HEALTH **I**NNOVATION NE**X**T GENERATION **P**AYMENT & PR**I**CING MODELS **(HI-PRIX):**

Balancing Sustainability of Innovation with Sustainability of Health Care

M11: Results of simulation on the impact of various payment schemes on cost differences for both, manufactures and society, specifically focusing on different sources of uncertainty

WP6 – Impact of innovative payment schemes on long-term competition in health technology markets, in particular the pharmaceutical market

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LIST OF ABBREVIATIONS

AC	Actual costs
FIX	Factor IX
IA	Instalment agreement
OHE	Office of Health Economics
PS	Pettersson score
RA	Refund agreement
RSA	Risk-sharing agreement
TC	Total costs
UHAM	University of Hamburg
UK	United Kingdom
WP	Work package

EXECUTIVE SUMMARY

This milestone, titled "M11 Results of simulation on the impact of various payment schemes on cost differences for both, manufacturers and society, specifically focusing on different sources of uncertainty", relates to Work Package 6 (WP6) – "Impact of innovative payment schemes on long-term competition in health technology markets, in particular the pharmaceutical market".

The advancement of gene therapies, such as Hemgenix for Haemophilia B, offers promising treatment options for chronic diseases but poses significant financial challenges due to their high costs and uncertain long-term efficacy. Risk-sharing agreements (RSAs), which link reimbursement to treatment outcomes, have been proposed to manage these financial risks. We selected Hemgenix as a case study to simulate the effects of RSAs on costs in healthcare systems in Germany, the United Kingdom (UK), and Italy.

We developed a microsimulation state-transition model to simulate disease progression and treatment pathways for patients receiving gene therapy with severe to moderately severe Haemophilia B. The model evaluated two types of RSAs: instalment agreements (IAs) and refund agreements (RAs).

The simulation results indicate that RSAs reduce healthcare costs for payers in all three countries for patients treated with Hemgenix. Cost savings from RSAs vary depending on the type of agreement and its duration. RAs generally yield higher savings over longer durations, aligning closer to the original costs of the gene therapy. In contrast, savings from IAs diminish over time although they remain positive throughout. In Germany, a risk pool, which compensates sickness funds for high therapy costs, alters the impact of RSAs. While RAs continue to provide savings, IAs increase costs for sickness funds due to the structure of the risk pool.

These findings highlight the need for policymakers to continuously reassess RSA terms and regulatory frameworks to ensure they meet their intended objectives. In Germany, reforms of the risk pool are necessary to enhance attractiveness of IAs. Additionally, the results suggest that RSAs could influence market competition, particularly in the gene therapy sector, by shaping the adoption and development of future therapies.

Our results demonstrate that while RSAs can effectively reduce costs for innovative therapies such as gene therapy for Haemophilia B, their design and implementation must be carefully tailored to the specific regulatory and market contexts of each country. Further research, including theoretical modelling and stakeholder interviews, will explore the broader implications of RSAs on long-term market competition. The results will inform ongoing discussions on the optimization of payment schemes for high-cost, innovative therapies.

1.Introduction

1.1. Purpose

Advances in personalized medicine and gene therapy have unlocked new treatment options for rare and chronic diseases that were once considered incurable. While these innovations offer great benefits for patients, they also present significant financial challenges to health care systems. In 2020, European Union countries spent € 1.07 billion on health care. Equivalent to 8.0 % of their gross domestic product, up from 5.9% in 1995.(1) Among others, these increasing healthcare expenditures are driven by the emergence of new and often expensive treatment options.(2) Policymakers face the challenge of deciding which innovative treatments should be made accessible to patients while ensuring the financial sustainability of healthcare systems. Various new payment schemes have been proposed to address these concerns by linking reimbursement to treatment outcomes.(3) We will collectively refer to these schemes as risk-sharing agreements (RSAs). This report explores RSAs as a tool to manage both costs and uncertainties regarding the efficacy of new and innovative therapies. After a thorough review of the existing literature, we selected gene therapy for Haemophilia B as a case study to simulate the effects of such agreements.

Specifically, for life-long and chronic diseases such as Haemophilia B, these therapies offer relief from the substantial burden on patients and the high costs associated with the previous standard of care.(4) Haemophilia B is a hereditary disorder characterized by a deficiency in the blood coagulation factor IX (FIX).(5) Depending on the severity of FIX deficiency, patients may experience spontaneous and persistent bleeding, particularly in the joints, leading to inflammation and irreversible damage over time.(5) People with mild to moderate FIX deficiency (between 6 - 49 % and 1 – 5 % of the normal FIX level respectively) can treat bleeds with on-demand FIX replacement therapy in case of injuries or invasive medical procedures. Those with severe haemophilia (< 1 % FIX level), on the other hand, require life-long prophylactic FIX replacement therapy several times per week.(6) Gene therapies such as Hemgenix (Etranacogene dezaparvovec) aim to enable the body to independently and sustainably increase FIX levels with just a single-dose treatment. Clinical trials of Hemgenix have demonstrated the potential to elevate FIX levels and significantly reduce bleeding episodes.(7)

However, concerns remain about the adequacy of evidence, particularly regarding long-term and real-world effectiveness of such therapies.(4) These concerns are compounded by the fact that gene therapies are often among the most expensive drugs globally. Stakeholders in the health care sectors have questioned the financial sustainability of covering such expensive treatments, given the uncertainties surrounding their real-world performance.(8) While RSAs have been used to bridge the gap between high costs and uncertainty for some time, publicly available information on their performance and feasibility remains scarce due to confidentiality agreements between stakeholders.(9)

1.2. WP6 and progress report

WP6 of the HI-PRIX project aims to examine the impact of RSAs on costs for manufacturers and payers under different sources of uncertainty and how these agreements influence long-term competition in health technology markets. The objectives are to propose a scientific model to simulate the impact of innovative payment schemes on the pharmaceutical market (O6.1), to obtain results from the simulation using one specific case study (O6.2), and to derive implications on long-term competition in health technology markets (O6.3). Based on the analysis conducted in task 6.1 of the WP partners selected Haemophilia B gene therapy (Hemgenix). Criteria for the case study selection were high annual therapy costs of the disease, the high cost of the therapy itself, published efficacy data, remaining uncertainty about the efficacy and lack of competition in the market. This report describes the results of the simulation performed as part of task 6.2 and the milestone M11 of WP6.

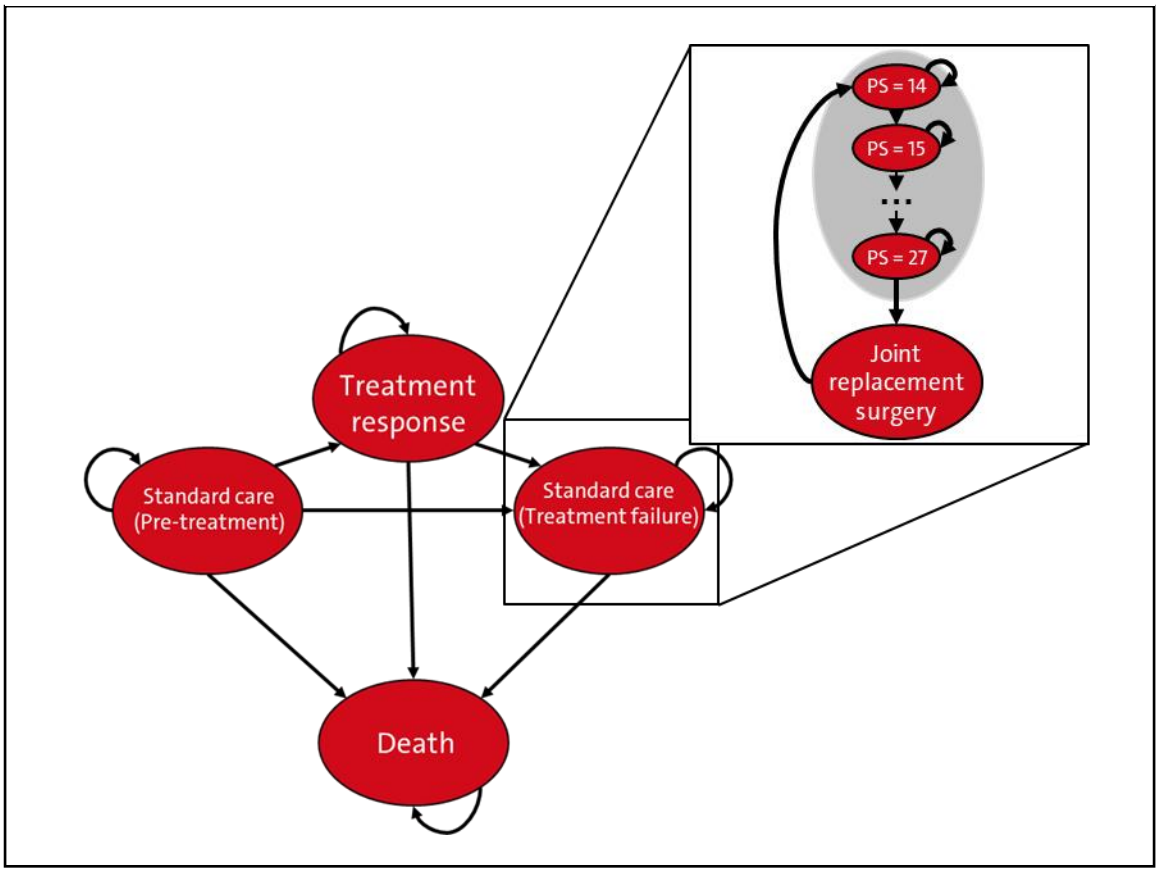
2. Data & Methods

2.1. Model

To simulate the treatment pathway for patients with Haemophilia B, we developed a microsimulation state-transition model as seen in Figure 1. The model consists of the four health states that patients could be in when being treated with gene therapy for haemophilia B. These are, "Standard care (Pre-Treatment)", "Treatment Response", "Standard Care (Treatment failure)", and "Death". Apart from "Death", each state also tracks the progression of joint arthropathy, meaning the damage of joints over time due to repeated bleeding, adapted from Tice et al. (10), using the so-called Pettersson Score.(11) Repeated joint bleeds damage the joint over time until replacement surgery is required, resetting the Pettersson Score. We simulated

100,000 male individuals, as Haemophilia B predominantly affects males,(6) aged 18 years with severe to moderately severe Haemophilia B (0 – 2 % of normal FIX level) over 100 years. The cycle length of the model is six months. In the "Standard care (Pre-Treatment)" and "Standard care (Treatment failure)" states, patients receive prophylactic FIX replacement therapy, whereas patients in the "Treatment response" state no longer require prophylactic treatment until gene therapy failure occurs. For the purpose of this study, treatment failure is defined as having a FIX level below 5 % which is the recommended threshold to initiate prophylactic FIX replacement therapy.(6, 12) Costs and utilities are calculated at the individual level based on expected resource use and averaged across the population. This model adopts the perspective of the health care systems from Germany, the UK, and Italy, using publicly available data and published literature to estimate costs. For Germany and Italy, the annual discount rate for both costs and utility is 3 % (13, 14), while for the UK it is 3.5 %.(15) The model was developed on the basis of the tutorial by Krijkamp et al. (16) and simulations were conducted using R 4.4.1.(17)

Figure 1: State-transition microsimulation model



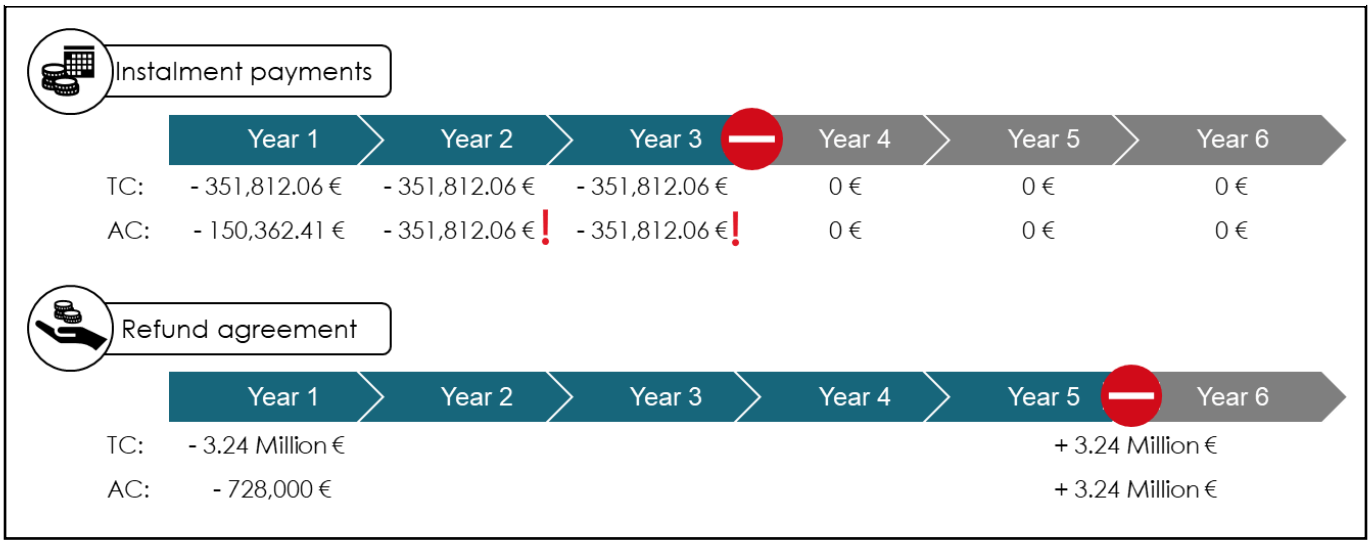
Source: Own illustration based on Tice et al. (2022); Notes: PS = Pettersson Score

2.2. Risk-Sharing Agreements

In this model, RSAs are implemented as instalment agreements (IAs) and refund agreements (RAs). An IA divides the initial payment for the gene therapy into multiple smaller annual payments, the size of which depend on the timeframe of the agreement. Additionally, agreements were varied by the duration of manufacturer liability for the product's performance, which may be shorter than the actual IA timeframe. If treatment failure occurs and manufacturer liability has not expired, the annual payments cease. We evaluated IAs with timeframes of 5, 10, 15 and 20 years, with liability duration of 20 %, 40 %, 60 %, 80 % and 100 % of the timeframe. For RAs, the initial price of the gene therapy is paid in full, but the manufacturers are liable for their product's performance for the duration of the agreement. If treatment failure occurs within this timeframe, the manufacturer refunds the payer. We evaluated RAs with durations of 1, 5, 10, 15, and 20 years and refund percentages of 25 %, 50 %, 75 % and 100 %.

Additionally, we identified a potential confounder for RSAs in Germany. Sickness funds in Germany collectively pay into a risk pool, which in return covers the treatment costs of insured individuals with high annual therapy costs. The risk pool was initially established between 2002 and 2008 and later reintroduced in 2021 to cover the cost of high-cost patients,(18) which is especially important for smaller sickness funds. Currently, 80 % of annual therapy costs above the threshold of 100,000 € are compensated by this risk pool. Figure 2 visualizes the interaction between the risk pool and RSAs. Importantly, only costs directly related to the treatment in the

Figure 2: Exemplary risk-sharing agreements and its interaction with a risk pool



Source: Own illustration; Notes: TC = Total costs, AC = Actual costs

respective calendar year is considered by the risk pool. Accordingly, refund payments are only considered in the first year of treatment but not in subsequent years. Furthermore, refunds from RAs are paid out in full to the sickness fund, regardless of how much they paid for the treatment and without any obligation to repay into the risk pool, therefore creating incentives to create profit from RAs.

3. Results

3.1. Base Case

When comparing the standard prophylaxis care with Hemgenix, we found that the gene therapy reduces lifetime costs of individuals with severe to moderately severe Haemophilia B in our models for Germany, the UK and Italy. In Germany, the lifetime costs were reduced by €353,000; in the UK, by £1,040,000; and in Italy, by €1,660,000. Across the estimated eligible populations, these savings amount to €104,140,000 in Germany, £263,630,000 in the UK, and €400,510,000 in Italy. In our model, the treatment effect of Hemgenix lasts, on average, 15.5 years before treatment failure occurs.

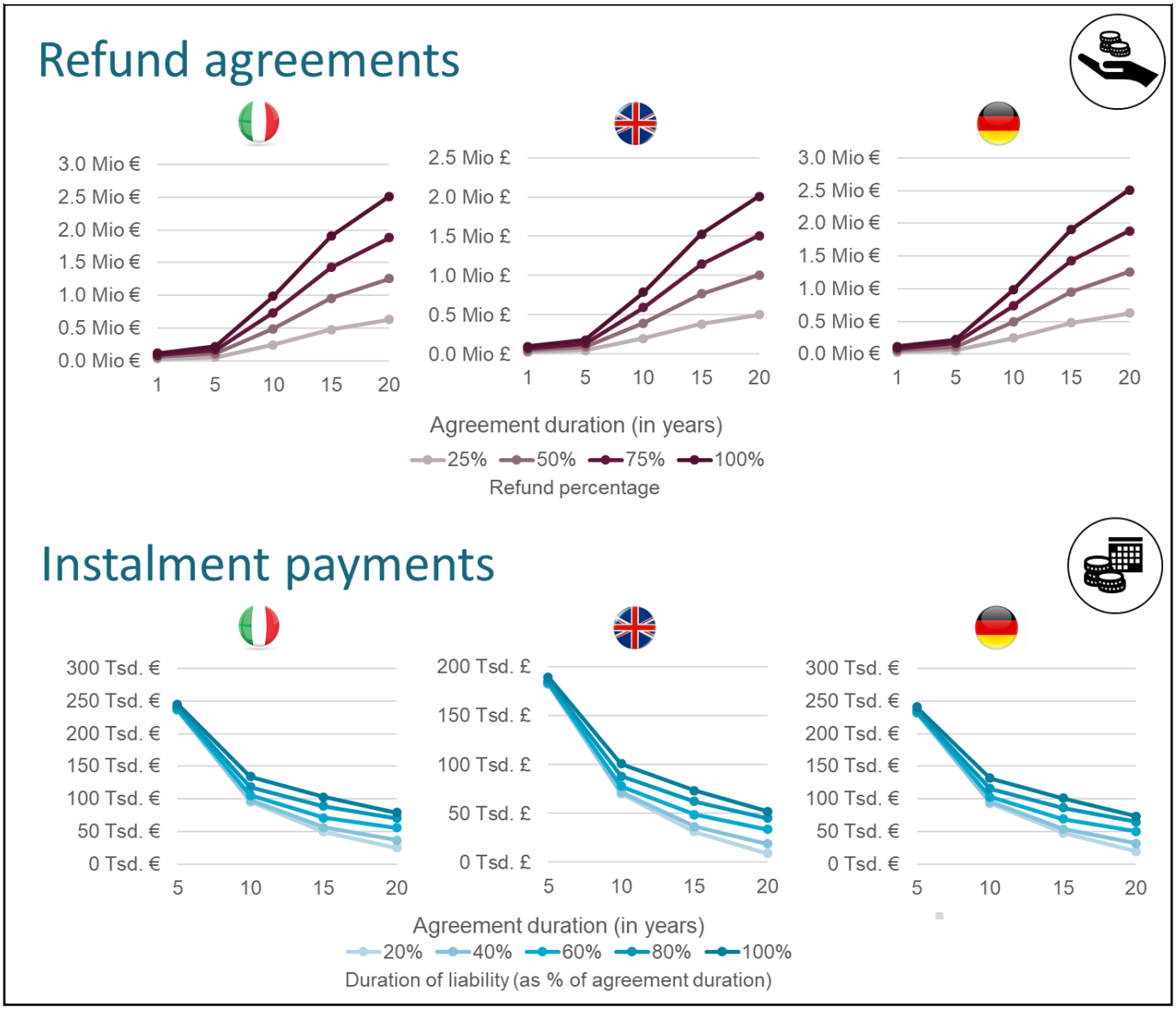
To evaluate RSAs, we compared the savings for payers between treating a patient with gene therapy with and without an RSA. The results are shown in Figure 3. Generally, we found that savings from both IA and RA are similar in Germany, the UK and Italy. For RAs, cost savings increase with the duration of the agreements. While savings are initially small, they steadily increase over time, reaching an inflection point after approximately 15 years, which is the average time until treatment failure. Additional savings achieved from longer agreement durations are smaller but positive.

Savings are also influenced by the refund share, with smaller shares flattening the potential savings curve and differences in savings increasing over time. Essentially, the longer the agreement duration and the higher the refund percentage, the closer the savings align with the original costs of the drug. Conversely, unlike RAs, savings from IAs diminish as their duration increases. Initially, savings are substantial, surpassing those from RAs, but they diminish over time—first rapidly, then more gradually. The duration of liability has minimal impact on savings in shorter agreements, although it becomes more significant as the overall agreement duration increases. Despite the reduction in savings over time, they remain positive throughout the entire agreement

period.

Overall, cost savings for the payer per individual over a lifetime from IAs range from €20,000 to €240,000 in Germany, from £9,000 to £190,000 in the UK, and €25,000 to €250,000 in Italy. For RAs, they range from €30,000 to €2,510,000 in Germany, from £24,000 to £2,010,000 in the UK, and from €30,000 to €2,510,000 in Italy. Across the estimated eligible patient populations, savings range from €5.9 million to €71.1 million in Germany, from £2.3 million to £48.1 million in the UK, and from €6.1 million to €59.3 million for IAs. For RAs, savings range from €8.6 million to €741.3 million in Germany, from £6.1 million to £508.5 million in the UK, and from €7 million to €608.4 million in Italy.

Figure 3: Simulation results of cost savings for payers

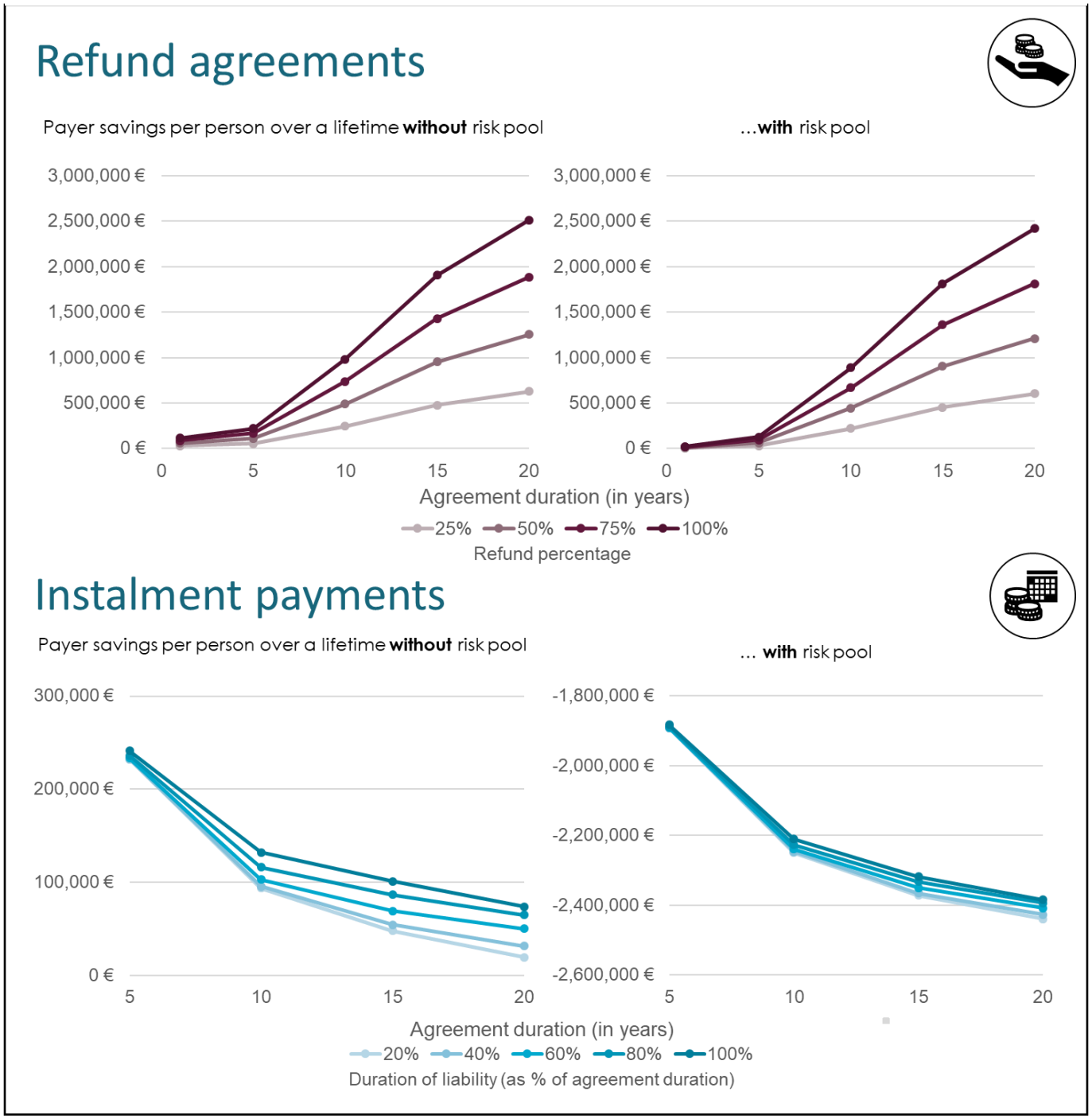


Source: Own illustration

3.2. Risk pool in Germany

The risk pool in Germany alters the cost-savings potential of RSAs, as seen in Figure 4. For RAs, savings remain comparable, although the absolute value of savings is reduced since the risk pool decreases overall costs. However, the savings curves remain similar relative to the total costs with

Figure 4: Simulation results for Germany with and without Risk Pool



Source: Own illustration

and without the risk pool. In contrast, savings from IAs change significantly. Instead of reducing costs, IAs increase costs for the sickness funds if a risk pool is present. Since instalment payments decrease with longer agreement duration and only the first payment is considered by the risk pool, fewer costs are covered by the risk pool, leaving the sickness fund to cover the remaining costs. Consequently, instalment agreements increase costs for sickness funds in the German healthcare system.

4. Discussion

The simulation results indicate that both IAs and RAs effectively reduce costs associated with Hemophilia B gene therapy from a payer perspective in the UK and Italy, as well as in Germany under certain conditions. However, the results suggest that the two RSAs may serve different purposes rather than being equivalent options. RAs appear to require longer agreement durations to achieve significant cost reductions, which is consistent with findings from a previous study on modeled RAs in Finland.(19) As the agreement durations extend, the likelihood of treatment failure increases, leading to an increase in the average refund to payers, which gradually approaches the initial payment for the therapy. In contrast, IAs yield greater savings with shorter agreement durations, while offering minimal savings over longer periods. Given that annual payments are fixed and money is discounted over time, the value of savings further in the future is reduced. Accordingly, while IAs may be financially more sustainable especially for smaller payers, they offer fewer savings overall for any long agreement compared to RAs.

Furthermore, this highlights the different incentives for payers and manufacturer in negotiating RSAs for innovative therapies. Payers would likely prefer RAs with longer durations for higher savings, whereas manufacturers likely favour IAs due to reduced costs and the absence of long-term financial obligations. Additionally, it is essential to consider negotiation and administration costs to assess the viability of RSAs. Although public information on these costs is limited, they are generally expected to be high.(20) Especially RSAs with lower savings, such as short-term RAs and long-term IAs, it is necessary to examine whether they cover these costs and still offer savings to payers.

In the case of Germany, there is currently no trade-off between RAs and IAs for sickness funds to consider. With the risk pool in its current form, there is no incentive for sickness funds to engage in IAs. Since the annual payments restrict how much of the costs can be compensated by the risk

pool, high initial payments with RAs or without any RSA are always preferable as they allow more costs to be diverted to the risk pool. The compensation of high annual therapy costs by the risk pool incentivizes the sickness funds to pursue larger initial payments. In 2022, the German Federal Office for Social Security published a report on the risk pool's interaction with pay-for-performance agreements and came to a similar conclusion, highlighting that the vast majority of RSAs in Germany are RAs.(18)

Considering the potential impact of RSAs on long-term competition in health technology markets, there is a unique relationship between single-use gene therapies and chronic diseases such as Haemophilia. Currently, it is uncertain whether patients can receive gene therapies more than once, regardless of treatment outcomes, due to the body's immune response to the therapy.(4) Therefore, once a gene therapy enters the market for a specific indication, the number of eligible patients for new gene therapies is reduced, and manufacturers must rely on patients who are not yet willing or able to receive gene therapy, or future new patients. RSAs with favorable terms for payers will likely increase the adoption of the first-mover, further limiting profits for any future gene therapies. Depending on the remaining market size and the cost of current and future gene therapies, several scenarios are possible for long-term competition. For example, competition may be stifled as incentives for developing new gene therapies for a specific indication decrease once an RSA for a gene therapy is implemented. On the other hand, incentives to develop a gene therapy that circumvents the immunity response may increase if the first mover underperforms, prices are high and existing RSAs simplify entering the market. New therapies could be aiming to offer an alternative treatment option to patients who initially experienced treatment failure while also targeting the rest of the market.

4.1. Policy implications

The simulation results show that savings for payers and therefore costs for the manufacturers vary greatly depending on uncertain parameters such as the FIX durability, as well as negotiated ones such as the agreement duration, definitions of treatment failure, and, most importantly, regulatory frameworks. This underscores the need for continuous re-evaluation of agreement terms and newly generated data to assess whether RSAs function as intended. Specifically, if policymakers set incentives to promote specific RSAs, they need to consider whether such RSAs are genuinely preferable to stakeholders and not disincentivized by regulatory frameworks such as the risk pool in Germany. Furthermore, the risk pool in Germany requires amendments to trace

reimbursements from RSAs to recover such payments from sickness funds. Additionally, reducing disincentives for using IAs could be achieved, for example, by ensuring that future annual instalment payments effectively count within the risk pool.(18) Lastly, stakeholders should carefully consider which gene therapy should be promoted through RSAs, as this treatment may be the only opportunity for patients to receive a potential cure. Such decisions should not be solely guided by cost savings from RSAs, which generally increase with treatment failure.

5. Conclusion

In conclusion, this report presents the results from the simulation of the impact of risk-sharing agreements on costs for manufacturers and society, fulfilling objectives O6.1 and O6.2 of WP6. The report outlines the outcomes of tasks 6.1 and 6.2 and offers first intuitions for task 6.3. All tasks cumulating in this milestone were performed in coordination with all members of the HI-PRIX consortium involved in WP6.

These results will inform the next steps in WP6. To contextualize the simulation results and derive implications for long-term competition in the pharmaceutical market, UHAM and OHE are developing a theoretical model. The simulation results, combined with explorative interviews conducted in the start of Task 6.1 by UHAM and interviews conducted by OHE in the context of WP1, are being used to develop and continuously adapt the model. The initial insights from the model have refined and informed interview guidelines adapted from the previous interviews conducted by UHAM and OH. These guidelines will be used in further interviews to supplement and complete the data gathered so far, providing information on the current use, regulatory measures, levers and barriers to widespread implementation, and impact on long-term competition of innovative payment schemes. Interviews are planned with stakeholders in Italy, the UK, Germany, Spain and France, and a list of relevant contacts has been generated by OHE and UHAM.

Finally, the simulation in this report will be further expanded upon and we aim to publish the results in more detail in a scientific journal.

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