcare professionals, medical centre accreditations, and improved readiness for future negotiations. In some contexts, additional benefits include the generation of real-world evidence which can inform future decision-making, or "political wins", such as showcasing innovation-friendly policy environments. For example, in the revenue guarantee model, manufacturers noted that revenue was not the only primary motivation for participation. They also placed significant value on the opportunity to engage in an innovative solution that could influence international policy and practice.

4.5. IPM Implementation Considerations

A key characteristic of the costs and benefits we captured to be associated with IPM implementation is their temporal and dynamic nature. We found that IPMs typically involve a trade-off: substantial costs are incurred across all phases of implementation, while the benefits —such as improved health outcomes, cost savings, or reduced uncertainty —tend to emerge and concentrate in specific phases, particularly during the adoption and implementation, and maintenance and sustainment.

To manage this trade-off, stakeholders may seek to optimise the balance between investment and return. One approach is to reduce implementation costs for manufacturers, payers, and providers. For example, a comparison of CAR-T therapy outcome-based instalment models in Italy and Spain revealed that Italy's payer and provider systems were more prepared to implement IPMs, resulting in lower implementation and monitoring costs compared to Spain.

However, this readiness may also explain a shorter period of early access observed in Italy. In that context, access to highly innovative technologies is likely to be facilitated by the well-established IPM infrastructure, which can potentially blur the observed incremental impact that

specific uses of IPMs have on early access. Although we do not have robust evidence to confirm this, we interpret the differences in early access impact between Italy and Spain based on this reasoning.

Another strategy is to design IPMs as temporary, transitional tools, used until standard agreements can be adopted. Stakeholders widely agreed that outcome-based agreements are particularly suited to addressing long-term uncertainty through real-world data collection. Once sufficient evidence is available, they highlighted that these agreements can be phased out, reducing administrative burden while preserving the benefits. Similarly, the portfolio agreement was considered especially valuable during the patent protection period of a medicine, after which a more conventional pricing model could be adopted.

In contrast, IPMs targeting market failures or structural challenges may require a more long-term implementation. For example, the Public Health Agency of Sweden proposed to further extend its antibiotic pilot scheme, recognising its continued importance in addressing the lack of commercial incentives for antibiotic launch in the Swedish market.

5. Conclusions

Innovative Payment Models (IPMs) can help address challenges such as limited or delayed access to pharmaceutical innovation, which are often experienced with conventional agreements and standard pricing. IPMs are flexible tools that offer a range of advantages for key stakeholders. helping to tackle issues related to risk-sharing, limited commercial incentives and returns, and value-based decision making in healthcare.

Payers' benefits from using IPMs are derived from cost savings, risk-sharing, and improved access to innovation; patients gain earlier access to health benefits; and the pharmaceutical industry sees improved risk-sharing and return on investment. However, IPMs are generally more complex and resource-intensive than traditional agreements, particularly during their design and implementation phases. To maximise their effectiveness, IPMs should be time-limited until the underlying issue is resolved and designed to deliver clear value to all stakeholders. This is more likely when implementation costs and administrative burden are minimised—though this is not always feasible in practice. Importantly, learnings from current IPM implementations are beginning to inform more streamlined approaches, which may reduce complexity and cost

over time and increase stakeholder readiness.

References

1. Moullin JC, Sabater-Hernández D, Fernandez-Llimos F, Benrimoj SI. A systematic review of implementation frameworks of innovations in healthcare and resulting generic implementation framework. *Health Research Policy and Systems*. 2015;13(1):16. doi:10.1186/s12961-015-0005-z

2. Glasgow RE, Harden SM, Gaglio B, et al. RE-AIM Planning and Evaluation Framework: Adapting to New Science and Practice With a 20-Year Review. *Front Public Health*. 2019;7:64. doi:10.3389/fpubh.2019.00064

3. Feldstein AC, Glasgow RE. A Practical, Robust Implementation and Sustainability Model (PRISM) for Integrating Research Findings into Practice. *The Joint Commission Journal on Quality and Patient Safety*. 2008;34(4):228-243. doi:10.1016/S1553-7250(08)34030-6

4. HI-PRIX HORIZON. Pay for Innovation Observatory. Published online 2023. https://p4i.hiprixhorizon.eu/tool

5. Fox J, Watrous M. Overcoming Challenges Of Outcomes-Based Contracting For Pharmaceuticals: Early Lessons From The Genentech--Priority Health Pilot. *Health Affairs Forefront*. Published online 2017. doi:10.1377/forefront.20170403.059442

6. Clopes A, Gasol M, Cajal R, et al. Financial consequences of a payment-by-results scheme in Catalonia: gefitinib in advanced EGFR-mutation positive non-small-cell lung cancer. *Journal of Medical Economics*. 2017;20(1):1-7. doi:10.1080/13696998.2016.1215991

7. Spark Therapeutics. Spark Therapeutics Announces First-of-their-kind Programs to Improve Patient Access to LUXTURNA™ (voretigene neparvovec-rzyl), a One-time Gene Therapy Treatment – Spark Therapeutics. Accessed October 23, 2023. https://sparktx.com/press_releases/spark-therapeutics-announces-first-of-their-kind-programs-to-improve-patient-access-to-luxturna-voretigene-neparvovec-rzyl-a-one-time-gene-therapy-treatment/

8. Novartis. AveXis Announces Innovative Zolgensma® Gene Therapy Access Programs for US Payers and Families. Novartis. May 24, 2019. Accessed July 27, 2023. https://www.novartis.com/news/media-releases/avexis-announces-innovative-zolgensma-gene-therapy-access-programs-us-payers-and-families

9. Novartis. AveXis receives EC approval and activates “Day One” access program for Zolgensma®, the only gene therapy for spinal muscular atrophy (SMA). Novartis. May 19, 2020. Accessed October 31, 2023. https://www.novartis.com/news/media-releases/avexis-receives-ec-approval-and-activates-day-one-access-program-zolgensma-only-gene-therapy-spinal-muscular-atrophy-sma

10. Moon S, Erickson E. Universal Medicine Access through Lump-Sum Remuneration — Australia’s

Approach to Hepatitis C. *N Engl J Med*. 2019;380(7):607-610. doi:10.1056/NEJMp1813728

11. Folkhälsomyndigheten - Public Health Agency of Sweden. *Tillgänglighet till Vissa Antibiotika – En Pilotstudie Av En Alternativ Ersättningsmodell*.; 2023. https://www.folkhalsomyndigheten.se/publikationer-och-material/publikationsarkiv/t/tillganglighet-till-vissa-antibiotika-en-pilotstudie-av-en-alternativ-ersattningsmodell/

12. Public Health Agency of Sweden. *Availability to Antibiotics of Particular Importance*.; 2023. https://www.folkhalsomyndigheten.se/publikationer-och-material/publikationsarkiv/a/availability-to-antibiotics-of-particular-importance/

13. Agenzia Italiana del Farmaco. *Riclassificazione Del Medicinale per Uso Umano Luxturna Ai Sensi Dell'art.*; 2020. https://www.aifa.gov.it/documents/20142/961234/Determina_DG-1344-2020_Luxturna.pdf

14. NICE. *Ranibizumab and Pegaptanib for the Treatment of Age-Related Macular Degeneration: Technology Appraisal Guidance [TA155]*. National Institute for Health and Care Excellence; 2008. Accessed November 4, 2023. https://www.nice.org.uk/guidance/ta155/chapter/4-Evidence-and-interpretation

15. Vertex Pharmaceuticals Incorporated. Vertex Announces Long-Term Reimbursement Agreement with the Republic of Ireland for ORKAMBI® (lumacaftor/ivacaftor), KALYDECO® (ivacaftor) and Future Cystic Fibrosis Medicines. June 1, 2017. Accessed November 17, 2023. https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-long-term-reimbursement-agreement-republic

16. Vertex Pharmaceuticals Incorporated. Vertex Announces Access Contract in Denmark for Current and Future Cystic Fibrosis Medicines. October 1, 2018. Accessed November 17, 2023. https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-access-contract-denmark-current-and-future

17. Vertex Pharmaceuticals Incorporated. Vertex Announces Agreement with NHS England for Access to All Licensed Cystic Fibrosis Medicines. October 24, 2019. Accessed November 17, 2023. https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-agreement-nhs-england-access-all-licensed

18. Vertex Pharmaceuticals Incorporated. Vertex Announces New Portfolio Reimbursement Agreement in Italy Including KAFTRIO®, SYMKEVI® and Additional Indications of ORKAMBI® and KALYDECO® for Eligible Patients With Cystic Fibrosis. June 25, 2021. Accessed November 17, 2023. https://news.vrtx.com/news-releases/news-release-details/vertex-announces-new-portfolio-reimbursement-agreement-italy

19. Rawson J. Portfolio access agreements – Lessons learnt from Vertex Pharma's Orkambi. Partners4Access. November 21, 2018. Accessed November 17, 2023.

https://partners4access.com/blogs/portfolio-access-agreements-lessons-learnt-from-vertex-pharmas-orkambi/

20. Main B, Csanadi M, Ozieranski P. Pricing strategies, executive committee power and negotiation leverage in New Zealand's containment of public spending on pharmaceuticals. *HEPL*. 2022;17(3):348-365. doi:10.1017/S1744133122000068

21. Caves KW, Singer HJ. Bundles in the Pharmaceutical Industry: A Case Study of Pediatric Vaccines. *SSRN Journal*. Published online 2011. doi:10.2139/ssrn.1908306

22. Jørgensen J, Hanna E, Kefalas P. Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries. *J Mark Access Health Policy*. 8(1):1715536. doi:10.1080/20016689.2020.1715536

23. Mestre-Ferrandiz J, Towse A, Dellamano R, Pistollato M. *Multi-Indication Pricing: Pros, Cons and Applicability to the UK*. Office of Health Economics; 2015. https://www.ohe.org/wp-content/uploads/2016/06/418-Multi-indication-pricing_0.pdf

24. 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*. Vol 115.; 2019. doi:10.1787/6e5e4c0f-en

25. Folkhälsomyndigheten. PART 2: Tillgänglighet till vissa antibiotika - Slutrapport från en pilotstudie av en alternativ ersättningsmodell. *Artikelnummer: 23168*. Published online 2023.

26. Cappell KM, Kochenderfer JN. Long-term outcomes following CAR T cell therapy: what we know so far. *Nat Rev Clin Oncol*. 2023;20(6):359-371. doi:10.1038/s41571-023-00754-1

27. 131305_Chapter_8-Health_Economic_Aspects_of_Chimeric_Anti.pdf.

28. Heine R, Thielen F, Koopmanschap M, et al. Health Economic Aspects of Chimeric Antigen Receptor T-Cell Therapies for Haematological Cancers. Present and Future. *2020*. Published online 2020.

29. Jørgensen J, Hanna E, Kefalas P. Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries. *Journal of Market Access & Health Policy*. 2020;8(1):1715536. doi:10.1080/20016689.2020.1715536

30. Jørgensen J, Kefalas P. The Use of Innovative Payment Mechanisms for Gene Therapies in Europe and the USA. *Regenerative Medicine*. 2021;16(4):405-422. doi:10.2217/rme-2020-0169

31. OECD. OECD Data Explorer • Average annual wages. 2023. Accessed December 17, 2024. https://data-explorer.oecd.org/vis?tm=average%20annual%20wage&pg=0&snb=26&vw=tb&df[ds]=dsDisseminateFinalDMZ&df[id]=DSD_EARNINGS%40AV_AN_WAGE&df[ag]=OECD.ELS.SAE&df[vs]=1.0&dq=.....&pd=2000%2C&to[TIME_PERIOD]=false

32. Ministerio de Sanidad. *Informe de Seguimiento de La Dirección General de Cartera Común de Servicios Del Sistema Nacional de Salud (SNS) Y Farmacia Sobre El Plan Para El Abordaje de Las Terapias Avanzadas En El SNS. 2022*. Ministerio de Sanidad, Spain; 2022. https://www.sanidad.gob.es/areas/farmacia/infoMedicamentos/terapiasAvanzadas/docs/20220715_infor_ms_seg_plan_terapias_avanzadas_sns.pdf

33. Iglesias-López C, Agustí A, Vallano A, Obach M. Financing and Reimbursement of Approved Advanced Therapies in Several European Countries. *Value in Health*. 2023;26(6):841-853. doi:10.1016/j.jval.2022.12.014

34. Menon J, Madaj K, Cock ED, Vossen C. Time to Approval of Chimeric Antigen Receptor-T Cells (CAR-T) Therapies among Nordic Countries. Published online 2023.

35. Newton M, Stoddart K, Travaglio M, Troein P. EFPIA Patients W.A.I.T. Indicator 2023 Survey. Published online 2023.

36. Martín García-Sancho A, Presa M, Pardo C, Martín-Escudero V, Oyagüez I, Ortiz-Maldonado V. Cost-Effectiveness Analysis of Axicabtagene Ciloleucel vs. Standard of Care in Second-Line Treatment for Relapsed/Refractory Large B-Cell Lymphoma in Spain. *Cancers*. 2024;16(13):2301. doi:10.3390/cancers16132301

37. Santasusana JMR, Saldaña A de A, García-Muñoz N, Gostkorzewicz J, Llinàs DM, Heredia CD de. Cost-Effectiveness Analysis of Tisagenlecleucel in the Treatment of Relapsed or Refractory B-Cell Acute Lymphoblastic Leukaemia in Children and Young Adults in Spain . *CEOR*. 2020;12:253-264. doi:10.2147/CEOR.S241880

38. AIFA. *Kymriah Report Tecnico*.; 2021. Accessed December 17, 2024. https://www.aifa.gov.it/documents/20142/1307543/Kymriah_Report_Tecnico_20.09.2021.pdf

39. AIFA. *Yescarta Report Tecnico*.; 2021. Accessed December 17, 2024. https://www.aifa.gov.it/documents/20142/1307543/Yescarta_Report_Tecnico_28.07.2021.pdf

40. partnersadmin. Evolution of payment models for cell and gene therapies in Italy » Partners4Access. Partners4Access. November 26, 2019. Accessed July 10, 2025. https://partners4access.com/evolution-of-payment-models-for-cell-and-gene-therapies-in-italy/

41. Simoens S, De Groote K, Boersma C. Critical Reflections on Reimbursement and Access of Advanced Therapies. *Front Pharmacol*. 2022;13:771966. doi:10.3389/fphar.2022.771966

42. Procedure di pagamento dei servizi per i Registri AIFA di Monitoraggio dei Farmaci. Accessed July 10, 2025. https://www.aifa.gov.it/en/-/procedure-di-pagamento-dei-servizi-per-i-registri-aifa-di-monitoraggio-dei-farmaci-30-11-2015-?utm_source=chatgpt.com

43. National report on medicines use in Italy - Year 2020. Accessed July 11, 2025. https://www.aifa.gov.it/en/-/l-uso-dei-farmaci-in-italia-rapporto-osmed-2020

44. National Report on Medicines use in Italy. Year 2019. Accessed July 11, 2025. https://www.aifa.gov.it/en/-/l-uso-dei-farmaci-in-italia-rapporto-osmed-2019

45. Folkhälsomyndigheten. *Availability to Antibiotics of Particular Importance: A Swedish Pilot Study of an Alternative Reimbursement Model*.; 2023.

46. Folkhälsomyndigheten. PART 1: Tillgänglighet till vissa antibiotika. *Artikelnummer: 22283*. Published online 2023.

47. Uppsala University. *Use of New Antibiotics Against Multidrug-Resistant Gram-Negative Bacteria in Swedish University Hospitals*. clinicaltrials.gov; 2024. Accessed July 17, 2025. https://clinicaltrials.gov/study/NCT05048693

48. Van Helden SR, Schulz LT, Wimmer M, Cancelliere VL, Rose WE. Finding value in novel antibiotics: How can infectious diseases adopt incremental cost-effectiveness to improve new antibiotic utilization? *Diagnostic Microbiology and Infectious Disease*. 2024;109(2):116245. doi:10.1016/j.diagmicrobio.2024.116245

49. Brassel S, Firth I, Chowdhury S, Hampson G, Steuten L. *Capturing the Broader Value of Antibiotics: A Research Roadmap for STEDI*.; 2023. https://www.ohe.org/publications/capturing-the-broader-value-of-antibiotics/

50. GKV-Spitzenverband. Pressemitteilung. Accessed December 19, 2024. https://www.gkv-spitzenverband.de/gkv_spitzenverband/presse/pressemitteilungen_und_statements/pressemitteilung_1718538.jsp

51. Inc BP. BioMarin Announces Agreement with German Health Insurance Fund on Reimbursement Amount for ROCTAVIAN® (valoctocogene roxaparvovec-rvox) for Severe Hemophilia A in Germany. Accessed February 4, 2025. https://www.prnewswire.com/news-releases/biomarin-announces-agreement-with-german-health-insurance-fund-on-reimbursement-amount-for-roctavian-valoctocogene-roxaparvovec-rvox-for-severe-hemophilia-a-in-germany-301999249.html

52. European Medicines Agency recommends the approval of thalidomide for the treatment of rare bone-marrow cancer | European Medicines Agency (EMA). January 24, 2008. Accessed December 16, 2024. https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-approval-thalidomide-treatment-rare-bone-marrow-cancer

53. Goldman-Mazur S, Visram A, Rajkumar SV, et al. Second- and third-line treatment strategies in multiple myeloma: a referral-center experience. *Blood Cancer J*. 2022;12(12):1-6. doi:10.1038/s41408-022-00757-8

54. Ministry of Health. 49 Dėl Kompensuojamųjų vaistų sąrašų patvirtinimo. n.d. Accessed December 17, 2024. https://www.e-tar.lt/portal/lt/legalAct/TAR.FA9CC3E1430C/LyZpSNySPe

55. VLK. *2023 m. PSDF biudžeto išlaidų ir pacientų priemokų kompensuojamiems vaistams ir*

medicinos pagalbos priemonėms analizė.; 2024. https://ligoniukasa.lrv.lt/media/viesa/saugykla/2024/3/P1IwWZ5qbjc.pdf

56. Ministry of health. 49 Dėl Kompensuojamųjų vaistų sąrašų patvirtinimo. n.d.b. Accessed January 10, 2025. https://e-seimas.lrs.lt/portal/legalAct/lt/TAD/TAIS.94805/asr

57. Rodiklių duomenų bazė - Oficialiosios statistikos portalas. Accessed January 17, 2025. https://osp.stat.gov.lt/statistiniu-rodikliu-analize?hash=56337c88-41ef-4222-9bf5-dfd9d388dbfb#/

58. Deniz B, Morgan G, Schey S, et al. Economic Evaluation of Lenalidomide Combined with Dexamethasone for the Treatment of Multiple Myeloma in the UK. *Blood*. 2008;112(11):2400. doi:10.1182/blood.V112.11.2400.2400

Appendix 1. Interview materials

In this subsection, we present samples of the materials used for the interviews: a pre-interview questionnaire and a cost–benefit–barriers–enablers (CBBE) framework. Both included questions on implementation barriers and enablers, as these data were also collected through the interviews to support other research tasks within the same project work package.

Sample of pre-interview questionnaire

We present a sample of the pre-interview questionnaire used for the interview with payers/HTA in the Spanish CAR-T model. Although the questionnaire was slightly adapted for each stakeholder in each case study, the sample shown here is representative of all versions, as it includes the common and core elements.

Questionnaire

Context and motivation questions for Innovative Payment Model implementation

Please read and answer the first set of questions in Table A.1.1. They aim to gather information about the context and the motivation leading to propose, design, negotiate and agree the IPM under discussion i.e. the CAR-T staged payments.

Table A.1.1: General questions

Context:	Question:	Answer:
Innovative Payment Models (IPMs) are often more costly and complex to implement than conventional models.	What specific problem motivated use of the IPM that could not have been addressed with a simple discount in a 'conventional' contract?	
Experiences with certain types of IPMs are limited, and IPMs are most often used to pay for treatments with high uncertainty.	What informed the design of the IPM? E.g., prospective modelling, scenario analysis, etc.	
Multiple stakeholders are involved in the implementation of an IPM	Can you please identify the relevant stakeholders and their role in the implementation process?	
Contracting context varies	How was the IPM	

between countries and health systems	proposed/negotiated?	

Questions on benefit/cost data for quantification

A phased approach for the assessment of Innovative Payment Model implementation costs, benefits, barriers, and enablers (CBBEs)

We have characterised the key CBBEs and identify the key stakeholders involved across four phases. These are:

1. **Inception & design:** involves determining the specific objectives of the IPM for each relevant stakeholder and defining the scope of CBBEs involved in this phase. For example, identify the core problems that motivated use of an IPM, the choice and design of the IPM, who was involved in making these decisions and the different CBBEs they faced at this stage for participating in the process.
2. **Adoption & implementation:** involves the potential set-up required once an IPM is agreed. For example, the establishment of the necessary systems for collecting, reporting and use data for the IPM, upskilling clinical and non-clinical resources at the NHS, accreditation of treatment centres, etc.
3. **Sustainment & maintenance:** involves the ongoing operation of the scheme during the period in which the usage of the product is covered under the IPM. For example, there may be ongoing costs related to additional data collection on usage or outcomes, costs of payment determination and other admin costs.
4. **Wrapping up & closing:** involves the period in which the product is no longer covered under the IPM, but there may be work related to the setting and reconciling of any outstanding payments, cost, investment

Please consider your perspective e.g., payer, HTA, manufacturer, provider/NHS/Hospital (clinical/management) or patient when answering the questions in Table A.1.2.

Table A.1.2: Benefit/cost data for quantification

Benefit/Cost Type	**General category of the CBBE followed by a brief description** (e.g., personnel cost: one Full Time Employee (FTE) to track every three hundred patients, Admin. cost: invoicing only for responding patients over time)	**During which phase is this CBBE relevant for this specific IPM implementation?** Phases: inception & design, adoption & implementation, sustainment & maintenance, and Wrap-up & closing	**Which party incurs this cost or receives this benefit?** (Payer, manufacturer, patients, …) How is it shared between stakeholders? Is it 'internal' or 'external'?	**Can this CBBE be estimated quantitatively and, if so, how?** **Are data available and, if so, how can we obtain it?**
Health system or financial costs of implementation for stakeholders, e.g., negotiation, data collection, data infrastructure, contracting costs, processing, and administrative costs, etc.				
Benefits for stakeholders, e.g., accelerated/expanded market access (patients/manufacturers), cost savings (payers), specific evidence, etc.				
Barriers to successful implementation, e.g., legal/regulatory hurdles, lack of stakeholder experience with IPMs, etc.				
Enablers for successful implementation, e.g., regulatory carve-outs, established data infrastructure, etc.				

Open discussion on barriers/enablers elements for future assessment

Please consider answering, from your perspective, the following set of open questions for a preliminary documentation of potential barriers and enablers for IPM implementation.

- Can you highlight and describe the barriers and enablers encountered during the implementation of the IPM?
- From those you have highlighted, which barriers and enablers were the most relevant for what stakeholder?
- In terms of these barriers and enablers, which stakeholders played crucial roles facilitating the implementation of the IPM? How were these barriers and enablers managed by involved stakeholders?
- Based on your experience, do you have any other thoughts and reflections you would like to share regarding barriers and enablers?

Sample of cost, benefit, barriers and enablers (CBBE) framework

We present here an empty template of the CBBE framework used for the interviews in Figure A.1.1. Researchers populated these frameworks with interviewees' responses to the pre-interview questionnaire and added clarifying questions to address unclear points or details in the data and evidence provided. The populated framework, together with the clarifying questions, was then shared with each interviewee in advance of the interview for preparation.

Figure A.1.1: Framework for data collection for IPM implementation cost, benefit, barriers, and enablers

Stakeholders	*Evaluation factor*	*Inception & Design*	*Adoption & implementation*	*Maintenance & Sustainment*	*Wrap Up & Closing*
Payer/HTA	Cost				
	Benefits				
	Barriers				
	Enablers				
Manufacturer	Cost				
	Benefits				
	Barriers				
	Enablers				
Health care providers	Cost				
	Benefits				
	Barriers				
	Enablers				
Patients	Cost				
	Benefits				
	Barriers				
	Enablers				
Additional stakeholders identified during the process	Cost				
	Benefits				
	Barriers				
	Enablers				

Questions, comments and clarifications:

1.

Appendix 2. Time to availability data for

the CAR-T treatments case study in Sain and Italy

Tables A.2.1. and A.2 capture the time to availability data used for the earlier access analysis. We collected data from the WAIT indicator.

Table A.2.1: Time to access of Kymriah™ and Yescarta™ in Spain compared to other European countries [33–35]

	Kymriah™		Yescarta™	
	Time to access	**Spain comparison**	**Time to access**	**Spain comparison**
Spain	4	N/A	10	N/A
Italy	15	11	21	11
Denmark	5.3	1.3	N/A	N/A
Sweden	8.8	4.8	12.5	2.5
Norway	3.8	-0.2	49.9	39.9
Finland	6.6	2.6	15.7	5.7
Scotland	12	8	13	3
Ireland	12	8	N/A	N/A
England	6	2	5	-5
Netherlands	6	2	6	-4
France	6	2	6	-4
Germany	24	20	8	-2
Average time to availability in EU	17.5	13.5	17.5	7.5
Average time to availability in EU - oncology	18.4	14.4	18.4	8.4
Average time to availability in EU - orphan	17.4	13.4	17.4	7.4
Average time to availability in Spain - all	21.7	17.7	21.7	11.7
Average time to availability in Spain - oncology	23.8	19.8	23.8	13.8
Average time to availability in Spain - orphan	23.2	19.2	23.2	13.2

Table A.2.1. presents the time (in months) required for patients to access Kymriah™ and Yescarta™ after approval in various European countries for the case of Spain. Spain comparison column indicates the difference in access time compared to Spain, with positive values meaning faster access times in Spain and negative values indicating longer access times. The six last rows of the table include average access times to across the EU, oncology treatments, and orphan drugs, and the same for Spain's access timelines.

Table A.2.2: Time to access of Kymriah™ and Yescarta™ in Italy compared to other European countries [33–35]

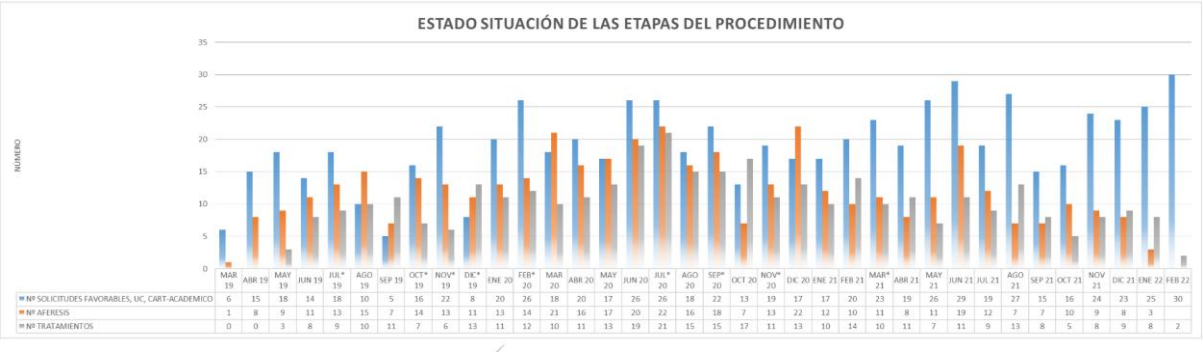
	Kymriah™		Yescarta™	
	Time to access	**Comparison Italy**	**Time to access**	**Comparison Italy**
Italy	11	0	14	0
Spain	4	-7	10	-4
Denmark	5.3	-5.7	N/A	N/A
Sweden	8.8	-2.2	12.5	-1.5
Norway	3.8	-7.2	49.9	35.9
Finland	6.6	-4.4	15.7	1.7
Scotland	12	1	13	-1
Ireland	12	1	N/A	N/A
England	6	-5	5	-9
Netherlands	6	-5	6	-8
France	6	-5	6	-8
Germany	24	13	8	-6
Average time to availability in EU	17.5	6.5	17.5	3.5
Average time to availability oncology in EU	18.4	7.4	18.4	4.4
Average time to availability orphan in EU	17.4	6.4	17.4	3.4
Average time to availability in Italy - all	13.9	2.9	13.9	-0.1
Average time to availability in Italy - oncology	13.7	2.7	13.7	-0.3
Average time to availability in Italy - orphan	14.2	3.2	14.2	0.2

Table A.2.2. presents the time (in months) required for patients to access Kymriah™ and Yescarta™ after approval in various European countries for the case of Italy. The Comparison Italy column indicates the difference in access time compared to Italy, with positive values meaning faster access times in and negative values indicating longer access times. The lower section of the table includes average access times across the EU, oncology treatments, and orphan drugs, and the same for Italy's access timelines.

Appendix 3. Early Access Impacts of CAR-T IPM in Spain: Data and Approach

We collected data on patients treated with CAR-T therapies in Spain from the Spanish Ministry of Health report *Informe de Seguimiento de la Dirección General de Cartera Común de Servicios del Sistema Nacional de Salud (SNS) y Farmacia sobre el Plan de Abordaje de las Terapias Avanzadas en el SNS*.[32] The report provides monthly data from March 2019 to February 2022, including the number of positive applications for treatment, the number of apheresis procedures completed, and the number of patients treated with CAR-T therapies. Figure A.3.1 presents the data from the Spanish Ministry of Health report.

Figure A.3.1. Monthly data on CAR-T therapy use in Spain, March 2019–February 2022



Source: Informe de Seguimiento de la Dirección General de Cartera Común de Servicios del Sistema Nacional de Salud (SNS) y Farmacia Sobre el Plan de Abordaje de las Terapias Avanzadas en el SNS.[32]

Assuming 19.2 months of earlier access for Kymriah™ and 13.2 months for Yescarta™, based on the comparison with average access times to orphan drugs in Spain, we estimated the total number of patients who benefited from earlier access by summing the patients treated from

March 2019 to October 2020 (both months included). In total, 211 patients were treated with CAR-T therapies during this period of assumed earlier access. All 211 patients can be attributed to treatment with either Kymriah™ or Yescarta™, as ARI-0001—the non-commercial CAR-T therapy developed and used in Spain for the same indications—was only approved in February 2021.

Specific data on the use of individual CAR-T therapies is not available in the report. To attribute the 211 patients to either Kymriah™ or Yescarta™, we applied assumptions based on approved indications. The report provides the total number of patients treated for Diffuse Large B-Cell Lymphoma (DLBCL), Primary Mediastinal B-Cell Lymphoma (PMBCL), and Acute Lymphoblastic Leukaemia (ALL). We calculated the proportion of patients in each indication by dividing the number treated for that indication by the total number treated with CAR-T therapies. These proportions were then applied to the estimated number of patients with earlier access, allowing us to estimate the distribution across indications. Table A.3.1 presents these estimates.

Table A.3.1. Estimates of patients with earlier access to CAR-T therapies by indication

Indication	Patients treated	Percentage	Patients treated earlier
DLCBL	266	73.8%	155
PMBCL	23	6.4%	14
ALL	71	19.8%	42
Total	360	100%	211

For attributing patients in each indication to a specific therapy, all ALL patients were treated with Kymriah™ and all PMBCL patients with Yescarta™, as these indications can only be treated with their approved CAR-T. Only patients with DLBCL received both therapies.

For attributing the 155 patients receiving earlier access in DLBCL to each therapy, we know that all patients treated from March 2019 to August 2019 received Kymriah™, as Yescarta™ was not yet available. A total of 30 patients were treated with CAR-T therapies during this six-month period (see Figure A.3.1). Using the proportion of DLBCL patients (see Table A.3.1), we estimated that 22 of these patients were treated for DLBCL with Kymriah™.

The remaining 133 DLBCL patients may have received either Kymriah™ or Yescarta™. Assuming an equal split, this results in 66 patients for each therapy (rounded to 67 for Kymriah). Adding

the 22 patients from the first six months to the 67 estimated for the following thirteen months, we attributed a total of 89 DLBCL patients to Kymriah™. All these numbers are presented in Table 6 of this report.

To estimate the number of positive treatment responses, we also used the Ministry's report. Sections 6.1 to 6.3 and Figures 11 to 13 provide patient outcomes and response-related data by indication across different time frames after treatment.[32] For example, complete response data are reported for 'before 3 months' ($\leq 3m$), 'between 3 and 18 months' ($> 3\text{-}18m$), and 'after 18 months' ($18m$). The data are based on the Valtermed registry. Mortality, partial response, and complete response with incomplete haematological recovery are also consistently reported. However, therapy-specific response data were not provided; therefore, we assumed uniform response, mortality, and progression rates across the two CAR-Ts.

Given that the scheme's second payment was fixed at 18 months, we used the Ministry's data to estimate rates of mortality, response, and progression beyond 18 months. To estimate the response rate, we assumed, for simplicity, that all complete responses (CR), complete responses with incomplete haematological recovery (CRi), and partial responses (PR) observed before 18 months were sustained. We then calculated the percentages of deaths, responses, and progressions for each indication using the formulas below. In these, the notation (≤3m, >3–18m, 18m) indicates that all responses and progressions at the different time points are summed.

$$Mortality\ rate\ before\ 18\ months = \frac{\#Deaths\ before\ 18\ months}{Total\ patients\ \ treated\ in\ the\ indication}$$

$$Response\ rate\ at\ 18\ months = \frac{Total\ PR(\leq 3m, > 3\text{-}18m, 18m) + Total\ CR(\leq 3m, > 3\text{-}18m, 18m) + Total\ CRi(\leq 3m, > 3\text{-}18m, 18m)}{Total\ patients\ \ treated\ in\ the\ indication}$$

$$Progresion\ rate\ at\ 18\ months = \frac{Total\ progressions\ (\leq 3m, > 3\text{-}18m, 18m)}{Total\ patients\ \ treated\ in\ the\ indication}$$

Applying these formulas to the data in the Ministry's report we estimated the mortality, response and progression rates presented in Table A.3.2.

Table A.3.2. Estimated mortality, response, and progression rates by indication.

Indication	Mortality	Response	Progression
DLCBL*	47.3%	27.8%	24.1%
PMBCL	20%	35%	45%
ALL	40%	40%	20%

*Percentages do not add up to 100% because two deaths occurring after 18m are not accounted in the mortality rate as they are not relevant for the payment scheme.

We applied the rates from Table A.3.2 to the patient numbers in last column of Table A.3.1 to estimate product-specific responses, progressions, and deaths. These estimates are presented in Table 7 and are subsequently used to calculate the health gains and cost impacts (risk-sharing) attributable to the early access facilitated by the CAR-T IPM in Spain. The cost impact was estimated using list prices and the therapy-specific payment schedule (timing of payment, instalment percentages, and outcomes), as described in Section 3.2.1 of this report.

To estimate LY and QALY gains we followed the approach below:

1. Since the life years (LY) of both Kymriah™ and Yescarta™ exceed the period of earlier access facilitated by the IPM in all indications, we attributed an LY gain equal to the earlier access period for each patient, regardless of indication. This was calculated using the following formula:

$$LY\ gain\ per\ patient = \frac{\#Months\ of\ earlier\ access}{\#12\ Months} \cdot 1LY.$$

2. We used the same approach to estimate QALY gains,

$$QALY\ gain\ per\ patient = \frac{\#Months\ of\ earlier\ access}{\#12\ Months} \cdot 1QALY.$$

3. We multiplied the per-patient LY and QALY gains by the corresponding number of patients in each month of earlier access to estimate the monthly health gains attributable to early access.

4. We then summed all monthly health gains to estimate the total health gain attributable to earlier access, as presented in Table 10.