Innovative solutions for paradigm changing new therapies

Policy report
based on multi-stakeholder
round tables

Innovative funding solutions for paradigm changing advanced therapy medicinal products (ATMP) in Belgium

Multi-stakeholder consensus on gene therapy funding solutions

Policy report

Ingrid Maes, Hafida Boufraioua, Walter Van Dyck, Lies Schoonaert

November 2019

Innovative solutions for paradigm changing new therapies – Policy report based on multi-stakeholder round tables

AUTHORS

Ingrid Maes (Inovigate), Hafida Boufraioua (Inovigate), Walter Van Dyck (Vlerick Business School), Lies Schoonaert (Vlerick Business School)

EXTERNAL EXPERTS PRESENTING AT THE MULTI-STAKEHOLDER ROUND TABLES

Prof. Dr. Thierry Vandendriesssche (VUB, KUL)
Prof. Dr. Cédric Hermans (UCL, Cliniques universitaires Saint-Luc)
Dhr. Patrick De Smet (vzw AHVH)

EXTERNAL EXPERT CONTRIBUTORS IN MULTI-STAKEHOLDER ROUND TABLES:

Francis Arickx (NIHDI), Claire Beuneu (FAGG), Prof. dr. Jean-Jacques Cassiman (Kom op tegen Kanker), Prof. Barbara Claus (UZ Gent), Kathleen Coppin (AHVH), Karel Coudré (AXA), Ann D'Haese (Inovigate), Kristel De Gauquier (Pharma.be), Prof. dr. Jacques De Grève (UZ Brussel), Patrick De Smet (vzw AHVH), Prof. Dr. Marc Dooms (UZ Leuven), Larysa Engelen (AXA), Prof. Dr. Cédric Hermans (UCL, Cliniques universitaires Saint-Luc), Prof. Isabelle Huys (KUL), Diane Kleinermans (Cabinet of Public Health), Tim Leest (FAGG), Jeroen Luyten (KUL), Evelyn Macken (Onafhankelijke Ziekenfondsen), Greet Musch (FAGG), Leo Neels (Itinera), Prof. dr. Kathelijne Peerlinck (UZ Leuven), Ward Rommel (Kom op tegen Kanker), Eva Schoeters (RaDiOrg), Prof. Dr. Thierry Vandendriesssche (VUB, KUL), Stefaan Van der Spiegel (European Commission – DG Health and Food Safety), Ellen Vanhaeren (Cabinet of Public Health), Chris Van Hul (Onafhankelijke Ziekenfondsen), Eline Van Overbeeke (KUL), Pascal Verdonck (AZ Maria Middelares), Prof. David Veredas (Vlerick), Bart Vermeulen (Cabinet of Public Health)

OBSERVING PARTICIPANTS OF THE MULTI-STAKEHOLDER ROUND TABLES

Rudy De Cock (Pfizer), Caroline De Meulder (Inovigate), Roman Erin (Vlerick), Laurenz Govaerts (Vlerick), Anne Hendrickx (Socialistische Mutualiteiten), Dimitrios Kolokas (Vlerick), Sissel Michelsen (KUL), Flore Pierloot (KUL), Micheline Vrancken (Pfizer)

COMMISSIONED BY

Jo De Cock (NIHDI)

SUPPORTED BY

Pfizer

PUBLICATION DATE:

September 2019

HOW TO REFER TO THIS DOCUMENT?

Maes I, Boufraioua H, Schoonaert L., Van Dyck W Innovative solutions for paradigm changing new therapies – Policy report based on multi-stakeholder round tables. 2019

Table of content

1. Preface

Advanced therapy medicinal products (ATMPs) and more specifically, gene therapies, have the potential to offer life-changing solutions for patients with few or no alternative treatments. However, their complexity and relative novelty present challenges to ensuring these therapies reach patients in need.

ATMPs differentiate from standard pharmaceuticals by:

- Their complex highly specialized manufacturing processes.
- One time or only few time treatment (no adherence challenges).
- Long lasting positive impact on Health and even curative potential.
- High upfront one or short-term cost.

ATMPs' potentially transformative effects on the health outcomes and treatment requirements of many serious diseases could generate significant cost savings for health systems e.g. fewer hospitalizations, co-morbidities and associated treatment costs.

The European Medicines Agency established specific EU marketing authorization pathways and expert committees (CAT) to ensure appropriate assessment and expedited approval of this new generation of medicines (ATMPs).There remain however several barriers that may hinder ATMPs from reaching patients in need in a timely manner.

This report provides an overview of the current challenges and proposals for future funding solutions for ATMPs and more specifically gene-therapies in Belgium. It also identifies hurdles to adoption and implementation and makes policy recommendations to address those challenges. Application of the preferred consensus funding solutions have been applied to a practical case (haemophilia A and B), to illustrate the issues and to test the preferred solutions.

The report brings together the views of the different involved stakeholder groups and the consensus reached over multiple round tables organised during 2018 and 2019. The project was coordinated and managed by Inovigate and Vlerick in collaboration with NIHDI and the Cabinet of the Minister of Health and Social Affairs and supported by Pfizer.

Project process — a comprehensive approach

The report draws on extensive research into the environment for gene therapies in Belgium, including:

- A targeted literature review on topics related to funding and access challenges, funding methods, and innovative payment models.
- Expert interviews.
- Board meetings with the design team (NIHDI, Cabinet De Block, Inovigate and Vlerick, Pfizer (as observer)), held in Brussels in 2018-2019.
- 4 multi-stakeholder round table meetings held in Brussels during 2018-2019, brought together academics, health-care professionals, insurance and health technology specialists, patient and patient associations, authorities and other stakeholders.

2. Executive Summary

2.a Problem statement and ambition of the multi-stakeholder round tables

We are living in an era of progress in human health. Advances in ATMP (Advance Therapy Medicinal Products), like cell and gene therapies address the root cause of disease and are beginning to yield breakthrough treatments for some of the most devastating illnesses. Several of these breakthrough therapies offer potential to cure these illnesses with one single treatment. Gene therapy is a platform-based technology, possibly providing game-changing long-term solutions for unmet medical need. Particularly in some rare, monogenic diseases gene therapies holds promise to deliver one-time, transformative therapies to patients.

ATMPs' extraordinary potential to offer durable, life-changing solutions for patients with few or no therapeutic alternatives is driving their growing share of the biopharma industry's development pipeline. That growth will accelerate as more products approach the market. Cell and gene therapies make up 12% of the pharmaceutical pipeline nowadays with an annual growth rate of 11%. Patient access for these breakthrough therapies present a unique set of challenges for all stakeholders in the healthcare system.

An important challenge is the funding challenge as these therapies cause a peak in the healthcare expenses for benefits that can be observed in the long-term and are uncertain at the time of administration. Therefore, innovative sustainable solutions are needed to avoid delay in access for patients, eligible for such breakthrough treatments with potentially long-term curing impact.

The challenge can be translated into the following three main questions:

1. **How will we make the therapy affordable in Belgium?**
2. **How will we deal with long-term uncertainty of the therapy?**
3. **How does innovation create room in the healthcare budget?**

ARM, the Alliance for Regenerative Medicine, has published a report "Get ready: Recommendations for Timely Access to Advanced Therapy Medicinal Products (ATMPs) in Europe", based on extensive research and stakeholder meetings for ATMPs in Europe, this year. The report provides an overview of the characteristics and benefits of ATMPs, and the current regulatory market and access frameworks in six European countries: France, Germany, Italy, Spain, Sweden, and the United Kingdom. It also identifies hurdles to adoption and makes EU-wide policy recommendations to address those challenges. The report brings together the views of a number of European policy makers and experts, ARM member organizations, and other stakeholder groups.

Also, the Massachusetts Institute of Technology (MIT) in the US recognized the fact that there is an urgent need for new financing and reimbursement models to ensure that the emerging cell- and gene-based therapies remain affordable for payers, while assuring patient access, and sustaining investment in innovation. The MIT Center for Biomedical Innovation launched the Financing and Reimbursement of Cures in the U.S.(FoCUS) project with the objective of further elucidating the challenges and financial impact created by durable/potentially curative therapies and providing implementable "precision" financial models to manage the cost burden on the US healthcare system. Numerous healthcare stakeholders, including public and private payers, providers, patient advocates, clinicians, regulators, developers and financiers, are currently involved with the MIT NEWDIGS Initiative FoCUS project to better understand cell and gene therapy characteristics and stakeholder considerations (MIT NEWDIGS FoCUS, 2019).

The ambition of pro-active multi-stakeholder round table (RT) meetings in Belgium was, to build constructive multi-stakeholder consensus on an optimal solution blueprint for gene therapies. The optimal solution should meet the critical success factors and addresses the short-term budgetary challenge for long-term benefits that are uncertain at the time of administration of the gene therapy. The critical success factors essential to assess and select preferred "precision" funding solutions in the Belgian healthcare system were defined based on multi-stakeholder consensus and are the following: feasibility within the Belgian context, financial attractiveness, equity impact and fairness and traceability.

This project does not address how to value these therapies or set their prices but rather seeks to create precision financing solutions for durable/potentially curative therapies with large, upfront costs whose benefits accrue over time.

Key conclusions on the achieved multi-stakeholder consensus on gene therapy funding solutions are highlighted below.

2.b Consensus for new innovative sustainable funding and reimbursement solutions

Based on international literature, a longlist of solutions has been investigated. The potential solutions based on private insurance models have not been further explored because they are not in line with the fundamental equity and solidarity principles of our Belgian social security system. Based on the critical success factors defined above, three preferred building blocks have been identified to build new innovative funding solutions.

The three preferred building blocks for funding ATMPs and more specifically gene therapies, selected in consensus by the different Belgian stakeholders during the multi-stakeholder round tables, answer the key affordability challenges. The following three preferred building blocks have been voted to define the preferred innovative reimbursement solutions:

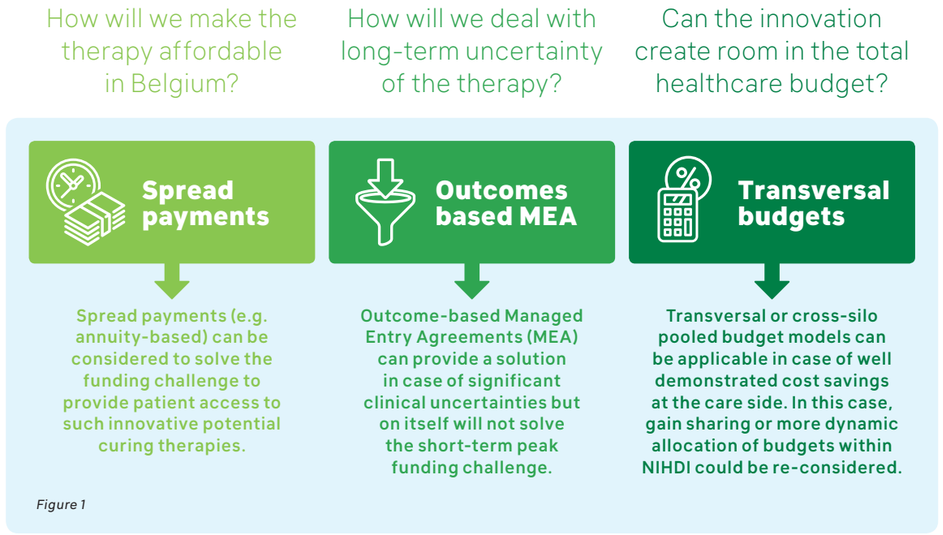

Figure 1

These 3 building blocks are complementary and will often have to be combined, depending on the type of gene therapy.

While above preferred solutions have emerged, each must be tailored to the specific context such as the target population, the nature of clinical benefit, the durability of effect and the delivery setting. To define the best solution or combination of solutions, the implementation conditions, criteria and thresholds of the 3 preferred building blocks, should be considered:

1 Spread payments (e.g. annuity-based)

Spread payments are a solution to bridge the gap between the willingness to pay and the capacity to pay.

Spread payments are only an option in case a short-term peak and affordability challenge needs to be addressed. This solution enables the access to immediate health benefit for society in the short-term and spread payment over time. In case the innovator would request financial compensations for annuity based spread payment, transparency will be required from the innovator concerning the cost of financing e.g. by clarifying the difference in price between the options without and with spread payment.

In order to implement the spread payment (e.g. annuity-based) solutions, compliance with the European Accounting Rules (ESA) and the NIHDI accounting rules is required. Potential solutions are being formulated in order to successfully implement the suggested solutions in the Belgian healthcare context.

2 Outcome-based Managed Entry Agreement

At this moment most initial MEA are mainly based on the clinical value of the new medicine demonstrated during the clinical trials (cfr. validated clinical endpoints in Randomized Controlled Trials (RCTs)). In case of important clinical uncertainties more complex outcome-based MEA could be considered. Clinical outcomes in real world /daily practices to be taken into account should also be objective, reliable and verifiable. In addition, objective, reliable and verifiable Patient QoL outcomes could also be considered. The outcome criteria should be defined and agreed upfront, per disease and in multi-stakeholder consensus (e.g. CTG). Electronic registries, linked to the electronic patient record, will be needed to register the outcomes in daily practice. Average aggregated population-based RWE is preferred (over variable individual outcome-based evidence). Such outcome-based MEA can reduce long-term clinical outcome uncertainties and help answer the question: How long will the treatment work for the patient?

Outcome-based MEA on itself however cannot solve the short-term peak funding challenge. To solve the funding challenge a combination of the outcome-based reimbursement solution with a spread payment solution will be needed. Outcome-based solution in combination with spread payments can reduce the long-term therapeutic risk profile of the spread payment.

3 Transversal or pooled budgets

Cost savings will need to be demonstrated (e.g. via cost of illness studies) to justify gain sharing or more dynamic allocation of healthcare budgets.

The combination of outcome-based and spread payments answers the "real value for money" requirement for gene therapies.

To put the above-mentioned conditions and criteria, to select the appropriate solution or combination of solutions per gene therapy, in practice, a decision tree to support the decision process and select the optimal solution(s), has been developed. The decision tree includes the three preferred building blocks with their eligibility criteria in a logical and practical decision process and enables the selection of the optimal (combination) solution for each gene therapy case. Moreover, a proposal has been developed to integrate this decision tree into the current reimbursement procedure.

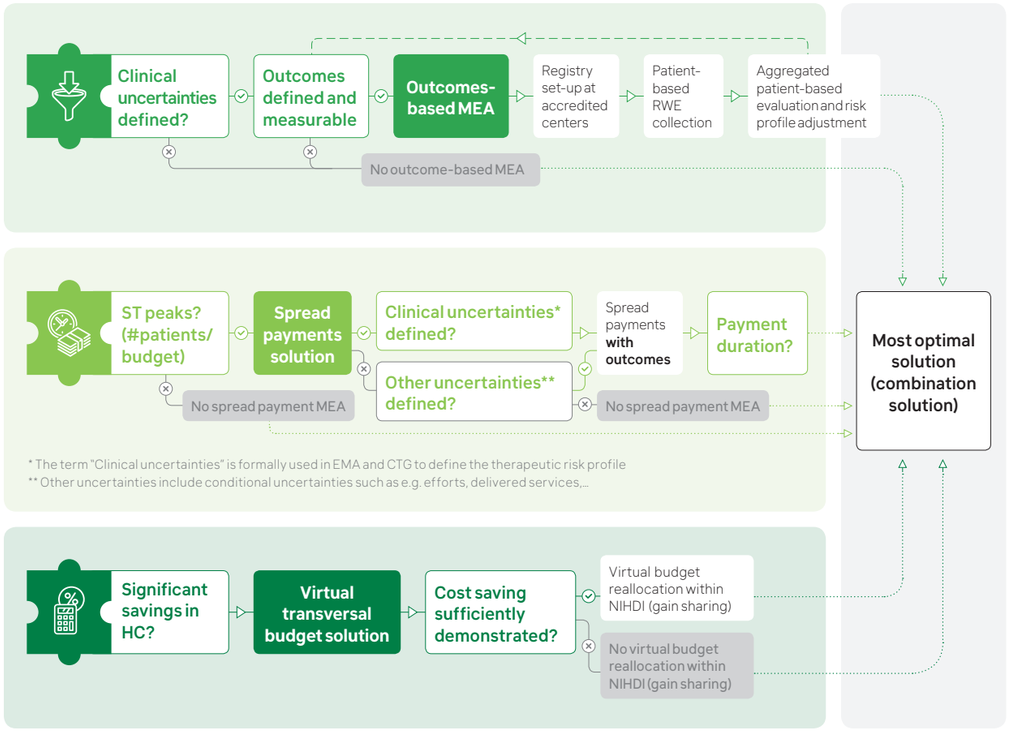

Figure 2

Also, the horizon scanning project is expected to facilitate early dialogue between authorities and innovators to identify proactively gene therapies eligible for above possible solutions.

A practical case, forthcoming gene therapies for haemophilia A and B, is chosen to illustrate the affordability and budget challenge, and to test the selected and preferred funding solutions (cfr section 11 Application to a practical case).

3. Recommendations

Belgian stakeholder representatives / experts in Belgium were consulted on how to best prepare for funding ATMPs (Advance Therapy Medicinal Products), and more specifically gene-therapies in a reasonable manner.

The experts recommended new payment models like spread payments (e.g. annuity-based), outcome-based Managed Entry Agreements (MEA) and transversal or cross-silo pooled budget model.

The group agreed on better adapted funding models, including greater use of real-world evidence (RWE). The group also recognized the significant challenges in implementing such payment models, adoption of new practices, evidence collection, and compliance with national and EU accounting rules. They recommended further development of the infrastructure required to collect and use high-quality real-world evidence, and expanded opportunities for early dialogue between pharma and payers via horizon scanning.

The initiative hopes that continued dialogue and debate, supportive policy decisions, and a willingness among all stakeholders to create a fair and equitable environment for patient access to gene-therapies will help overcome existing hurdles.

RECOMMENDATION 1

Leverage international horizon scanning project and facilitate early dialogue

Continuing the constructive multi-stakeholder dialogue with all involved stakeholders in Belgium. Leveraging international horizon scanning to facilitate early dialogue between authorities and innovators. Considering the specific needs of gene-therapies and the patient populations they are targeting; early dialog supports:

- Proactive identification of the gene therapies eligible for any of the preferred innovative funding solutions.
- Alignment on the optimal solution(s) for any eligible gene therapy tailored to the specific type of gene therapy (such as the target population, the nature of clinical benefit, the durability of effect, the delivery setting).
- Agreement on evidence (patient outcomes and RWE data) and relevant outcome endpoints.

This would offer developers early insight on ways to address product specific uncertainties and mitigation of them.

RECOMMENDATION 2

Favor application of new funding arrangements to new gene-therapies

New payment models are needed to ensure timely patient access to innovation while preserving sustainability of healthcare system. Without the adoption of these new models, some transformative therapies may not reach patients

An optimal solution, that meets the critical success factors and addresses the short-term budgetary challenge and uncertain long-term benefits, should be based on:

- spread payments (e.g. annuity-based),
- outcome-based Managed Entry Agreements (MEA),
- transversal or cross-silo pooled budget model.

RECOMMENDATION 3

Develop initiatives to create adoption of new funding arrangements to new gene-therapies

- There is unlikely to be a single route for all gene therapies, as this is a broad, growing, and highly heterogenous class. Therefore, it is important that new funding approaches for accelerating access continue to be tested and refined, and, where possible, lessons learned are shared to support future progress.
- The use of a decision tree could facilitate the selection of the optimal reimbursement solution for any eligible game-changing therapy tailored to the specific context such as: the target population, the nature of clinical benefit, the durability of effect and the delivery setting.
- Encourage pilot projects and explore possible cases and best practices to support adoption.
- For example, justification of more dynamic transversal budgeting and/or gain sharing by demonstration of potential cost savings due to high burden of disease/cost of illness.

RECOMMENDATION 4

Establish evidence collection (patient outcomes and RWE data) infrastructure and policies to facilitate electronic evidence capture and use

Real-World Evidence (RWE) development is instrumental in addressing uncertainties on long-term effect, safety, health-related quality of life, and use of healthcare resources. There is a need to develop RWE infrastructure, a common framework and procedures at Belgian (and also European level) to support long-term evidence generation and to enhance the quality of evidence collected specifically for gene-therapies.

- To achieve this a well-functioning health data ecosystem and IT infrastructure (e.g. Finland, Denmark, Estonia) as well as a proper guidance and governance will be needed to facilitate collection and access to Belgian patient outcomes and RWE data which are needed to enable the implementation of outcome-based conditional reimbursement.
- As the administrative burden to register patient outcome data in daily practice, remains a hurdle for healthcare providers, incentives for HCPs, hospital centres and/or patients need to be considered (e.g. via reimbursement criteria, NIHDI Conventions with expertise centres).
- Policies to clarify which type of data can be captured and shared anonymously in compliance with GDPR and guidance (e.g. FAIR) to facilitate capture, sharing, and quality control of patient data, are needed.
- Leverage whenever applicable EMA's request for post-authorization patient real-world outcome data from standardized EU registries (especially for ATMPs and/or Orphans with more limited nr of patients enrolled in the RCT).

RECOMMENDATION 5

Confirm compliance of spread payment-based solutions with NIHDI and EU accounting rules

Confirmation is needed that within Belgian context spread payments are in compliance with the European Accounting Rules (ESA) and the NIHDI accounting rules under below formulated conditions:

- Milestone payment per realised health outcome, translated in a health currency or delivered data package.
- Payment for data services: per delivered data package to the payer per year or as an "early access program" in upfront payment and additional fee, based on performance and realised savings.

Under these conditions the payer does not pay any longer for the breakthrough medicine, but for the long-term health outcome proven in medical practice, as well as for non-expenses related to health care costs that are no longer needed (savings).

4. Background

Paradigm-changing new therapies that will transform future healthcare

Currently we are living in an era of progress in human health. Advanced Therapy Medicinal Products (ATMPs) include cell therapies, gene therapies, and tissue engineered products. These highly complex treatments differ from traditional medicines, both in terms of how they are made and administered and in the type of benefits they may provide. Some gene therapies, for example, address the root cause of disease, offering patients the prospect of a cure after just a single administration. One abnormality or "typing error" in the human genome can have devastating consequences. An individual born with a defective gene can lead to a life-threatening disease. Standard therapies for life-threatening disease are limited and the individual is faced with battling a chronic condition for life.

Advances in ATMPs and more specifically in cell and gene therapies are beginning to yield breakthrough treatments for some of the most devastating illnesses. Several of these breakthrough therapies offer potential to cure these illnesses with one single treatment and gene therapy is a platform-based technology, possibly providing game-changing long-term solutions for different diseases. These transformational therapies are designed to restore the function of a patient's defective gene by introduction of a healthy copy, with the potential to permanently correct the abnormality and cure the patient. Cell and gene therapies leverage the patient's own biology and offer cures for congenital blindness, aggressive forms of paediatric leukaemia and neurological genetic conditions in infants and many more in the near future (CNBC, 2019).

Two different modalities of gene therapy exist:

- Gene editing: fixing "broken genes" by editing the gene directly in situ.
- Gene addition: adding a functioning normal gene in "somatic" cells. As a result, this genetic correction cannot be passed to the children.

Cell and gene therapies already make up 12% of the pharmaceutical pipeline with an annual growth rate of 11% (Berggren R, 2018). The gene therapy pipeline is growing, especially since 2014, with over 700 development programs running in 2018. Oncology and Rare diseases are focus therapy areas accounting for 64% of the pipeline in total (Micklus A, 2018).

While gene therapies' R&D pipeline is growing, affordability and patient access present a unique set of challenges including (Micklus A, 2018):

- Great uncertainty about long-term benefit.
- Defining the value considering multiple stakeholder perspectives.
- Perceived high cost by payers.
- Administrative burden and financial pressure created for HCPs / hospital by payers, requiring demonstrating the medical need and funding request for these therapies.

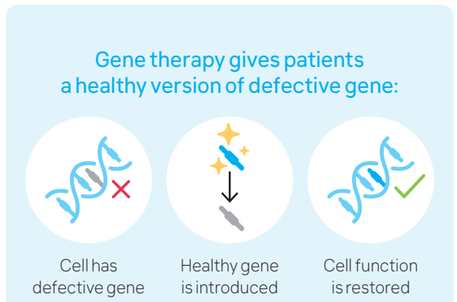

Figure 3 – What is Gene Therapy?
Source: St Jude Children's research Hospital

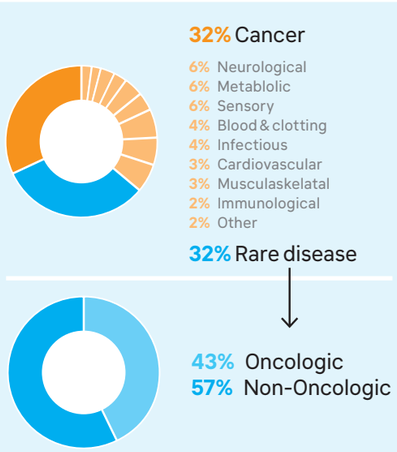

Figure 4 – Percentage of rare disease, percentage of Oncologic / Non-oncologic among rare disease.

4.a The problem we need to solve to finance game-changing gene therapies

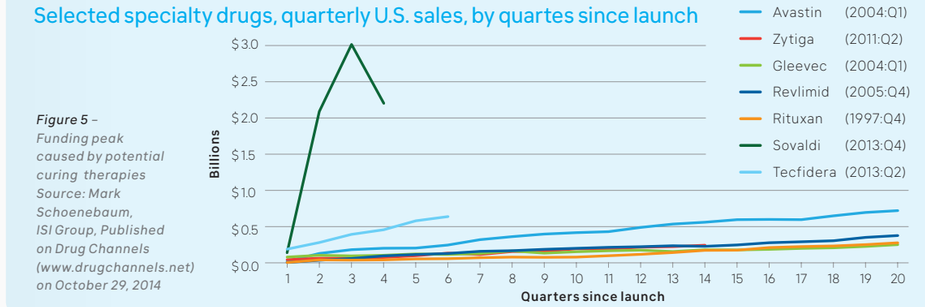

Figure 5 – Funding peak caused by potential curing therapies Source: Mark Schoenebaum, ISI Group, Published on Drug Channels (www.drugchannels.net) on October 29, 2014

Gene therapies bring along challenges for stakeholders in the healthcare system. Our current healthcare system adopts a pay-as-you-go model accustomed to treating symptoms of chronic diseases in the long-term. The system is unprepared for immediate funding (peak challenge) which is needed for benefits in the long-term that are also uncertain at the time of administration. More specifically, traditional approaches to assess the value of medicine are no longer applicable to measure the full benefits of these transformational therapies (CNBC, 2019).

Therefore, the funding challenge needs to be solved to ensure early access for patients to these types of therapies. Innovators and payers face different challenges. The innovator's challenges are related to the development and bringing-to-market of the therapies. Payers have concerns about affordability and long-term uncertainty of outcomes. Even though most therapies are cost-effective, the high upfront costs will threaten the sustainability of the healthcare system. In addition, innovation and affordability need to be balanced. Hence, the ambition of the proactive, constructive multi-stakeholder round tables to explore possible innovative solutions for the funding problem and build multi-stakeholder consensus. Three key questions need to be addressed for these breakthrough therapies:

To answer these three key questions, innovative funding solutions are essential to avoid delay in the access for patients, eligible for gene therapy. However, it should be stressed that these funding solutions are not a way to dismiss or avoid the price justification and price debate with the industry.

1. How will we make the therapy affordable in Belgium?
2. How will we deal with long-term uncertainty of the therapy?
3. Can the innovation create room in the total healthcare budget?

4.b A comprehensive approach to define consensus solutions for gene therapy financing

To answer the above mentioned 3 key questions, a clear process has been followed. The consultation of stakeholders through 4 multi-stakeholder round tables were organized throughout 2018 – 2019.

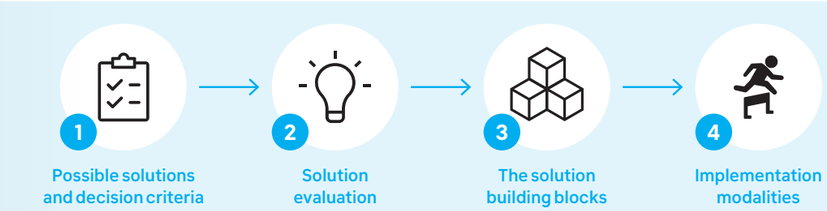

Figure 6 – Clear step-wise process comprising 4 steps

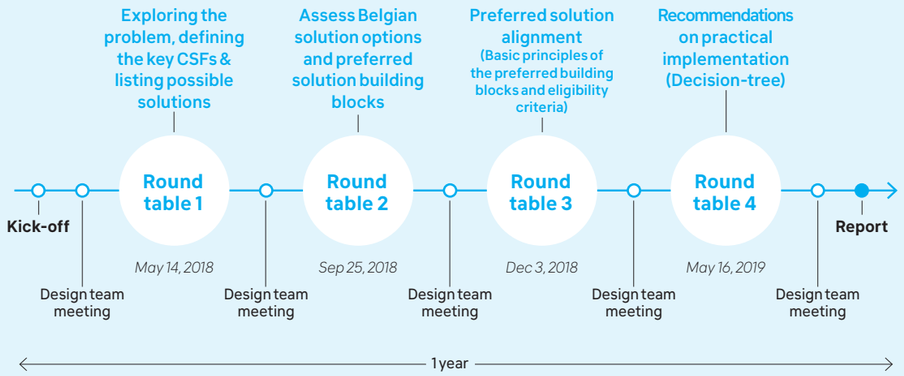

Figure 7 – Process for multi-stakeholder engagement

In step 1, possible solutions and decision criteria were discussed. In step 2, potential solutions were evaluated, and the building blocks were defined in step 3. Finally, the implementation modalities were discussed.

The four round tables were spread over 1 year to enable participating stakeholders to sufficiently reflect on the content and align internally within their stakeholder group. The objective of each round table builds further on the input from the previous round table and focussed on reaching broad alignment and consensus.

Multiple stakeholders from the Belgian healthcare system were represented and have participated in the round tables (see fig.6 below).

Research was performed to prepare each round table including review of the international literature, policy documents, national and international reports. The insights of the research were shared with the stakeholders before and during the round tables to enable informed discussions with the stakeholders. In addition, before each round table, a pre-read was sent to the participants to prepare for the round table, and minutes were made after every round table summarizing the key messages and take-aways.

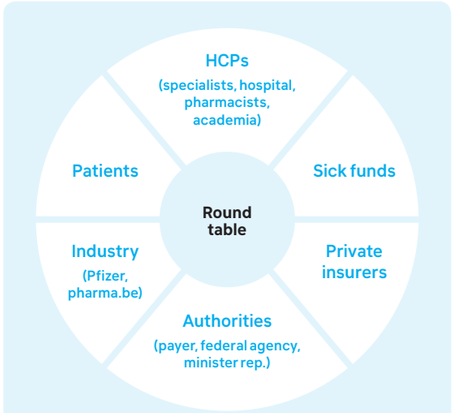

Figure 8 – Belgian healthcare stakeholder representaOon

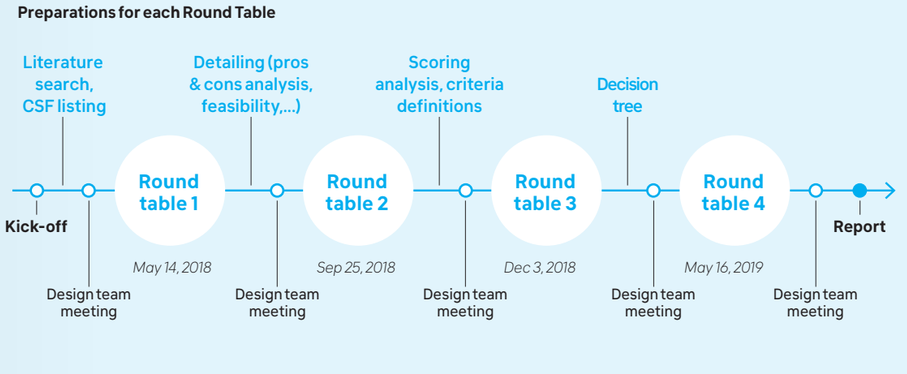

Figure 9 – Preparatory research, pre-reads and minutes were made for each Round Table

Multiple interactions during the round tables enabled in-depth discussions and build consensus. These interaction formats included:

- Break-out sessions to enable in-depth discussion within stakeholder groups. Four break-out groups were made per stakeholder group:
  1. Sick funds (incl. private insurance);
  2. Authorities (incl. Cabinet, NIHDI, FAGG);
  3. Academia and patients (incl. patient associations)
  4. Industry (incl. pharma.be).
- Plenary sessions to enable discussions with all participating stakeholders and support confrontation of viewpoints and consensus building.
- One-on-one discussions between stakeholders (interviews).

During each round table, participants were asked to score the solutions using the solution assessment matrix with predefined and agreed critical success factors (CSF). The solutions were scored on the critical success factors and feasibility in the Belgian context.

Before and after each round table, design team meetings were organized with NIHDI and the Cabinet of Health to analyse and agree on next steps.

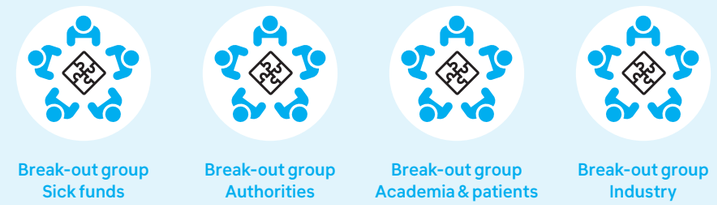

Figure 10 – Four stakeholder break-out groups during the break-out sessions

5. Possible innovative funding solutions, summary of the literature review

Based on the international literature, 10 possible funding solutions for the gene therapies have been identified. The longlist of 10 solutions below has been further explored:

1 Outcome-based Managed Entry Agreements

Pay-for-performance agreement where the funding of the therapy is related to the performance of the product in the real-world environment

2 Spread payments (e.g. annuity-based)

Spread payments to replace the high upfront cost with a stream of payments.

3 Intellectual Property (IP)-based payment

IP-based payment where the manufacturer receives payment in return for full government control over production and distribution (public buy-out) of the therapy.

4a Combined/pooled budgets

Combining NIHDI Pharmaceutical budget and NIHDI Care budget for specific innovative products allowing for bundled payments per episode of care or patient cured depending on saving impact on the cost of illness.

4b National silo fund (pooled budgets outside NIHDI)

NIHDI Pharmaceutical budget puts budgets into a dedicated condition-specific innovation fund based on horizon scanning feedback and depending on healthcare priorities.

5 Patient-based extra insurance

Increase co-payment of the patient for this treatment, which can be covered by additional private health insurance.

6 Hedge fund

A third party hedge fund provides loans to NIHDIand bears the risk if the payer stops repayment in case the patient deceases or the therapy is not effective.

7 Payer reinsurance

NIHDItakes an insurance policy to protect against the ex-post risk (after treatment administration) of exceeding the budget for gene therapies. The insurer pays NIHDIfor the claims incurred by high-cost patients receiving gene therapy.

8a Social impact bonds

Pay for success scheme (e.g. health benefits) where funders (e.g. private insurers) get a return when the public interest initiative achieves positive results (therapy is effective).

8b Manufacturer-based gene bonds

Financial market instrument available to innovative manufacturers to insure them against therapy risk, including against payers halting spread payments while the therapy is not (sufficiently) delivering promised outcome.

The figure on the next page summarizes the longlist of ten different solutions and illustrates the key differences between the solutions, with the blue arrows indicating the financial flows between the involved stakeholders.

Based on the common elements of each of these solutions, 3 categories of solutions can be made:

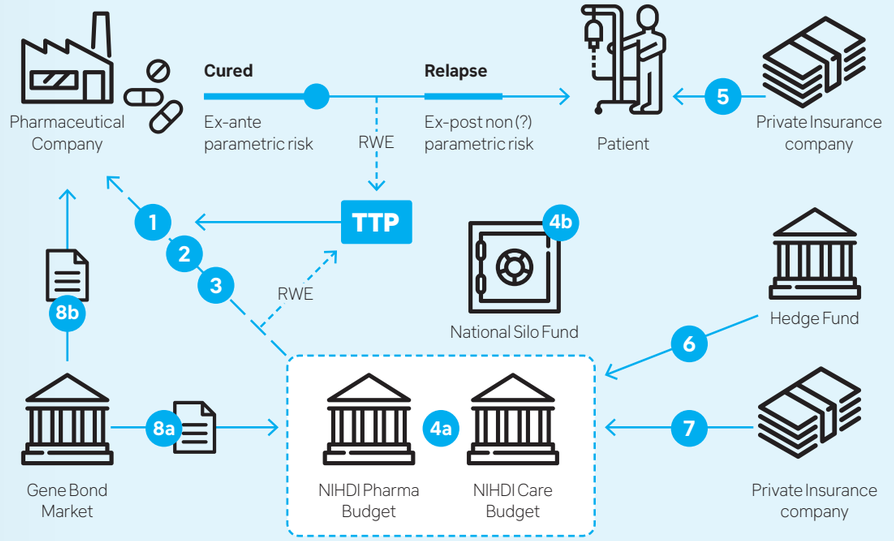

Figure 11 – Overview of funding solutions based on international literature

- *Ex-ante risk (e.g. therapy risk) occurs before the therapy is administered*
- *Ex-post risk (e.g. side-effects) occur after the therapy is administered*
- *TTP: Trusted Third Party*
- *The thick blue arrows indicate the financial flows between the different stakeholders in healthcare.*

1. Outcome-based solutions: Solutions where the collection and evaluation of the patient outcomes is key. This can happen within electronic patient registries in a standardized way by the treating clinicians and collected centrally via a Trusted Third Party (TTP).

2. Transversal / pooling budgets: Solutions where pooling of budgets, more dynamic budget reallocation or gain-sharing between healthcare budgets (e.g. pharmaceutical medicines budget and care budget) are considered.

3. Insurance-based solutions: Solutions including a private insurance player to fund the breakthrough innovations.

The longlist of 10 solutions can be categorized into these three categories as illustrated in Figure 10 below.

The longlist of solutions is also based on 4 building blocks:

- outcome-based payment
- spreading costs
- pooled budgets
- private insurance-based payment.

These building blocks are complementary and allow for combination of possible funding solutions.

	Outcomes-based solutions			Transversal / pooling budgets		Insurance-based solutions				
	1	2	3	4a	4b	5	6	7	8a	8b
1. outcome-based payment	✓	✓	✓							
2. spreading costs	✓	✓	✓			✓	✓	✓	✓	✓
3. pooled budgets				✓	✓					
4. private insurance-based payment					✓	✓	✓	✓	✓	✓

Table 1 – Longlist of solutions and the key building blocks

A comprehensive in-depth analysis and literature study has been performed, to evaluate each solution. The following elements were detailed per solution and shared as an in-depth analysis with the participants:

- Mechanism – how the solution works.
- How it addresses the funding challenge.
- Examples/cases in the world.
- Critical success factor assessment (see chapter 6 for the critical success factors).
- Pros and cons.
- Feasibility of the solution within the current framework.
- Fit of the solution within the Belgian context.
- Risks of the model.
- Relevance – which therapies are most relevant for the specified solution.

6. Preferred success factors to evaluate the innovative funding solutions

The innovative funding solution(s) has to meet the selected critical success factors (CSF). This will ensure that the preferred solution is most appropriate and feasible in the Belgian context and acceptable for all stakeholders. The critical success factors were identified and discussed with the stakeholders in the first round table followed by a scoring to define priorities. They represent the joined ambition of paradigm-changing therapies and what success looks like for the stakeholders.

Based on a priority scoring (Delphi method), the following CSFs were identified in order of priority:

1. **Financial attractiveness:** Solution considers the ROI on health and healthcare spending.
2. **Fairness/equity impact** including patient access; fair and transparent for all stakeholders involved.
3. **Traceability:** Solution with measurable endpoints (e.g. biomarkers) to be able to monitor the evolution of outcomes.
4. **Predictability:** Ability to estimate expenses in healthcare.
5. **Generalizability:** Structural solution that can be used for other breakthrough therapies in other disease areas.
6. **Flexibility:** Solution can be adapted to the most recent state and progress of science and is reversible.
7. **Manageability/burden:** Solution requires a minimum of resources and administrative burden and can be implemented in the long-term.
8. **Transferability to EU:** The extent to which the solution can be implemented in other countries.

The first 3 criteria (financial attractiveness, fairness/equity impact, traceability) received the highest scoring compared to the other 5 criteria. Table 2 provides the detailed scoring of the CSFs by the stakeholders in 2 Delphi-rounds.

The first three CSFs were used consistently during the whole process to evaluate the proposed solutions, with further in-depth analysis, together with additional criteria for the evaluation of the solutions: pros and cons analysis, risk, feasibility, etc.

Table 2 – Aggregated scoring of the critical success factors in Round Table 1

		Round 1		Round 2			
CSF	Definition	Total score	Ranking	Total score	Ranking	Relative weight	Final Ranking
Financial attractiveness	For payer: Solution takes into account the ROI on health and healthcare spending / budget sustainability For manufacturer: Solution takes into account the ROI	38	1	51	1	**35%**	1
Equity impact and fairness	Fair and transparent for society (for patients and all stakeholders)	35	2	37	2	**26%**	2
Traceability	Solution with measurable outcomes and endpoints (e.g. biomarkers) to enable to monitor evolution	29	3	22	3	**15%**	3
Predictability	Ability to estimate expenses in healthcare	16	6	13	4	**9%**	4
Generalizability	Structural solution that can be used for other breakthrough therapies in other disease areas	14	4	9	5	**6%**	5
Flexibility	Solution can be adapted to the most recent state and progress of science + reversibility	12	5	9	5	**6%**	6
Manageability/ burden	Solution requires a minimum of resources and administrative burden and can be implemented in the long term	5	7	2	7	**1%**	7
Transferability to EU	The extent to which the solution can be implemented in other countries	1	8	1	8	**1%**	8

7. Assessment of the funding solutions, summary of the multi-stakeholder discussions

Based on the discussions in the first round table, the fourth building block *"private insurance-based"* was not broadly supported because of its contradiction with the fundamental philosophy of the Belgian social security system, based on solidarity and equity. Local private insurers seem not interested in payer-based solutions because (1) the volume is too small to make the business case sufficiently attractive and (2) defining the risk index will be challenging, because no historical data is available. Therefore Solutions 5 to 8B have been withheld from further discussions and assessment. However, private insurers might be more inclined towards international innovator-based solution for Solution 8B, which would allow for an international risk modelling.

In addition, there was no broad support for Solution 3 (IP based payment), because it would not solve the affordability problem NIHDI would face and therefore will not facilitate patient access to the innovative therapies.

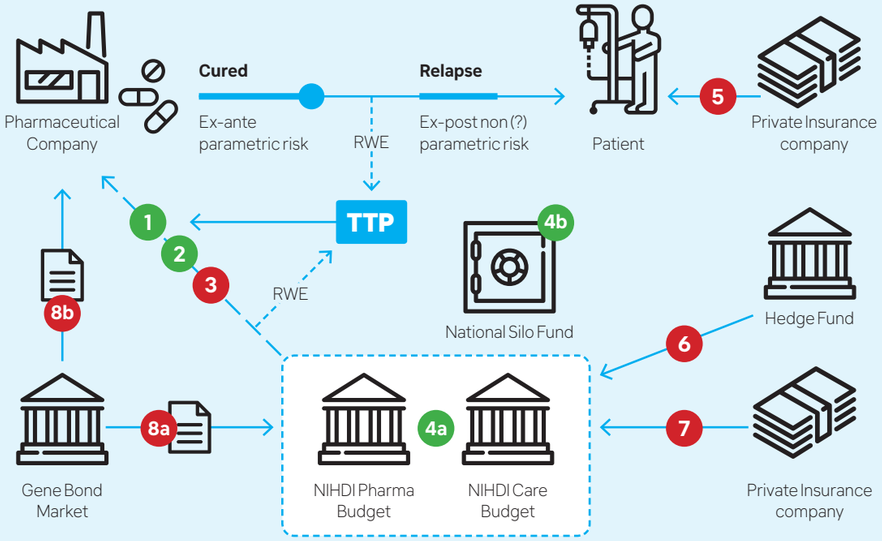

Figure 12 — Preferred solutions by the stakeholders, not including the private insurance based solutions

Based on the feedback from the different stakeholders in the first round table, the following potential and preferred solutions have been selected:

- The recommended funding model must be based on outcome-based results.
- Spread payments (e.g. annuity-based) should be considered to improve the affordability challenge to provide access for gene therapies. However, payment schemes should comply with EU Accounting rules. Potential public finance solutions are to be tested and confirmed for implementation by NIHDI.
- In case gene therapies would generate significant reduction in healthcare cost, more dynamic transversal budget models could provide an opportunity to consider gain sharing, but a sound reasoning and documentation illustrating the cost savings will be needed.

7.a Multi-stakeholder analysis of the three preferred solutions illustrates a preference for combination solutions

During the second round table the key principles of the short-listed potential solutions of the first round table have been further discussed based on their pros, cons analysis and challenges. The solutions were further discussed and tailored to the Belgian context in break-out sessions.

None of the individual shortlisted solutions on themselves is clearly the most preferred solution. Multi-stakeholder analysis illustrates a preference for combination solutions. The overall preferred solution is a combination of solution 1 and 2, with elements from solution 4 (4A and 4B), resulting in an outcome-based solution potentially combined with a spread payment solution for a limited amount of time (TBD per case).

7.b Building block principles and conditions for optimal solution selection

During the third round table the fundamental principles per building block to define the optimal funding solution were listed and agreed, as well as the conditions for the selected building blocks. The resulting conditions are outlined in the "solution house" below (see fig. 13).

For example, compliance of spread payments (e.g. annuity-based) with EU and Belgian accounting rules need to be further investigated. For outcome-based MEA, good end-points for outcomes definition are required and have to be agreed upfront (before applying for reimbursement). Also, outcomes data collection in registries have to include patient outcome data. Pooled or transversal budgets, require that cost savings need to be analysed and documented. Especially the potential impact of curing for both patient and environment (family, caregivers,…) across silos (e.g. via cost of illness study) has to be assessed. In case of a pooled budget, also transversal budget monitoring will be needed.

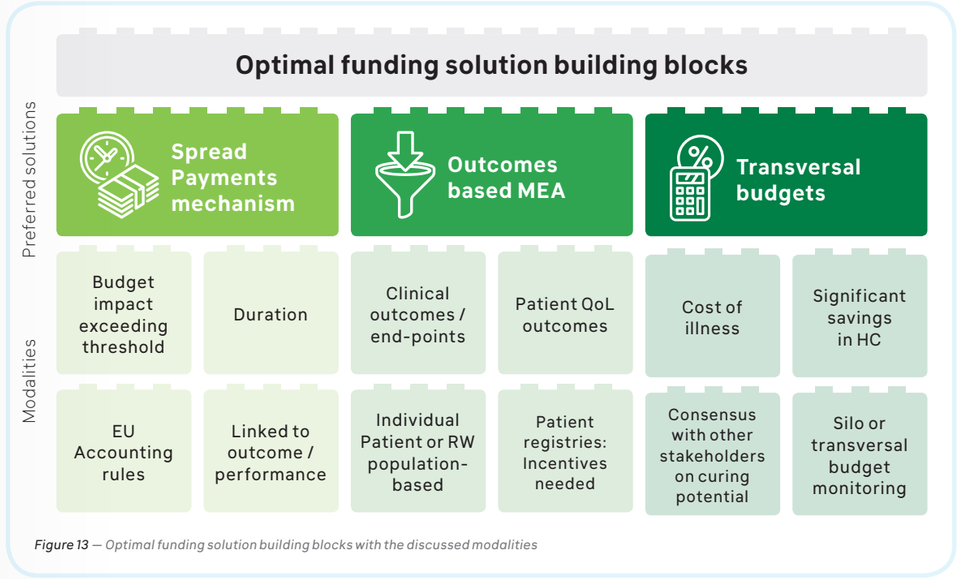

Figure 13 — Optimal funding solution building blocks with the discussed modalities

8. Multi-stakeholder consensus on preferred solutions

8.a Assessment of preferred solutions

The solutions have been assessed based on the 3 selected CSF (financial attractiveness, equity impact and fairness, traceability) and the feasibility within the Belgian context. Stakeholders were requested to score the solutions for each CSF. In addition, combination solutions were added to the list of solutions as it was also a preferred solution indicated by the stakeholders. An average score on ten per CSF and per stakeholder group was calculated. The table below provides the overview of the scoring per funding solution.

	CSF 1		CSF 2	CSF 3		
	Financial attractiveness for payer	Financial attractiveness for innovator	Equity impact & fairness	Traceability	Feasibility	RT 3 Overall score (on 10)
Outcome-based Managed entry agreements (MEA) – Art.111, 112, 113	8,19	8,30	8,52	7,06	7,38	**7,89**
Spread payments	4,52	6,36	6,77	5,29	3,91	5,37
Transversal/pooled budgets						
• Combined budgets within NIHDI	6,28	7,67	7,50	5,50	5,67	6,52
• National silo innovation fund (pooled budget outside NIHDI)	3,44	6,11	5,61	4,11	3,89	4,63
Combination solution Outcome-based solution with spread payments (combination of solution 1 and 2)	5,86	6,60	6,70	5	4,31	5,69

Table 3

The following can be concluded from the scoring:

- The overall aggregated score of the solutions shows a clear preference for outcome-based MEA, followed by transversal/pooled budgets within NIHDI. The combined outcome-based solution with spread payments solution was ranked third in the voting.
- The outcome-based MEA solution was scored the highest by authorities, sick funds, patient groups and industry.
- The spread payment solution was scored the least by authorities, sick funds and private insurers.
- The scoring for the spread payment solution decreased during the third round table compared to the scoring in the second round table as a result of unclarities about 1) the practical implementation at NIHDI and in Belgium and 2) the financial compensation innovators would potentially request and lack of transparency of potential impact on the list price.

The selected three preferred solutions answer best the three key questions for gene therapies.

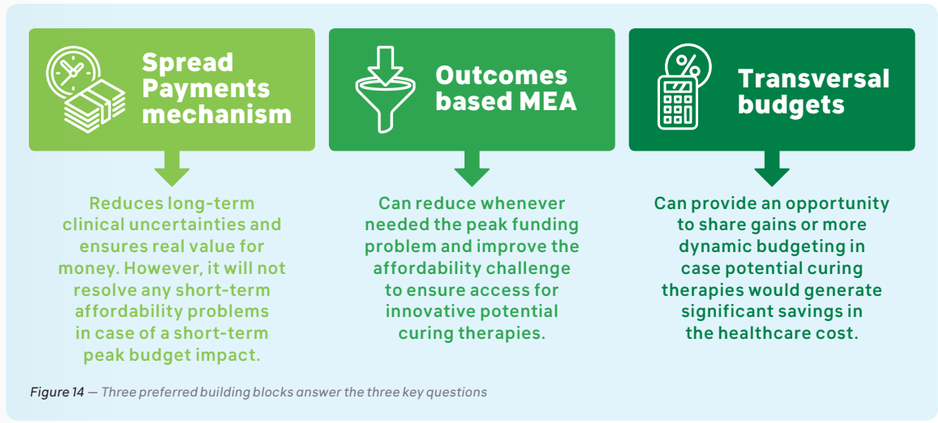

Figure 14 — Three preferred building blocks answer the three key questions

In addition, the three preferred solutions can also be complementary solutions as illustrated in the figure below.

Figure 15 — The three preferred building blocks are complementary

8.b The basic principles per preferred solution.

For each of the funding solution building blocks, the following key recommendations were formulated based on broad consensus among the stakeholders:

For outcome-based funding, the following basic principles were agreed:

- At this moment most initial MEAs are mainly based on the clinical value of the new medicines demonstrated during the randomized clinical trials (RCTs). In case of important clinical uncertainties more complex outcome-based MEA can provide a solution.
- EMA's request for post-authorization patient real-world outcome data from standardized EU registries could be leveraged (especially for ATMPs and/or orphans with more limited number of patients enrolled in the RCTs).
- Clinical outcomes in real world /daily practice need to be taken into account and should be objective, reliable and verifiable (cfr. validated clinical endpoints in RCTs).
- In addition, objective, reliable and verifiable Patient QoL outcomes should also be considered.
- The outcome criteria should be defined and agreed upfront, per disease and in multi-stakeholder consensus (e.g. CTG).
- Electronic registries, linked to the electronic patient record, will be needed to register the outcomes in daily practice.
- Incentives for HCPs, centres and patients need to be considered, taking into account the resources and time needed to register the data.
- Infrastructure to facilitate capture, sharing and quality control of patient data as well as clear guidance on the type of data that can be captured and shared, is required. A well-functioning health data system should be considered (cfr. best practices in Finland, Denmark, Estonia).
- Average aggregated patient-based RWE is preferred over variable individual outcome-based evidence.

This solution will reduce the long-term clinical outcome uncertainty (how long will the treatment work for the patient and/or how long will be the duration of the potential curing), but on itself will not solve the short-term peak funding challenge. To solve the funding challenge a combination of the outcome-based reimbursement solution with the spread payment solution will be needed. An outcome-based solution in combination with annuities can reduce the long-term therapeutic risk profile of the spread payment. Spreading payments over multiple years is most appropriate for products with long expected efficacy but significant uncertainty regarding the durability and efficacy performance consistency among patients. The solution also allows substantial spreading of the payments over time to better match costs with benefits and finance a potential surge of initial patients.

A shorter payment solution (e.g. 1 year) is more appropriate for products with upfront uncertainty compared to treatment success, and for products whose one-year performance is indicative of their longer-term performance.

Such a shorter spread payment solution may alleviate the short-term performance risk while reducing the implementation hurdles. This solution could be preferred for oncology products such as CAR-T, due to the shorter durability of these therapies and the incidence- driven population characteristics of oncology limiting the backlog surge effect. In such cases upfront payment for medicines by the payer combined with milestone refund by the innovator, based on a easy performance metric, could also be considered.

For spread payments (e.g. annuities), the following basic principles were agreed:

- Spread payment can only be applied in case there is a peak of patients waiting to be treated (diseases with high prevalence and low incidence) or a peak in budget expense.
- Spread payment is only an option in case a short-term peak and affordability challenge needs to be addressed.
- Spread payment enables access to immediate health benefit for society in the short-term and spread payment over time.
- In case the innovator would request financial compensations for a spread payment, transparency will be required from the innovator concerning the cost of financing e.g. by clarifying the difference in price between the options without and with spread payment.
- In order to implement the spread payment (e.g. annuity-based) solutions, compliance with the European Accounting Rules (ESA) and the NIHDI accounting rules is required. Potential solutions are being formulated in order to successfully implement the suggested solutions in the Belgian healthcare context.

For transversal or pooled budgets, the following basic principle was agreed:

- Cost savings will need to be demonstrated to justify gain sharing and/or more dynamic budgeting (e.g. via cost of illness studies).

For the combination solution consisting of outcome-based and spread payment:

- Combination solution enables "real value for money" for breakthrough therapies.

The above preferred solutions have to be further tailored to the specific context such as the target population, the nature of clinical benefit, the durability of effect and the delivery setting.

9. Decision-tree to enable assessment of the most optimal solution for each novel breakthrough therapy

The outcome of the round table discussions revealed a need for an integrated reimbursement decision-making process. Therefore, a decision-tree has been developed to support the selection of the optimal solution(s) for any eligible game-changing therapy. This funding solution assessment will have to be integrated within the current reimbursement process.

The implementation of horizon scanning should facilitate early dialogue between authorities (HTA and payers) and innovators, which will enable to proactively identify gene therapies eligible for above possible solutions. Early dialogue is essential in preparing the reimbursement and innovative funding solution assessment and proactively prepare for solving the 3 key questions:

1. How will we make the therapy affordable in Belgium?
2. How will we deal with long-term uncertainty of the therapy?
3. Can the innovation create room in the total healthcare budget?

The reimbursement process is initiated by the innovator. The innovator can include these innovative funding proposals already in his initial application. The funding solution assessment can be performed in the appraisal phase by the CRM in order to define the optimal funding solution for the novel breakthrough therapy. Thereafter, in the Managed Entry Agreement, any financial compensations of the optimal funding solution can be included in the contract together with the conditions that need to be met (e.g. registry set-up,...).

The funding solution assessment process is based on a decision tree including the 3 preferred solution building blocks in a logical and practical decision process. This decision tree allows to define the most optimal funding solution for each novel gene therapy. In addition, it also allows for combination solutions with different building blocks.

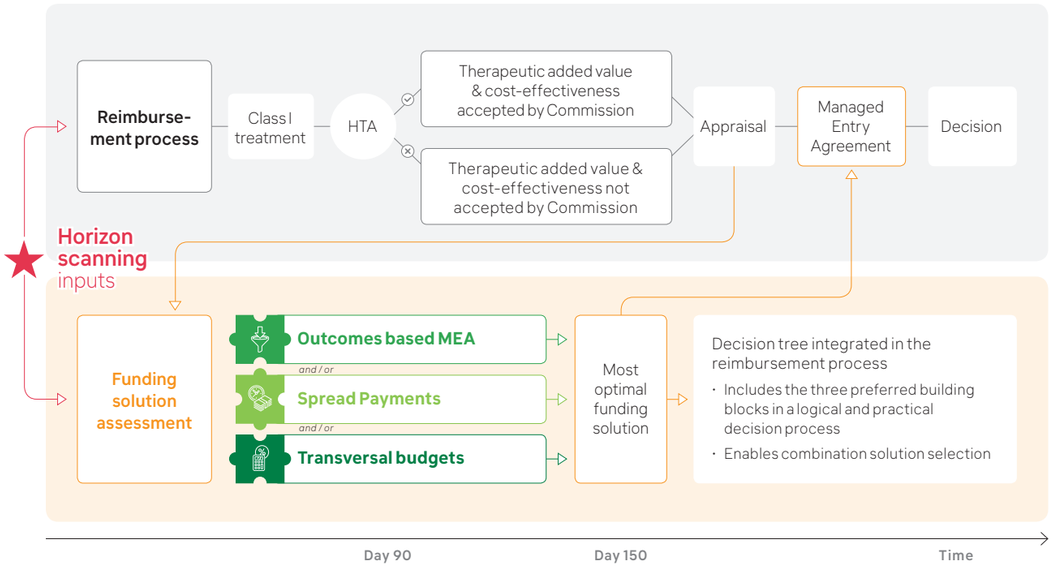

Figure 16 — The alternative funding solution assessment integrated in the current reimbursement process

9.a Outcome-based building block of the decision tree

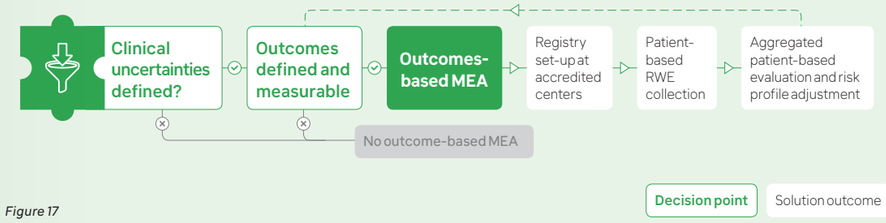

Figure 17

In case of important clinical uncertainties, outcome-based MEA could be considered. Clinical outcomes in real world should be taken into account and should also be objective, reliable and verifiable. The decision-process for the outcome-based building block includes also another important question that needs to be answered: Are the relevant outcomes defined and measurable? In case the answer is no, the novel breakthrough therapy will not be suitable for an outcome-based solution in first instance. In case the answer is yes, an outcome-based solution could be considered to address the long-term clinical uncertainties. As outcome based MEA are more complex compared to finance-based MEA, multiple steps are critical to enable implementation. First, registries will need to be set up at accredited centers. Second, real-world evidence of the patient will need to be collected and registered in the registries. Third, improved access to the available anonymous real-world health data need to be foreseen. Finally, the aggregated patient-based evaluation and risk profile adjustment can be performed by both the authorities and the innovator.

Furthermore, the basic design principles for this building block are:

- Both clinical outcomes in real world and patient QoL should be objective, reliable and verifiable.
- Outcome criteria (incl. complete and if needed partial response) should be defined and agreed upfront, per disease and in multi-stakeholder consensus (e.g. CTG).
- Access to standardized electronic registries, linked to the electronic patient record, will be needed.
- Registries set-up will initially happen at accredited centres but later on, the registry can be expanded to the entire network the centre is affiliated with. This should be discussed upfront, very early on with the authorities. In addition, the accredited centres need to be validated by the authorities, not only based on their experience and expertise but also to ensure a good spreading over Belgium. This also to avoid monopoly of only a few hospitals (e.g. only those centres involved in the RCTs).
- A well-functioning health data system and IT infrastructure will be needed (cfr. best practices in Finland, Denmark, Estonia).
- Incentives for HCPs, centres and patients need to be considered, taking into account the resources and time needed to register the data.
- Access to digital standardized patient outcomes data needs to be improved via i.e. governance with multi-stakeholder consensus, ...
- Aggregated patient-based (average population-based) RWE is preferred.
- The main responsibility of dealing with the uncertainty must remain with the innovator.
- This solution will reduce the long-term clinical outcome uncertainty, but on itself will not solve the short-term peak funding challenge. To solve the funding challenge a combination of the outcome-based reimbursement solution with spread payment solution will be needed.
- A long-term communication campaign will be needed to enable a mentality switch of HCPs and patients to be aware of the accountability and duty in turn for receiving and reimbursing breakthrough treatments.

9.b Spread payment building block of the decision tree.

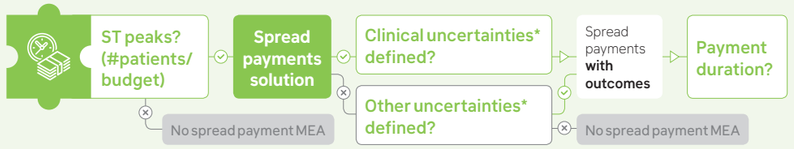

Figure 18

** The term "Clinical uncertainties" is formally used in EMA and CTG to define the therapeutic risk profile*
*** Other uncertainties include conditional uncertainties such as e.g. efforts, delivered services,...*

The decision process for the spread payment building block includes 3 fundamental questions that need to be answered subsequently:

- Is there a short-term peak (in number of patients or budget) caused by the novel breakthrough therapy?
  - *If no, a spread payment solution will not be applicable to the novel therapy.*
  - *If yes, a spread payment solution is applicable, and the following questions needs to be answered.*
- Are the clinical uncertainties (therapeutic risk profile) defined?
  - *If yes, a spread payment solution with outcomes will be applicable.*
  - *If no, a spread payment solution with other conditions will be applicable*
- How long will the payment duration last?

The basic design principles have been defined to answer the question about the duration of the spread payment, because currently there are no published guidelines to determine the number of payments. The principles are the following:

- Minimum duration of spread payments is set by maximum affordable net annual budget impact.
- The payment duration also depends on the available clinical evidence, beyond which outcome is an unknown-unknown, to be discovered by the capture of real-world therapy outcome evidence.
- Spread payment becoming perpetuities is not preferred amongst others to limit additional administrative and accounting complexities associated with this solution and the possible burden on the future medicines budget.
- In case the innovator would request any financial compensation, transparency about the cost of financing is required from the innovator. From the payer side, this cost of financing cannot exceed the public market rate for government bonds.

Furthermore, basic design principles for this building block are:

- Spread payments are only an option in case a short-term peak and affordability challenge needs to be addressed. It can reduce the peak funding problem and improve affordability to ensure access to potential curing therapies.
- Spread payments can only be applied in case there is a peak of patients waiting to be treated (diseases with high prevalence and low incidence) or a peak in budget expense.
- Spread payments are a solution to bridge the gap between the willingness to pay and the capacity to pay.
- While risk profiles will need to be defined to select the optimal duration of the spread payments, in general a maximum period of 5 years was preferred.
- Spread payments enable the access to immediate health benefit for society in the short-term and spread payment over time. It avoids that reimbursement and access would be delayed for Belgian patients.
- Spreading payments fit also well with the multi-year budgeting concept of the horizon scanning.
- Spread payments are however not a way to dismiss or avoid the fundamental price justification debate with the industry.

9.c Combination of outcome-based and spread payment building blocks of the decision tree

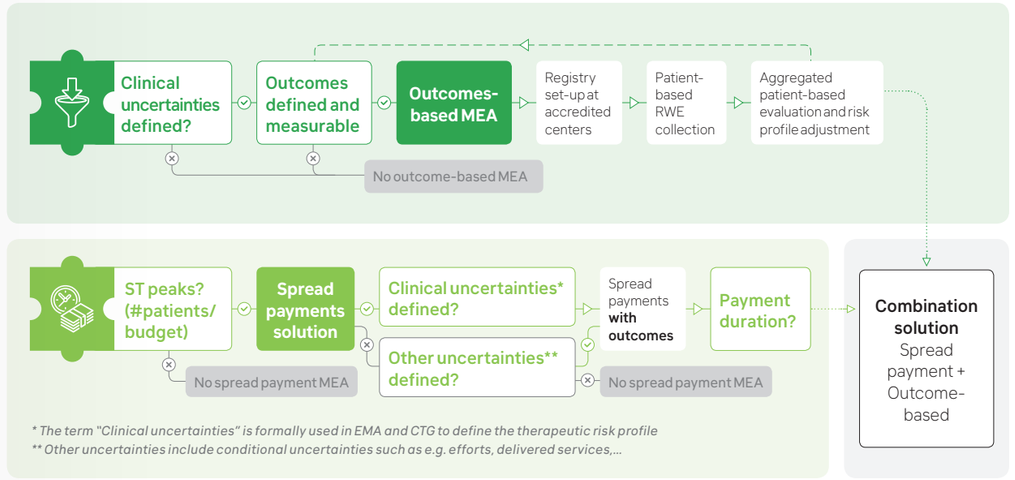

Figure 19

The combination tree of the two building blocks allow for a combination solution of outcome-based and spread payment solution.

The basic design principles for these combined building blocks are the following:

- To solve the funding challenge a combination of the outcome-based reimbursement solution with spread payment solution will be needed.
- Outcome-based solution in combination with spread payment can manage the long-term therapeutic risk profile of the spread payment.
- Spread payment linked with outcome-based funding allow for "real value for money".
- Furthermore, the following design principles were also defined for the duration of spread payment in combination with outcomes:
  - *The spread payment profile should minimally capture the risk profile dynamic (percentage of responders to correct for the annuities), making it outcome-based, which diverts the risk to the innovator.*
  - *The treatment risk profile maps the RCT-derived probability of success or Result Rate of a treatment over time, as measured by a determining biomarker.*
  - *For the payer to induce the value at risk to the manufacturer during the payment period, real annuities paid to the manufacturer are corrected for the annual proportion of real responders of the total treated patient population.*

9.d Virtual transversal budget building block of the decision tree

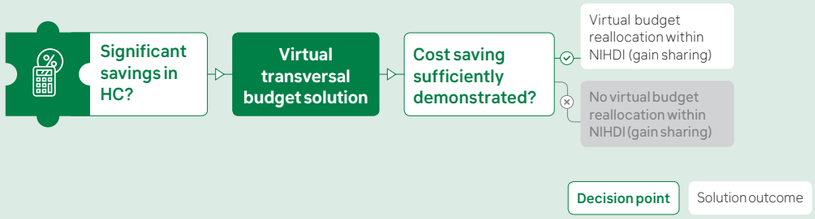

Figure 20

The decision process for the virtual transversal budget building block includes 2 fundamental questions that need to be answered subsequently:

1. Are there significant savings to be observed in healthcare?
   - *If yes, virtual transversal budget solution is applicable.*
   - *If no, virtual transversal budget solution is not applicable.*
2. Is the cost saving sufficiently demonstrated?
   - *If yes, virtual combined budgets within NIHDI is applicable.*
   - *If no, virtual transversal budgets is not applicable.*

The basic design principles for this building block are the following:

- Provides an opportunity in case such gene therapies would generate significant savings in healthcare cost. In addition, gain sharing and / or more dynamic budget allocations should be considered and encouraged.
- In case the potential savings of gene treatment are much larger than the pharmaceutical budget expense, it creates room in the healthcare system by avoiding chronic care costs.
- Strong eligibility criteria will be applied to consider this funding solution for a gene therapy for which significant savings can be demonstrated.
- Gene therapies initiate an evolution from pharmaceutical specialties product budgets to virtual budgets of therapies (combining product and health service) as a whole. In this respect, cost-benefit analyses for advanced therapies should be considering the total joint budget impact of the potentially budget-reduced healthcare provider process and the increased pharmaceutical specialties budget. A time-driven Activity Based Cost (t-ABC) study, conducted in this virtual cross-budget context, can be the basis for gain-sharing to be applied between the budget benefiting from the advanced treatment intervention (the HCP budget) and the budget providing access to the enabling treatment (i.e. the pharmaceutical specialties budget).
- Virtual transversal budgets can be interpreted in a very broad sense i.e. broader than the healthcare budget. However, the feasibility is rather low in the short-term of this type of budget interpretation.

9.e Additional modalities were discussed in the final round table regarding 3 specific topics

Three additional modalities have been discussed:

Incentives for HCPs, centres and patients to continue to populate the registries

- The registration responsibility is considered a requirement to allow reimbursement for the patient treatment, especially if via spread payments and / or in case of expensive treatment costs (e.g. Tardis reimbursement of biologicals for RA patients).
- Data collection is considered a joint responsibility of all stakeholders involved.
- Moreover, healthcare providers in daily practice are considered to be accountable for the registration of outcomes data in a structured way that could be considered as good medical practice as well as to increase insights on the therapy.
- In addition, patients should also be aware and accountable to go to regular check-up consultations because of its importance for their own health and to contribute to the knowledge and insights of the disease and treatment.
- A long-term communication campaign will be needed to enable a mentality switch of HCPs and patients to be aware of the accountability and duty in turn for receiving breakthrough treatments.

Registry remains the responsibility of the innovator

- Answering the uncertainty is a responsibility of the innovator.
- The HCPs provide the data in the registries, however generating insights into the data is a responsibility of the scientific HCP associations and the innovator.

The health data ecosystem that is virtually connected

- A virtually connected health data ecosystem will be essential for these breakthrough therapies (e.g. Finland, Denmark).
- In addition, any stakeholder (researcher, government, pharma,…) should be able to apply for access to specific aggregated data for prespecified purposes via a Trusted Third Party (like ScienSano).
- Access to aggregated data via this health data system will enable a successful implementation of the outcome-based solution and can contribute to evolve towards a more dynamic virtual transversal budgeting model.
- Authorities are accountable for providing the infrastructure for health data collection.

9.f Decision tree

The overall decision tree enables a tailored combination solution for each novel breakthrough therapy. The selection of the three building blocks happen in parallel to come to the most optimal solution for each novel gene therapy. It is essential for this decision-tree to be integrated into the reimbursement process. However, these funding solutions are not a way to dismiss or avoid the price justification and/or the fundamental price debate with the industry.

Finally, the decision tree could be used during the contract negotiations. Stakeholders raised the question about transparency as the confidential financial compensations within any contract negotiations are not disclosed. However, the decision for a specific funding solution for a gene therapy should be disclosed according to academia.

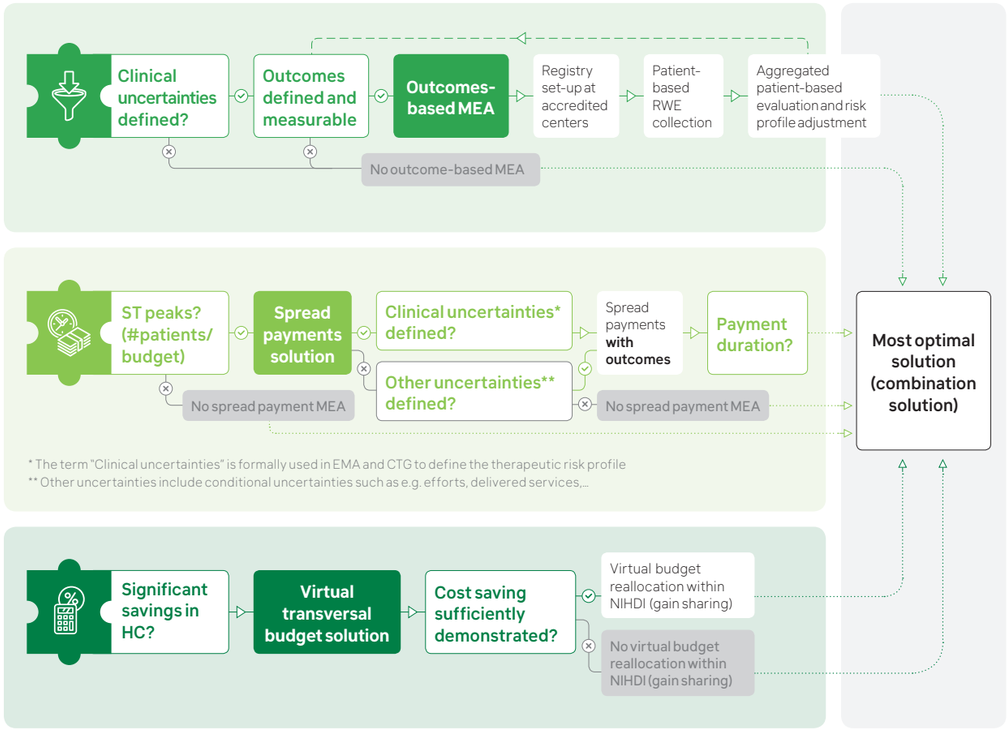

Figure 21

9.g Final scoring of the decision tree illustrates multi-stakeholder consensus

The decision tree has been scored by the stakeholders based on the 3 selected critical success factors (financial attractiveness, equity impact and fairness, traceability) and the feasibility within the Belgian context. An average score per CSF and per stakeholder group was calculated.

The overall aggregated score on the decision tree is 6.8/10. The traceability (CSF 3) was scored the lowest (5.87/10), which could be a result of the concern of the stakeholders regarding the transparency of the chosen funding solution for a specific breakthrough therapy.

	CSF 1		CSF 2	CSF 3		
	Financial attractiveness for payer	Financial attractiveness for innovator	Equity impact and fairness	Traceability	Feasibility	RT 4 Overall score (on 10)
Overall decision tree including the 3 building blocks	6.87	7.53	7.73	5.87	6.0	6.80

Table 4

10. Specific solutions for the European Accounting Rules and NIHDI accounting rules are required

The implementation of a spread payment or annuity-based funding solution requires compliance with the European System of Accounts (ESA) and the NIHDI accounting rules. Compliance to these rules have an impact on the possible implementation of the spread payment solution.

10.a ESA rules

The ESA 2010 regulations support the harmonisation of EU member state (MS) accounts according to Maastricht criteria and are reported to Eurostat (Matthijs H, 2015). The ESA 2010 (also called EUROSTAT rules) is a budget law or a set of regulations known as European System of National and Regional Accounts 2010, dealing with the public deficit and debt involved in specific "projects" and use of special financial instruments due to annuity. The following criteria (Maastricht criteria) have been defined: annual budget deficits must not exceed 3% of the GDP, total government debt must not exceed 60% of GDP. To compare accounts between EU member states, they have to be kept and reported in a uniform way, hence a uniform framework for drafting national accounts of Member States.

ESA2010 regulation EU 21.05.2013 is a statistical accounting standard. ESA is needed to have a reliable overview of the economic situation of each Member-State, for macro-economic analysis and international comparability: compare MS, economic indicators, such as the annual budget deficit (<3% of GDP) and the total government debt (<60% of GDP) according to the Maastricht treaty, 1992. Each country has to report accounts conform the ESA 2010-methodology, to Eurostat (European Statistical department).

The "accountant point of view" on annuities defines that: "All capital expenditure incurred in arrangements should be recorded in government accounts as debt and has an immediate impact on deficit."

The ESA 2010 classifies annuity-based payments as a liability. The triggering accounting event for a liability (recorded in accounting books" and recognized in the financial statements) is defined as follow:

- When an unconditional obligation to pay exists.
- Timing of payments and cash flows are not important to define the triggering event.
- Substantial and substantive uncertainty about outcome can delay triggering event.

This means that an annuity-based model is possible in case of a large and independent uncertainty about outcome. In addition, liability criteria in ESA 2010 5.06 is defined as: liabilities are established when a debtor is obliged to provide a payment or a series of payments to a creditor, and timing of the payments is not important. Furthermore, a contingent liability is defined in ESA 2010 5.08 as: contingent liabilities are agreements whereby one party is obliged to provide a payment or series of payments to another unit only where certain specific conditions prevail. It is treated as an off-balance item and real substance about uncertainty of condition must exist. When uncertainty about criteria is reduced / resolved, it is a liability.

This means that an annuity-based model is possible in case of a conditional obligation.

The problem associated to annuity-based payment in the Belgian healthcare context is the following (from an accountant point of view):

- Even if payments will be spread over a number of years, the ESA will dictate that the full cost of the treatment will be consolidated and reflected as one cost in the year that the treatment is delivered.
- The Treasury will see any such deferred payment as the Government effectively borrowing the deferred cash payments from the supplier, which costs more than a governmental loan.
- Therefore, ESA prohibits agreements made to pay or receive a specified sum at a future date, because the accounts will reflect that sum at the time of the agreement, destroying the spread payment advantage of annuity-based models.

Possible solutions to ensure compliance

Looking at this problem from another point of view (lawyer view), a potential solution can be defined as follow:

First, a vested legal practice of commitment appropriations versus payment appropriations needs to be defined (ESA95, EU budget headings and ceilings, EU Commission). Commitment appropriations are the total cost of legal obligations (contracts, grant agreements/ decisions) that could be signed in the current financial year. These are legally binding and promise to spend the money (future cash-out) which may be disbursed over several financial years. Furthermore, they have a long-term effect on governmental debt.

Payment appropriations are appropriations covering expenditure due in the current year, arising from legal commitments entered in the current year and/or earlier years. These are the actual amounts that are authorized for disbursement in a given budget year. Furthermore, they have year per year effect on budget deficit.

	1	2	3	4	5	6	7	8	9	10
Commitment appropriation	100	90	80	70	60	50	40	30	20	10
Payment appropriations	10									
		10								
			10							
				10						
					10					
						10				
							10			
								10		
									10	
										10

***Table 5** – Example*

Second, the rule with a statistical objective is balanced against the overarching objective of creating access for valuable breakthrough therapeutics. Currently in ESA 2010, "goods" are defined as recorded and valuated when institutions become the new owners of the goods (ESA2010, 3.118). "Medical treatments" are defined as a social transfer in kind and are recorded at the time the services are provided (ESA2010, 4.111).

However, in accordance with health economic insights, this regulation needs to be read in the sense of what is paid for in reality. In reality for the breakthrough therapies, the payer does not pay for the medicine that is administered, but for the long-term health outcome (defined in QALYs, as a health currency translated in monetary currency) to be proven in medical practice / real world, as well as the non-expenses for health care costs that are no longer needed (savings). This means that an annuity model for gene therapies, delivered as a service (in QALY's) with savings, is compliant to ESA 2010. The benefit outweighs the limitations to ask for an exception on a statistical accounting rule (an "EU ruling").

Spread -based funding can be integrated within MEA reimbursement conditions in function of milestone payments or delivery of patient data combined: with or without outcomes conditions (performance-based) and with or without savings realisation.

Possible workarounds could be:

- Milestone payments per realised health outcome translated in a health currency (e.g. QALYs) or delivered data packages.
- Payments for data services: per delivered data package to the payer per year or as an "early access program" in upfront payment and additional fee, based on performance and realised savings.
- An alternative fund as separate fund created on national or on EU level could also be considered as a potential solution.

Confirmation is needed that within Belgian context spread payments are in compliance with the European Accounting Rules (ESA) and the NIHDI accounting rules under below formulated conditions:

- Milestone payment per realised health outcome, translated in a health currency or delivered data package.
- Payment for data services: per delivered data package to the payer per year or as an "early access program" in upfront payment and additional fee, based on performance and realised savings.

Under these conditions the payer does not pay any longer for the breakthrough medicine, but for the long-term health outcome proven in medical practice, as well as for non-expenses related to health care costs that are no longer needed (savings).

10.b NIHDI accounting rules

NIHDIadheres to specific accounting rules regarding the reimbursement of medical treatments. The following 5 issues emerged in case of the implementation of spread payments:

- High pre-financing of large budgets by hospitals: there is a need for the creation of an organizational framework (process, business, financial, legal) allowing direct financial transactions between companies and NIHDI (other than 'voorschot' and 'afrekening').
- Legal issues regarding central purchasing body principles: There is a need for review of the level framework regarding the ownership and responsibility of the medicines. In addition, the question was raised regarding the need for tendering procedures.
- Accountability: Probable need for verification of invoices based on individual patient information (privacy and medical secret need to be taken into account). In addition, a need for review of the confidentiality of the contract.
- Accountancy complexity: Review of the expenditures on pharmaceutical budget versus the income / savings on 'globaal beheer'.
- Framework/system: need for a review of the financial / budgetary framework.

A theoretical non-confirmed solution is developed and proposed by NIHDIfor therapies that, based on clinical evidence, offer a cure in case of a life-threatening indication, and consists of the following elements according to Chapter IV:

- According to Chapter IV, a cure can be interpreted as a first moment of treatment administration to the patient followed by several (for example yearly) data registration moments (on patient outcome) following or conditional upon which, a spread payment can be paid by NIHDI. Part of the payment from NIHDI to hospital can be made dependent of the provision of registered data.
- In the most probable case of yearly spread payments this means that the company receives each year, starting from the first year, the total sum divided by the number of years also depending on the outcomes (to be agreed within outcome based MEA).
- In agreement with the innovator, a market entry agreement can be convened such that these conditional multiple spread payments will be paid by the hospital to the company. At contract termination potentially missing registrations can be compensated to the company now directly paid by NIHDIto the innovator.

11. Application to a practical case: haemophilia A and B gene therapy

Several companies are developing gene therapies in order to cure haemophilia A and B patients. In haemophilia A: Pfizer, Biomarin, Roche, Shire, and in haemophilia B: Pfizer, UniQure, Sangamo are developing gene therapies. Forthcoming gene therapy for haemophilia A and B has consequently been chosen as a practical case to illustrate and test the preferred funding solutions (outcome-based MEA, spread payment solutions and transversal budgeting).

Current treatment of Haemophilia

Haemophilia is an inherited clotting factor deficiency in factor VIII (haemophilia A) or factor IX (haemophilia B). Patients with haemophilia have levels of clotting factors between 0% and 40% (compared to healthy individuals with levels between 50% - 150%). Therefore, patients suffer from spontaneous internal bleeding complications in the muscular-skeletal system (muscles and joints). Patients with clotting factor levels between 1% - 40% suffer from mild to moderate haemophilia which results in an annual bleeding rate (ABR) between 1 and 5. However, patients with clotting factor levels of less than 1%, suffer from severe haemophilia which results in an ABR of 52.

The difference in clinical phenotype (number of annual bleedings) between severe and moderate haemophilia provides the rationale for prophylaxis. The prophylaxis consists of replacement of the missing clotting factors by exogenous clotting factor concentrations given by repeated intravenous injections. However, current treatment has several limitations as illustrated in table. The efficacy of current replacement therapy is evaluated using the Annual Bleeding Rate (ABR) and the rate of patients achieving zero bleedings. The circulating clotting factor levels (peaks, troughs) are not measured as a routine efficacy outcome.

Limitations of the current blood factor substitution therapy

Current blood factor substitution therapy has multiple limitations including:

- Huge treatment burden (several intravenous infusions/weeks – vials/ syringes, waste, supply, storage, ...).
- Increase in clotting factors levels from < 1 % to > 1-2 % - No haemostatic correction (impossible to maintain FVIII > 30 to 50 % permanently).
- Does not provide full protection from spontaneous bleeding episodes.
- Few patients experience zero bleed/year.
- No steady state / fluctuant effect on blood coagulation (peaks-troughs) – major impact on life-style, physical activities, freedom, fear of bleed...
- Extra-treatment required in case of surgery – invasive procedure - trauma.
- Need for regular clinical assessment, follow-up, monitoring, adaptations.
- Risk for immunogenicity at initiation of treatment.
- Treatment has to be personalized with major inter-individual variability (including patient treatment compliance).

Table 6

Advantages of future gene therapy

Gene therapies hold great promise to deliver one-time, transformative therapies to patients in areas of high unmet medical need, particularly in rare, monogenic diseases.

Since an effective gene therapy for haemophilia A would represent a potential cure for a chronic orphan condition, with high potential cost, offsets based on avoiding FVIII therapy and administration costs, the Massachusetts Institute of Technology (MIT) selected haemophilia A as a case study for their FoCUS project (MIT NEWDIGS FoCUS, 2019).

In their preliminary analysis in the US healthcare system context, their conclusion was that 'current financing mechanisms and one-year milestone-based payment were considered the most feasible, with performance-based annuity also being an option if patient mobility, patient data collection and policy issues could be overcome'. This implies we need to investigate this further for our European health policy context.

A gene therapy offers the solution to correct the production of clotting factors in the liver, by integrating genetic information required for endogenous stable long-term production of Factor VIII or Factor IX. A study of Rangarajan et al. (2017) illustrates that the gene transfer of Factor VIII in severe haemophilia A results in the correction of Factor VIII deficiency and reduction of bleeding episodes and intravenous infusions of exogenous Factor VIII.

As gene therapy can stabilise the clotting factors in the blood, the circulating factor level appears to be an objective and non-surrogate endpoint. (This has also been suggested in a study of Pierce, et al in 2017.)

Advantages of haemophilia gene therapy include:

- Correction (partial or complete) of Factor VIII or FIX deficiency / factor activity level.
- Absence (abolition vs reduction) of (spontaneous, break-through) bleeding episodes.
- Less burden, no need for IV infusions of Factor VIII or Factor IX concentrates.
- Stable and prolonged correction of Factor VIII or Factor IX, therefore no fluctuations.
- Standardized treatment and therefore predictable cost per patient and no need for individualised treatment.
- Improved QoL – major impact on lifestyle, social-private-professional life, well-being, mental health, …
- No need for regular clinical follow-up, no issue with adherence.
- Beneficial impact on healthcare resources.

Table 7

The budget and affordability challenge of future potential curing gene therapies for Haemophilia

One of the main budget and affordability challenges of future potential curing gene therapies is that short-term payment and long-term benefit of treatment become misaligned as illustrated below:

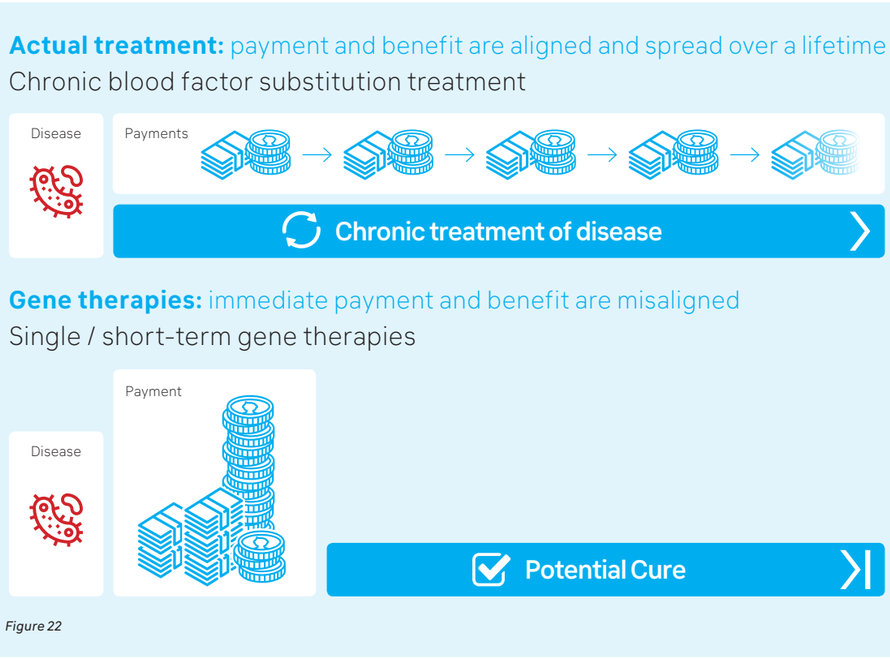

Figure 22

11.a Application of outcome-based MEA solution for haemophilia gene therapy

For the implementation of an outcome-based MEA for the haemophilia gene therapy, the right outcome parameter should be best selected to measure clinically relevant patient outcome and to define response in daily practice.

According to Professor C. Hermans (UCL) measuring and monitoring the clotting factor levels in the blood is more suitable as a primary efficacy endpoint and an outcomes-based criterion for performance-based reimbursement, then the ABR. ABR is an imprecise and subjective endpoint due to the fact that bleedings can be subclinical (small bleedings) and asymptomatic.

However, the following issues with the factor level measurement need to be further clarified:

- Need for a reliable assay as currently, discrepancies between assays exist.
- Definition of the minimal acceptable factor level.
- Definition of the minimum duration of the treatment .
- Determining the best age range to administer gene therapy (current clinical studies include patients from 18 years old).

In addition, other patient relevant endpoints can be considered. If the gene therapy leads to a reduction of bleeds close to zero, haemostatic outcomes may no longer be the only relevant outcome for patients. Improvement in HRQoL (health-related quality of life), activity level and participation, can be used as additional endpoints. Disease-specific HRQoL questionnaires (haemophilia specific scale), can be used for this purpose.

Haemophilia registry

The collection and evaluation of haemophilia patient outcomes from a specific patient registry is a fundamental requirement to allow outcome-based funding solutions for haemophilia. Haemophilia is a rare disease and a chronic disease. Hence, collecting long-term outcomes in patient registries is particularly important. National registries can provide insight into clinical practice especially for rare diseases. Consequently, several countries have already initiated haemophilia registries including Austria, Germany, UK, France, Finland and The Netherlands (cfr. tables Orphanet and RD-Connect Registry and Biobank Finder).

During a haemophilia registries workshop organized by EMA, all involved stakeholders have been encouraged to collaborate in order to ensure that all haemophilia registries can collect the core data elements specified in the FVIII Guideline. This EMA guideline lists common data elements and additional data elements to be collected for novel products including gene therapies.

In Belgium, the convention between NIHDI and the Belgian Haemophilia expertise centres foresees the implementation of a national haemophilia registry. However, the implementation is still in its infancy. While patient registries are perceived especially valuable for patients with rare diseases, the administrative burden for healthcare providers remain a hurdle to enable implementation. Multi-stakeholder collaboration, a good IT infrastructure and Real-World Data collection platform as well as a proper governance will be needed to accelerate the implementation of a national standardized digital registry for haemophilia patients in Belgium. This will be an essential source to allow for the implementation of outcome based MEA.

11.b Application of spread payment solution for haemophilia gene therapy

For the implementation of a spread payment solution for haemophilia gene therapy, two key questions have been addressed:

Are gene therapies for haemophilia A and / or haemophilia B eligible for spread payments and what would be the optimal duration of the spread-based payments?

- In function of short-term budget peaks and / or
- In function of available long-term clinical data and budget impact?

To better assess, the correlation between the optimal duration of the spread payment and the strength of the available evidence has to be made. The following assumptions are made based on the available clinical evidence from the pivotal RCT: open-label, non-randomized, multicenter, single arm

- 40 patients.
- Clinical endpoints: factor IX C levels and annual bleeding rates (ABR).
- Duration: 6 years
  - *1st year for establishing primary efficacy, safety/tolerability (40 patients).*
  - *Followed by 5 years of extended follow-up.*
  - *Real world follow-up via patient registries.*

Estimation potential impact of haemophilia A gene therapy on medicines budget

Cost comparison for 1 haemophilia A patient: single administration gene therapy vs current chronic F VIII substitution treatment

Actual cost chronic FVIII substitution treatment for haemophilia A patients is estimated at approx. 295 K € per year.

For this illustrative case, the example price for a single administration of haemophilia gene therapy is assumed at 2 million €. This theoretical price for a single administration of gene therapy would correspond with the actual chronic FVIII treatment cost for 7 years.

In case the long-term efficacy of the gene therapy would be maintained during at least 10 years, the upfront investment in a potential curing gene therapy at the theoretical price of 2 million € could potentially generate 950.000 € in savings per haemophilia A patient over a period of 10 years.

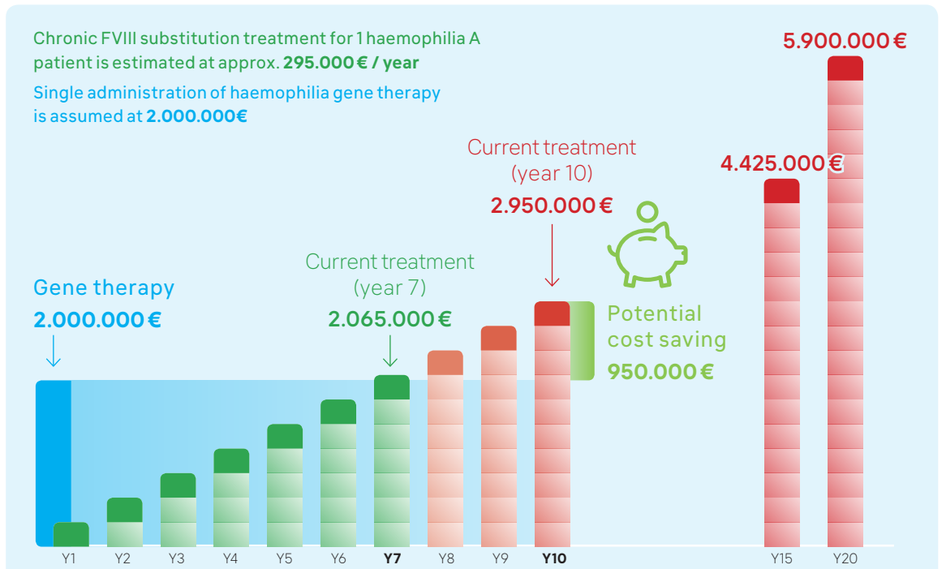

Figure 23 — Cost comparison over time for 1 patient on gene therapy vs current treatment

Number of eligible haemophilia A patients in Belgium

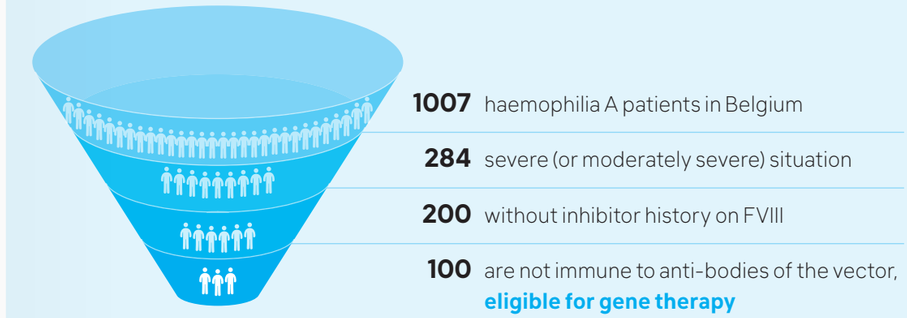

Figure 24 — Number of eligible Haemophilia A patients in Belgium
(Not taking into account: patients with active hep B & C / patients preferring to stayon current treatment.)

Based on the calculation above, 100 haemophilia A patients are estimated to be eligible for gene therapy in Belgium (calculation based on severity of the disease, inhibitor history and anti-body presence against vector). In this estimation, patients with active hep B&C were not taken into account, as well as patient who prefer to stay on the current F VIII treatment.

Impact on medicines budget for 100 haemophilia A patients with a single administration of gene therapy A compared to chronic F VIII substitution treatment

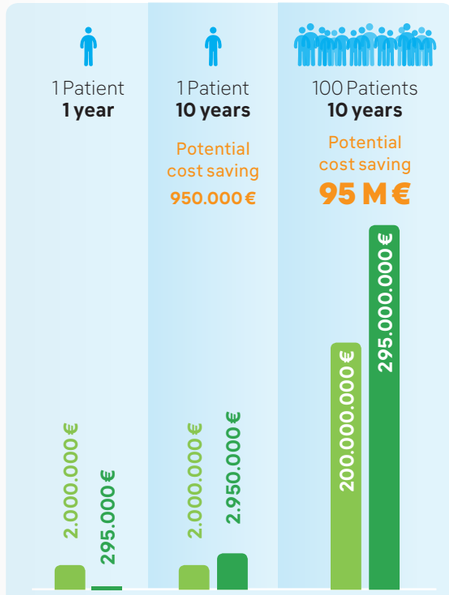

Figure 25 — Cost comparison over a period of 10 years illustrates cost savings generated by the gene therapy

Based on the calculation earlier on, 95 million € in savings in the medicines budget can be generated over a period of 10 years, at an assumed potential price of 2 million € for a single administration of a potential curing haemophilia A gene therapy.

In conclusion, the key questions can be answered as follow for haemophilia A:

- Question 1 – is this gene therapy for haemophilia A eligible for spread payment:
  Answer: yes, considering short-term expense peak of approx. 200 million € after launch and the uncertain long term clinical outcomes.
- Question 2 – What would be the optimal duration of the spread payments?
  Answer: In general a maximum duration of 5 years has been preferred based on the long-term evidence. In the above specific case, a period of 7 years would be budget neutral for NIHDI / NIHDI considering the cost of 7 years treatment with F VIII substitution is estimated at 2.065.000 € per patient.

The actual limitation of the budget impact assessment to 3 years will be too short for potential long-term curing gene therapies.

Estimation potential impact of haemophilia B gene therapy on medicines budget

Cost comparison for 1 haemophilia B patient: single administration gene therapy vs current chronic F IX substitution treatment

Actual cost chronic FIX substitution treatment for haemophilia B patients is estimated at approx. 375 K € per year. For this illustrative case, the example price for the haemophilia gene therapy is assumed at 2 million €.

This theoretical price for a single administration of gene therapy of 2 million € would correspond with the actual chronic FIX treatment cost of approx. 5,3 years.

In case the long term efficacy of the gene therapy would be maintained during at least 10 years the upfront investment in a potential curing gene therapy at the theoretical price of 2 million € could potentially generate 1.750.000 € in savings per haemophilia B patient over a period of 10 years.

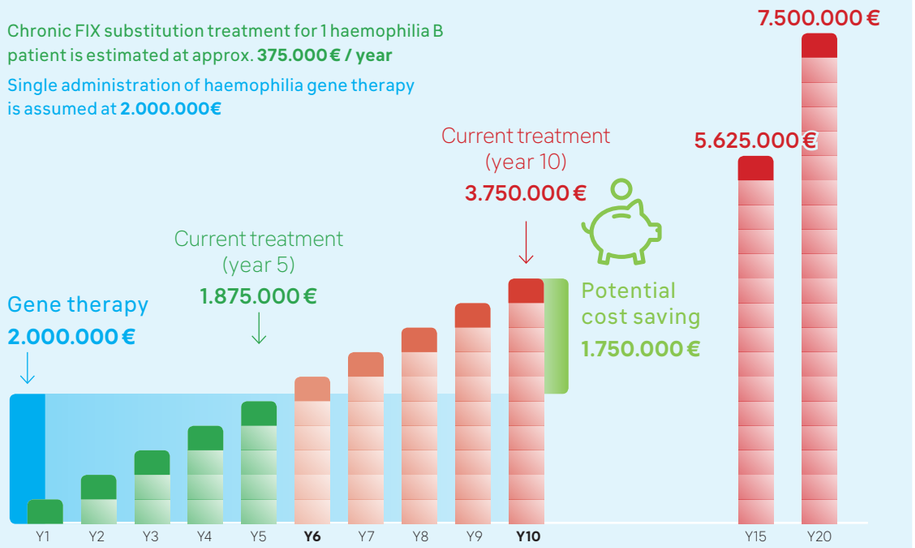

Figure 26 — Cost comparison over time for 1 patient on gene therapy vs current treatment

Number of eligible haemophilia B patients in Belgium

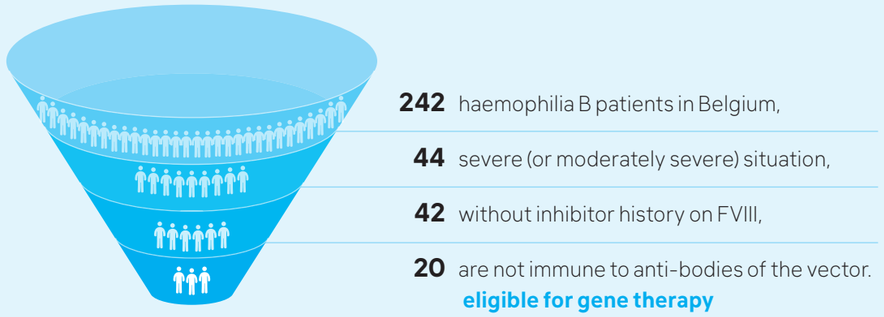

Figure 27 — Estimation of haemophilia B patients eligible for gene therapy
(Not taking into account: patients with active hep B & C / patients preferring to stayon current treatment).

Based on the calculation above, 20 patients are eligible for gene therapy in Belgium (calculation based on severity of the disease, inhibitor history and anti-body presence against vector). In this estimation, patients with active hep B&C were not taken into account, as well as patient who prefer to stay on the current F IX treatment.

Impact on medicines budget for 20 haemophilia B patients with a single administration of gene therapy B compared to chronic FIX substitution treatment

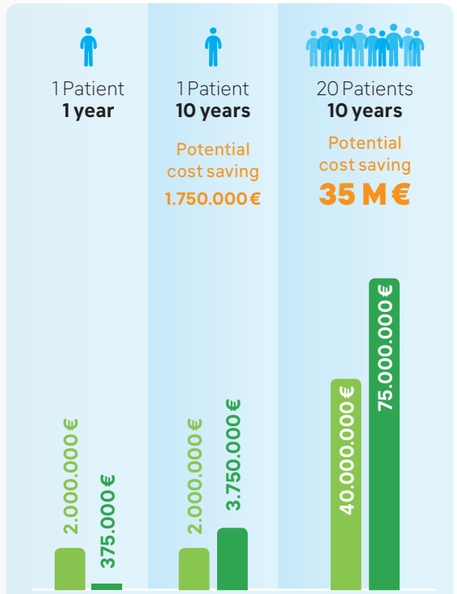

Figure 28 — Cost comparison over a period of 10 years illustrates cost savings generated by the gene therapy

Based on the calculations above, approximately 35 million € in savings in the medicines budget can be generated over a period of 10 years, at an assumed potential price of 2 million € for a single administration of a potential curing haemophilia B gene therapy.

In conclusion, the key questions can be answered as follows for haemophilia B:

- Question 1 – Is this gene therapy for haemophilia B eligible for spread payment?
  Answer: Yes, the budget peak of approx. 40 million € after launch is considered important enough and there are still long-term clinical uncertainties about the therapy.
- Question 2 – What would be the optimal duration of the spread payments?
  Answer: While in general a maximum duration of 5 years has been preferred based on the long-term evidence, in the above specific case approx. 6 years could also be considered. In this specific case a period of 5,3 years would be budget neutral for NIHDI.

The actual limitation of the budget impact assessment to 3 years will be too short for potential long-term curing gene therapies.

The graph below illustrates how a potential budget peak of 2 million € per patient could be spread over e.g. max 5 or 6 years to become more affordable for the payers also compared to actual lifetime annual expense of actual standard of care (SOC).

Linking spread payment to treatment outcomes

Spread payment linked with outcome-based funding therefore provides more certainty to payers allowing "real" value-based pricing and "real" value for money. A spread payment funding mechanism in association with outcome-based funding diverts the risk to the manufacturer. To link repayment to on-going value creation a treatment risk profile should be determined.

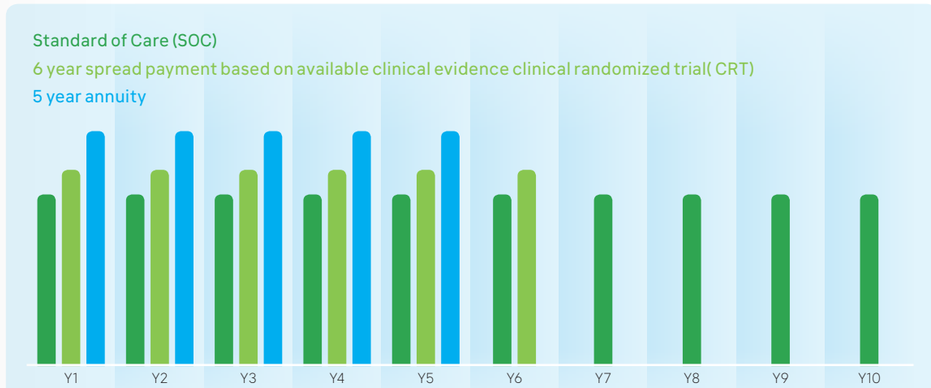

Figure 29 — Comparative yearly budget impact for type B patients in Belgium (illustrative, r=2%)

11.c Application of transversal budgets for haemophilia gene therapy

In case gene therapy would generate significant reduction in healthcare cost, more dynamic transversal budget models could provide an opportunity to consider gain sharing.

Haemophilia represents both an economic and health burden, especially on an individual patient level. A study of the health and economic burden of Haemophilia in Belgium has been published by Henrard et al. in the Orphanet Journal of Rare Diseases in 2014. The results of this study indicated that the mean total lifetime costs reached 7.8 million € per patient with haemophilia, 94.3% being direct costs and 5.7% indirect costs. Treatment with blood clotting factors accounted for 82.5% of direct costs.

An updated cost of illness study would be helpful to assess whether a potential curing gene therapy for Haemophilia would generate significant reduction in health care and societal cost to facilitate the forthcoming debate whether such curing therapy would justify a potential gain sharing and or re-allocation of NIHDI budgets.

12. Conclusions

Gene therapies hold promise to deliver one-time, transformative therapies to patients in areas of high unmet medical need, particularly in rare, monogenic diseases. Innovative "precision" solutions are needed to ensure affordability and to avoid delay in the access for patients of eligible gene therapies with potentially long-term curing impact (e.g. gene therapies).

The ambition of the multi-stakeholder round tables was to build multi-stakeholder consensus on an optimal solution that meets the critical success factors and addresses the short-term affordability challenge for long-term benefits that are uncertain at the time of administration. The critical success factors to evaluate the funding solutions in the Belgian healthcare system included 1) feasibility within the Belgian context, 2) financial attractiveness, 3) equity impact and fairness and 4) traceability.

Broad consensus was first built on the preferred solutions and building blocks that contribute to the optimal funding solution. The preferred building blocks with broad consensus are spread payments, outcome-based payments and the pooled budget solution building blocks. In addition, broad consensus was reached on the key implementation conditions and criteria for each building block.

While the preferred solutions have been defined, each must be further tailored to the specific gene therapy context such as the target population, the nature of clinical benefit, the durability of effect and the delivery setting. To support this, a decision tree has been defined that includes the three preferred building blocks in a logical and practical decision process. It includes key decision criteria per building block and allows for combination solutions to be assessed for each novel breakthrough therapy. This decision tree can be integrated into the reimbursement procedure and is broadly supported by the stakeholders participating at the round tables.

To implement the spread payments-based solutions, compliance with the European Accounting Rules (ESA) and the NIHDI accounting rules is required. Potential solutions are being formulated in order to successfully implement the suggested solutions in the Belgian healthcare context.

Finally, the following recommendations were made to best prepare for funding ATMPs and more specifically gene-therapies in a sustainable manner:

RECOMMENDATION 1
Leverage international horizon scanning project and facilitate early dialogue

RECOMMENDATION 2
Favor application of new funding arrangements to new gene-therapies

RECOMMENDATION 3
Develop initiatives to create adoption of new funding arrangements to new gene-therapies

RECOMMENDATION 4
Establish evidence collection (patient outcomes and RWE data) infrastructure and policies to facilitate electronic evidence capture

RECOMMENDATION 5
Confirm compliance of spread payment-based solutions with NIHDI and EU accounting rules.

We thank all health care experts for their active participation and much appreciated contributions to this multi stakeholder meeting. We hope this report will inspire and facilitate further funding solution innovation and real-world pilots to prepare patient access to these important therapies in a sustainable manner for all healthcare stakeholders.

Used abbreviations list

RWE	Real-World Evidence
MEA	Managed Entry Agreement
ESA	European System of Accounts
TTP	Trusted Third Party
ABR	Annual Bleeding Rate
MIT	Massachusets Institute of Technology
HRQoL	Health-Related Quality of Life
SOC	Standard of Care
WTP	Willingness to Pay
P4P	Pay-for-performance
IP	Intellectual Property
RR	Result Rate
HCP	Health Care Professional
RT	Round Table
ATMP	Advanced Therapy Medicinal Products
RCT	Randomized Clinical Trial
HA	Haemophilia A
HB	Haemophilia B
CSF	Critical Success Factors

References list

- Berggren R. et al. (2018). R&D in the 'age of agile', McKinsey, October 2018.
- Carr, D. R., & Bradshaw, S. E. (2016). Gene therapies: the challenge of super-high-cost treatments and how to pay for them. Regen Med, 11(4): 381-393.
- "Commentary: Novartis CEO: Gene therapies offers hope of cures in one treatment, but US needs new pricing and payment model", CNBC, 17 May 2019, tinyurl.com/y3tod72r.
- Danzon, P. M. (2018). Affordability challenges to Value-Based Pricing: Mass diseases, orphan diseases, and cures Value In Health, 21(March): 252-257.
- Edlin, R., Hall, P., Wallner, K., & McCabe, C. (2014). Sharing risk between payer and provider by leasing health technologies: an affordable and effective reimbursement strategy for innovative technologies? Value In Health, 17: 438-444.
- ESA 95 manual on government deficit and debt, Eurostat European Commission, 2002, tinyurl.com/y4abcqfn.
- "EU budget headings and ceilings", European Commission, tinyurl.com/yyvnxf2t.
- European System of Accounts ESA 2010, Eurostat European Commission, 2013, tinyurl.com/y2utcygn.
- Foundation, K. B. (2011). Fund for rare diseases and orphan drugs. www.archipelkbs.org/fund.
- Hampson, G. et al. (2018). Gene therapy: evidence, value and affordability in the US health care system. J Comp Eff Res, 7(1): 15-28.
- Hanna, E. et al. (2018). Funding breakthrough therapies: A systematic review and recommendation. Health Policy, 122(3): 217-229.
- Hettle, R. et al. (2017). The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. Health Technol Assess, 21(7): 1-204.
- Jaroslawski, S., & Toumi, M. (2011). Market Access Agreements for pharmaceuticals in Europe: diversity of approaches and underlying concepts. BMC Health Serv Res, 11: 259.
- Katz, A. S. et al. (2018). Social Impact Bonds as a Funding Method for Health and Social Programs: Potential Areas of Concern. Am J Public Health, 108(2): 210-215.
- Kleinke, J. D., & McGee, N. (2015). Breaking the Bank: Three Financing Models for Addressing the Drug Innovation Cost Crisis. Am Health Drug Benefits, 8(3): 118-126.
- Marsden, G. et al. (2017). Gene Therapy: Understanding the Science, Assessing the Evidence, and Paying for Value. London: ICER - Office of Health Economics Research.
- Matthijs, H. (2015), Overheidsbegrotingen, p. 79-80.
- Micklus, A. (2018), "Gene Therapy: A Paradigm Shift in Medicine", Pharma Intelligence, November 2018.
- MIT NEWDIGS FoCUS (2019). White Paper 2019F201-v023 Precision Financing Solutions for Durable / Potentially Curative Therapies. Retrieved from Massachusetts Institute of Technology.
- Montazerhodjat, V., Weinstock, D. M., & Lo, A. W. (2016). Buying cures versus renting health: Financing health care with consumer loans. Sci Transl Med, 8(327): 327ps326.
- Rosenberg-Wohl S. et al. (2017). Private Payer Participation In Coverage With Evidence Development: A Case Study. Health Affairs Blog.
- Towse, A., & Garrison, L. P. (2010). Can't get no satisfaction? Will pay for performance help? Toward an economic framework for understanding performance-based risk-sharing agreements for innovative medical products. Pharmacoeconomics, 28(2): 93-102.
- Zettler, P. J., & Fuse Brown, E. C. (2017). The challenge of paying for cost-effective cures. Am J Manag Care, 23(1): 62-64.

Notes

13 Appendix list

13. Appendix

13.a Solution assessment matrix based on CSFs

Solution assessment matrix

Fill-out form

Your stakeholder group:	Authorities	Academia	Sick funds	Industry	Patients	Private insurer	*(Please indicate to which stakeholder group you belong)*
Your name:	..... *(please fill in)*						

Attractiveness scoring of CSFs: 5: High 3: Medium 1: Low

Scoring of Feasibility: ++: Very feasible -: Not feasible

	CSF 1: Financial attractiveness for payer	CSF 1: Financial attractiveness for Innovator	CSF 2: Equity impact & fairness	CSF 3: Traceability	Feasibility	Comments	Overall score
Outcomes-based solutions **Solution 1: Managed entry agreements (MEA) – Art.81**							
Solution 2: Annuity based payment							
Solution 3: Intellectual-based payment (licensing)							
Pooling budgets **Solution 4A. Combined budgets within RIZIV/INAMI**							
Solution 4B. National silo innovation fund (pooled budgets outside RIZIV)							
Insurance based solutions: **Solution 5. Patient-based extra insurance**							
Solution 6. hedge fund							
Solution 7. Payer reinsurance carve-out							
Solution 8A. Social impact bonds							
Solution 8B. Manufacturer-based gene bonds							

13.b Detailed overview of the funding solutions

13.b.1 Outcome-based solutions

At this moment most initial MEA are mainly based on the clinical value of the new medicine demonstrated during the clinical trials (cfr. validated clinical end-points in Randomized Controlled Trials (RCTs)). In case of important clinical uncertainties more complex out-come-based MEA could be considered.

For this building block, it is crucial to determine which outcomes are key to define performance of the treatment. In addition, the way of collecting outcomes data (registries, …) and to ensure quality of these out-comes data is essential to define. But there are multiple dimensions of outcomes and related value, depend-ing on the perspective (HC provider, patient, payer, …). For value perception: clinical value, patient value (QoL), economic value, expands value dimensions. The humanistic burden is expanding the burden of disease / treatment burden, and reflects the impact on patients / caregivers, including morbidity, mortality, and overall patient quality of life. For haemophilia gene therapies, the most appropriate outcome-based criteria for per-formance-based funding / reimbursement are clotting factor levels in blood as a primary efficacy endpoint.

For outcome-based MEA, a choice between funding based on average population- or individual patient-based outcomes determination, has to be made. The difference between both options is illustrated by the following 2 MEA examples

- Outcome based pay for performance with payment based on average % responders in the real-world population versus % response in pivotal RCT:
    - *Initial upfront payment per patient, based on average % response or responders in the pivotal study.*
    - *After an agreed payment period (e.g. 1 year), the innovator is corrected retroactively, based on average effectiveness in the real-world population (versus efficacy in pivotal RCT).*
- Real-world pay for performance with upfront payment per patient depending on performance:
    - *Payer incurs a one-time cost after it has been confirmed to be effective in this individual patient (e.g. for haemophilia this is 12-16 weeks post administration).*
    - *The innovator covers part or the total cost of the gene therapy in case of a partial or no response (e.g. for haemophilia after 12 or 16 weeks).*

Funding based on average real-world outcome in the treated population (in comparison with the average population response in pivotal RCT) is preferred over a potential funding /reimbursement based on the indi-vidual variable outcome on a patient per patient basis. The latter would be more complex and could result in patient selection. In addition, with population-based outcomes, risk-sharing becomes possible.

On patient outcomes data collection in registries, the following topics need to be further clarified:

- Belgian sick insurance agency (NIHDI) feels that registration and follow up of outcomes data by health care provider in daily practice should be considered as a mandatory responsibility. Moreover, such registration responsibility could be considered as a requirement to allow reimbursement for his/her patient treatment (e.g. Tardis reimbursement biologicals for rheumatoid arthritis (RA) patients) especially in case of expensive treatment costs.

The implementation of a national electronic stand-ard haemophilia patient registry, foreseen by the Bel-gian haemophilia reference centres, is recommended to enable among others the future implementation of outcome-based funding/reimbursement solutions.

A. Outcome-based Managed Entry Agreements (MEA) – Art. 111, 112, 113

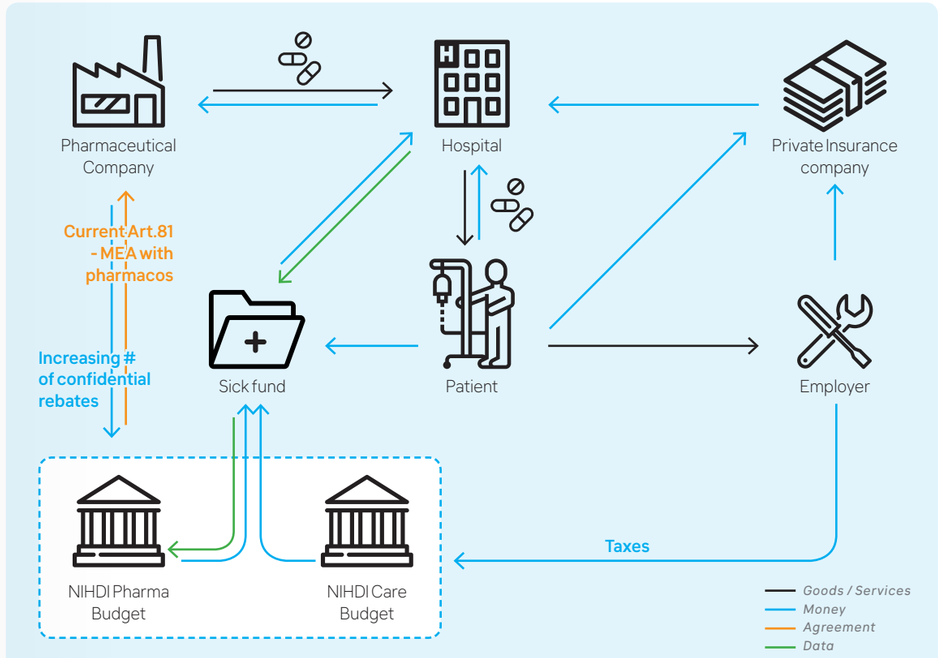

Figure 30

How does it work? (Detailed description)

Art 111, 112, 113 with emphasis on outcome-based or Pay-for-Performance (P4P) agreement i.e. a contract between payer and manufacturer where "the price level and/or revenue received is related to the future performance of the product in either a research or a real-world environment" (Towse & Garrison, 2010).

In the Belgian context, a MEA for gene therapy would initially start from a Willingness to Pay (WTP) cost level contingent upon (1) the expected performance as spec-ified in the ICER for each indication and (2) of its over-all budget impact. Subsequently, this cost will then be corrected for real world evidence (RWE) on outcome performance provided within a certain time frame, to be documented in the MEA.

RWE can be analysed using patient- or popula-tion-based methods.

How does it address funding challenges?

For gene therapies whose potential curing char-acteristics make them good candidates for possible amortized payment options, MEA's can combine an outcome-based agreement with instalment payments (Marsden, Towse, Pearson, Dreitlein, & Henshall, 2017).

P4P agreements ensure market access for inno-vative promising therapies, demonstrate value, allow sharing the risk between payers and manufacturers and limit total budget impact (Hanna et al., 2018).

MEAs attempt to reduce the scale of the payer risk of making the wrong decision, that is, paying for a tech-nology that is not good value for the health care system, primarily by reducing the total budget impact or by cre-ating an opportunity for the development of additional information to inform future reviews of the funding decision (Edlin et al., 2014).

Examples, cases:

Counter-example provided by organ or hip replacements, although expensive being reimbursed regardless of future benefits, this due to the admin cost of measuring PROMS outweighing the benefits (Danzon, 2018).

CSF assessment:

Financial attractiveness: Lack of incentives for clinicians to register patient outcome data in a standardized way and to compensate admin work. Potentially high transaction and administrative costs (Danzon, 2018; Marsden et al., 2017).

Equity impact and fairness: Real world outcome data needs to be captured by the treating clinicians and collected via a Trusted Third Party (TTP). It helps to address the growing concerns of the quality of clinical evidence from Randomized Clinical trials (RCTs) submitted at time of market access and make informed decisions on value of the new therapy in daily practice. In addition, it helps reassessing the value of the therapies on the market.

Consensus by the different stakeholders on the data to be registered (e.g. ongoing discussions concerning Haemophilia patient registry).and on the (co)ownership of these patient outcome-data is needed. The treating physicians and the patient must be willing to share their data in an anonymised way.

Traceability: Collection of real-world evidence will be useful in determining the long term effectiveness of gene therapies in daily practice. This could be key to establishing the durability of effect and identifying any unintended consequences over time.

The major issue is to engage clinicians and hospitals to register the patient outcome data within their patient registries in a standardized electronic way as they don't see a benefit for them and lack of sufficient incentives. This will be one of the priority actions for change needed to enable performance based MEA.

Pros:

- Possibility of re-evaluation of the value of the drug based on RWE.
- Allows for performance-based risk-sharing agreement between payer and manufacturer.

Cons:

- The biggest obstacle is the difficulty and cost of collecting evidence on outcomes (Danzon, 2018; Marsden et al., 2017).

Feasibility within the current framework:

- Belgian experience with MEA within NIHDI WG article 111, 112, 113.
- Belgian NIHDI Tardis example engaging Rheumatologist to collect RWD for some expensive biological medicines to enable reimbursement for their RA patients.
- Availability of the technical infrastructure Healthdata.be to collect standardised electronic patient outcomes data.
- Need for optimization in data registration based on FAIR data principles (FAIR Accessible Interoperable Reusable) (Wilkinson et al., 2016).
- Availability of trusted-third party (TTP) e.g. ScienSano, others.
- Payment / reimbursement is linked to practice patterns (e.g. adherence of the patient to the treatment) or is granted only for patients that satisfy eligibility criteria for example as a result of a genetic test. (cfr. below solution 2 spread payments solution).
- Patient-based RWE retrospective analysis on databases might be difficult to achieve given administrative cost hurdles at the healthcare provider side. In contrast, RWE can also be collected at the population level using prospective observational outcome studies.

Fit within the Belgian context:

- Art 111, 112, 113 already in place.
- Availability of Healthdata.be platform/infrastructure and a Trusted Third Party (e.g. ScienSano, others) to collect the patient outcome data electronically from standardized electronic patient registries.
- Outcome-based market entry agreements for gene therapy will require the specification of contractual terms – what constitutes "success" and "failure" and what will be paid for or not paid for (Marsden et al., 2017).
- The high cost nature of gene therapy emphasizes the need for a horizon scanning system to be put in place. This will facilitate the necessary early and proactive dialogue between payer and manufacturer.

Risks:

- No or insufficient buy-in from the medical community to set up and comply with a data collection system.

Relevance:

- The basis for a conditional instalment (annuities-based) payment system which is linked to the collection of post-launch RWD.
- Post-launch data collection may also be a prerequisite or even a requirement for insurance-based approaches to financing, or more specifically for outcome-based payments.

B. Spread payments (amortization)

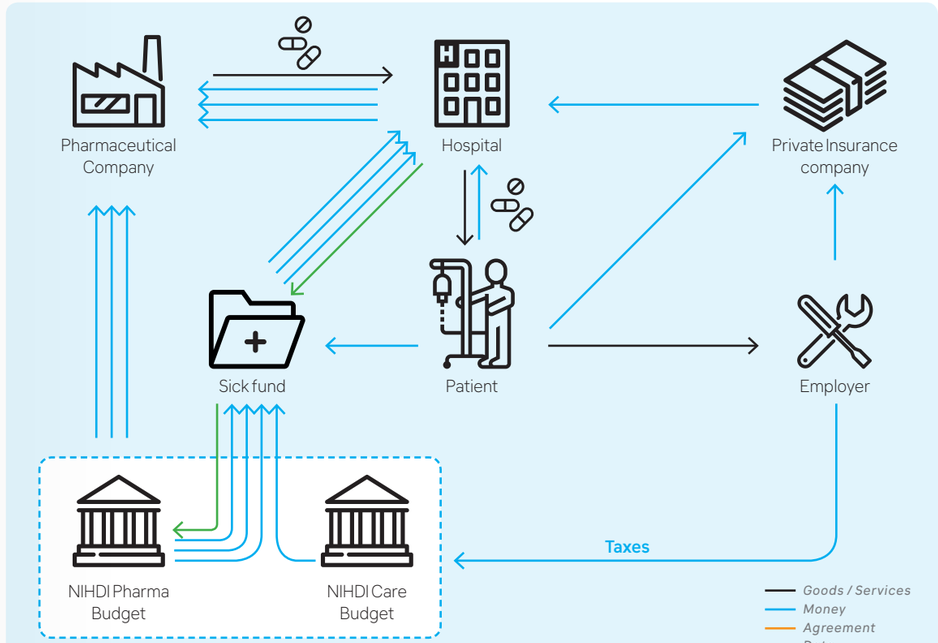

Figure 31

How does it work? (Detailed description)

The agreement between manufacturers and payers aiming to replace the high upfront cost with a stream of payments triggered by the achievement of patient outcome.

Payment by instalment aligns the payments to the flow of health benefits and cost savings (Danzon, 2018).

The spread payments (annuities) due for each period of health delivered could be established by calculating a stream of payments over the expected lifetime of the technology that has the same expected net present value as the agreed price (Edlin et al., 2014).

Risk-based amortization for curative gene therapy will be most useful when (1) the price of the treatment has been based on an agreed approach to assessing value, (2) there is a population group of a size that merits incurring the transaction costs of such an arrangement, and (3) there is a high certainty of durability of effect (Marsden et al., 2017).

The payment continues until the debt is repaid, the payer defaults or the benefit from the drug ends, whichever occurs first (Marsden et al., 2017).

How does it address funding challenges?

Because long-term effects of any new technology are uncertain, the strongest case is for future payments that are contingent on the actual health outcomes and savings realized. This shifts outcome risk from the payer to the producer, aligning the producer's incentives to design a product with the best possible long-term benefit-risk structure (Danzon, 2018).

Addresses, at the same time, the high immediate budget impact and the performance uncertainty.

Examples, cases:

Contingent payment contracts that have been adopted primarily target treatments with uncertain outcomes that are easily measured in the short- to medium-term, such as progression-free survival for cancer, blood sugar for diabetes, or gene therapy for blindness (Danzon, 2018; Jaroslawski & Toumi, 2011). Trastuzumab in early breast cancer as an exemplar of a technology leasing reimbursement scheme (Edlin et al., 2014).

CSF assessment:

Financial attractiveness: Spread payments and payer credits spread costs over time. The distribution of payments over time will have to be negotiated between payer and innovative manufacturer to fit the payer's present and future budget whilst incentivizing manufacturer present outcome delivery and sustained innovation. One possibility could be to pay a sum upfront to cover the administration cost and pay the rest of the amount outcome-based through amortization. Adequate interest rates will have to be agreed depending on the duration of the annual payments.

Equity impact and fairness: Because contingent instalment payments shift the risk to producers, producers would prefer an upfront, lump-sum payment unless the lump-sum payment is significantly less than the discounted sum of the expected instalments (Danzon, 2018). Risk-based amortization seems justified for gene therapy while such treatments have long enduring high value to justify their high price, thus making them suitable candidates for long term payments (Marsden et al., 2017).

Traceability: Needs to be based on post-authorisation registries and documented in a performance based MEA (see Solution 1), measured by a Trusted Third Party. Selection of appropriate end points to measure clinical outcomes must be validated by CTG/HTA commission (Carr & Bradshaw, 2016). Duration of the spread payments will have to be negotiated also considering the available long-term clinical evidence and the remaining clinical uncertainty in function of time.

Pros:

- A performance-based contract can align the payment and benefits stream over time and shift performance risk to the producer, who is likely to be more informed and more able to influence the product's actual performance (Danzon, 2018).
- Ensure optimal patient access limiting treatment/funding to responder's Awards innovation (Carr & Bradshaw, 2016).
- Spreads the costs for the payer (Carr & Bradshaw, 2016).
- Limits the financial risk if linked appropriately to health outcomes (Carr & Bradshaw, 2016).
- Help to increase the overall value of the treatment to payers by reducing the cost for those cases where the treatment is not effective (Hampson, Towse, Pearson, Dreitlein, & Henshall, 2018).

Cons:

- An important challenge lies in defining the clinical endpoints, which may be critical (Carr & Bradshaw, 2016). Would surrogate end points be accepted or are hard end-points required (Carr & Bradshaw, 2016)?
- May have operational challenges in practice such as insufficient budget to fund data collection or inadequate data collection systems (Hanna et al., 2018; Rosenberg-Wohl S., 2017).
- For manufacturers: streaming the payments over a much longer time period would increase the time-to-return on R&D investments, with implications for investments in developing future innovative technologies (Edlin et al., 2014).
- Observational level evidence has a greater risk of bias (Hampson et al., 2018; Hettle et al., 2017).
- Introduction of amortization could lead to higher prices and threaten the future sustainability of the health care system (Hampson et al., 2018).
- The necessity of a measuring these outcomes and collecting/analysing these data adds other stakeholders who will take a cut (Marsden et al., 2017).
- Clinicians and hospitals who need to register the data in a standardized way, don't see a benefit for them. When registering data during clinical trials, they are paid to do this; As soon as the medicine is reimbursed, the same effort is needed without reward.

Feasibility within the current framework:

- The biggest obstacle is the difficulty and cost of collecting evidence on outcomes over the whole care process, which also would require a Trusted Third Party analyzing the collected data. The technological framework is already in place (Healthcata.be) to collect the data.
- Need for early engagement and planning between manufacturers, regulators, payers and patients is fundamental (Carr & Bradshaw, 2016).
- There is likely no one-size-fits-all reimbursement template to suit every gene therapy, so linking annuity-style payments to the correct outcomes becomes a point of collaboration between manufacturers and payers, that will balance risk appropriately between the two without disadvantaging patients by delaying or restricting access (Carr & Bradshaw, 2016).
- Biomarker capturing must happen at the same frequency as the annuities.

Fit within the Belgian context:

- In Belgium, if patient-based RWE collection methods are chosen, the technological platform to collect the data is available (Healthdata.be). A centralised database system is available, which allows the safeguarding of the quality of the data over time. However, an independent Trusted Third Party (TTP) is missing that can independently analyse the data.
- Who pays for the transaction costs: payer and/or manufacturer?
- Following Belgian public accounting rules, it can be more appropriate to have the NIHDIpay the manufacturer directly instead of staying with the current way of working through hospitals and sick funds.
- The solution needs to comply with ESA guidelines (European System of Accounts) that only allow a government to have a debt towards manufacturers if there is the possibility to pay back with effective conditionality (hence where the risk exist that the full amount is not paid back in full). Outcome-based instalment contracts might fit these guidelines.

Risks:

- Transaction or admin costs monitoring patient outcome outweigh the benefit of reducing access decision uncertainty (Edlin et al., 2014).

Relevance:

- Risk-based amortization is relevant for therapies with following characteristics: when the price of treatment has been based on an agreed approach to assessing value, there is a population group of a size that merits incurring transaction costs of such an arrangement, the therapy is curative and there is a high certainty of durability of effect. (Marsden et al., 2017). Gene therapy fits this profile.

For this building block, the principles have been clarified and discussed including the eligibility criteria, the annuity duration, and the €-amount of the annuities.

Firstly, annuity-based payment can be applied on all breakthrough therapies with short-term affordability challenges. Annuity-based payment implies a loan-based scheme in which the innovator loans to the Payer. Therefore, this solution has public finance and accounting implications that need to be resolved.

ANNUITY ELIGIBILITY

Two annuity conditions have been detailed:

- The incremental medicine budget impact exceeding threshold (e.g. 0,5% of medicine budget): The eligibility criteria to apply annuity-based payment can be defined by means of the incremental annual net budget impact, the incremental cost per therapy, and the immediate medical need for the product. When considering the incremental annual net budget impact as a criterium one has to take into account the comparator treatment and target population. In Belgium, the CTG/CRM currently looks at a 3-year budget impact of the treatment on the medicines budget and whenever appropriate health care budget. However, in the case of curing gene treatment the time horizon for the peak budget impact and potential affordability challenge will be shorter also depending of the available pool of patients with this genetic disease needing or waiting for this potential curing treatment (which also depends of the fact whether any alternative treatment is already available) After further reflection on the medicine budget thresholds (0,5% of medicine budget = 20 – 25 million €) initially suggested by some stakeholders (sick funds) were considered significantly too low.
- Cost per patient: e.g. 100.000 € per year: As it was felt hard to propose hard numbers to define eligibility thresholds at patient cost- or treatment budget level the need to define strict quantitative financial eligibility criteria was questioned. Instead, it was suggested to take a treatment portfolio horizon scanning view and restrict the use of at least the annuity-based solution to those cases where there's a high medical need in combination with a short-term unaffordability issue.

DURATION SPREAD PAYMENT

Duration spread payments can vary depending of the longer-term therapeutic risk profile of the new therapy. This clinical uncertainty can be limited by linking the annuity to an outcome/performance based MEA. Currently, no guidelines are published to determine the duration, therefore, the following design principles have been proposed:

- The duration should consider the latest clinical evidence justifying expected duration of response and longer-term clinical uncertainties. The stronger the clinical RCT evidence in the long-term, the lower the risk and therefore the shorter the duration of annuities (e.g. for Haemophilia gene therapy RCT with 6 years follow up is being recommended).
- The minimum duration should be set by maximum affordable net annual budget impact.
- The Round Table suggested generally to limit the duration of spread payments to a maximum of 5 years. Spread payments becoming perpetuities is not preferred, nor for the payer or innovator, because it limits innovation on the manufacturer side (allowing for faster availability of cheaper next therapeutic generations) and diverting the payment burden to later generations.

ANNUITY €-AMOUNT

An annuity (A) is the payment or receipt of (equal) amounts of money per period for a specified period of time. Thus, in this case a principal amount (I), representing the negotiated full treatment cost, is split up over a number (n) of years.

$$A_t = \frac{rPV}{1 - \left(\frac{1}{(1+r)^n}\right)}$$

Figure 32

For illustration in Fig below, e.g. for a treatment cost of present value PV = 1000K to be uniformly spread (constant annuities) over 5 years this would not amount to an annuity A of 200K a year while the financing cost r still needs to be added following the above formula. Instead, in this example, if the interest rate for providing this amortization schedule is r=5%, the yearly annuity would amount to 231K to recoup the 1000K lump sum. This can be verified as 231K= 0.05*1000K/[1-(1/(1+0.05)^5]. Expressing the interest rate of 5% in extra annuity €-amounts above the split-up principal one gets n*A=5*231K minus I = 1000K, which gets us to a total of 155K to be added to the treatment cost of 1000K.

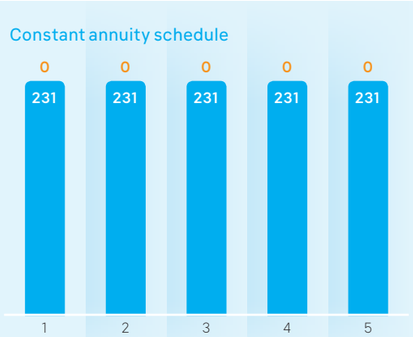

Figure 33 — Base Annuity & Value @ Risk

Summarizing from the illustrative examples above, the net yearly annuity €-amount is fully defined by the present value of the treatment cost (I), the number of periods (n) chosen and the applicable interest rate (r). Lower treatment cost, more periods and a lower interest rate will lower the required annuity amounts. An important remark relates to the interest rate amount.

Here, while the annuity scheme represents the repayment of a debt held by the National Payer to the innovative manufacturer, as a target interest rate a five-year government bond, issued by the BE government can be used. This would then situate r in the range of 2-5% max. The Round Table wanted the innovator to be transparent about this financial cost by quoting, if applicable, a treatment price with and without annuities.

LINKING SPREAD PAYMENT-TO TREATMENT OUTCOMES

Spread payment is a solution to deal with the funding challenge, but how to deal with failure and non-responders? Spread payment linked with outcome-based funding therefore provides more certainty to payers allowing "real" value-based pricing and "real value for money. A spread payment funding mechanism in association with outcome-based funding diverts the risk to the manufacturer. To link repayment to on-going value creation a treatment risk profile should be determined. The treatment risk profile maps the RCT-derived probability of success p(s) or Result Rate (RR) of a treatment over time, as measured by a determining biomarker (for Haemophilia the rate of patients for whom the clotting factor stays above a certain threshold, could be used).

A gene therapy typically features an administration period in year 1, followed by a life-long cured period. Hence, as can be verified in the illustrative Fig example below, we took an initial RR =0.8, derived from RCT or RWE captured from registries. Then, after successful administration we assumed the yearly measured RR (=% of initially treated patients still featuring in year i, a clotting factor above threshold) to be 90%, now to be derived from RWE.

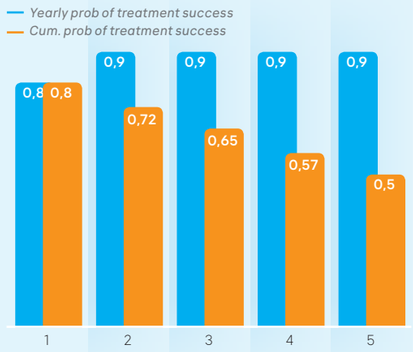

Figure 34 — Illustrative treatment Risk Profile

To link annuity repayment to treatment outcome performance we are interested in the Cum RR; the cumulative RR. So, for a Year 1 RR=0.8 followed by 4 periods of p=0.9, we get the following illustrative treatment Risk profile expressed as a table of yearly and cumulative RR:

231	0,8
462	0,9
693	0,9
924	0,9
1.155	0,9

Figure 35 — Illustrative treatment Risk Profile

To get to an outcome-corrected annuity scheme, each annuity now needs to be multiplied by its corresponding Cum RR. Doing so for this illustrative case results in Fig. below where the 231K constant annuity schedule now should be corrected by the value that is at risk of not being realised. In this specific case this means that in comparison with the non-outcome contingent annuit schedule, of the yearly 231K received by the innovator company, now in Year 1 through 5, respectively 46K, 65K, 81K, 96K, and 110K are maximally at stake, to the extent RWE cannot corroborate the planned for RR, as evidenced by RWE.

As a summary indicator for the risk run by the innovating company, to not be able to fully get reimbursed for its treatment, we define;

$$\text{Value @ risk (\%)} = (I - I_{RR})/I$$

Figure 36

Where I_{RR} is the cumulative RR-corrected initial I. The Value at Risk in this case amounts to 34% over the 5-year annuity schedule duration. Expressed in absolute €-amounts, Value at Risk goes up with r and n. So, a higher interest rate r or a longer annuity period n increase the Value at Risk in absolute terms.

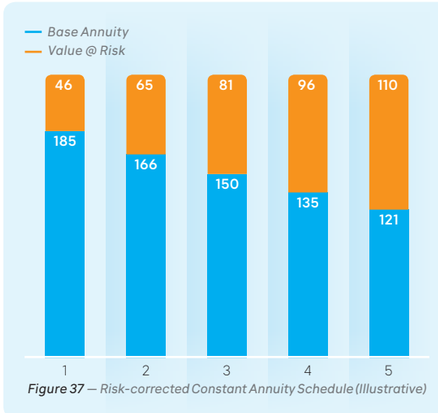

Figure 37 — Risk-corrected Constant Annuity Schedule (Illustrative)

C. Intellectual-based payment (licensing)

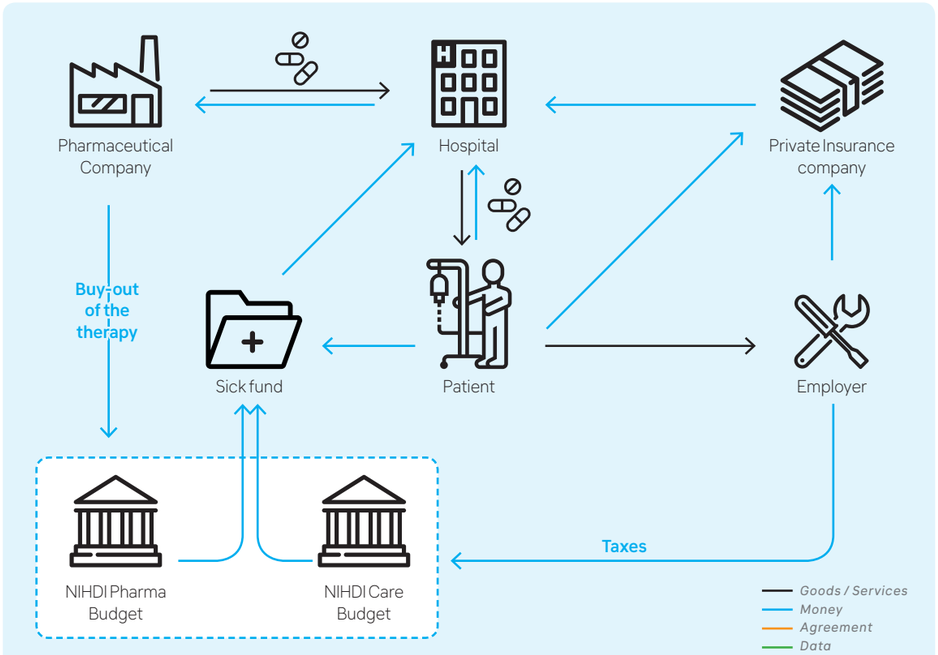

Figure 38

How does it work? (Detailed description)

IP-based payment awards the innovative manufacturer with a large financial sum in return for full government control over production and distribution, a public buy-out of the therapy. A second option is to license out these production and distribution rights to public or private payers, while the manufacturer maintains intellectual property (IP) rights (Carr & Bradshaw, 2016; Hanna et al., 2018).

How does it address funding challenges?

After buying the IP from the company, the remaining costs are completely controlled by the payer, hence potentially seen to have a price-lowering effect.

Examples, cases:

Simpler agreements have been proposed in the computer software industry. However, these are not ideal for gene therapies since they do not solve the problem of uncertainty for a one-time treatment and are, in fact, better suited to chronically administered drugs in this respect (Carr & Bradshaw, 2016).

CSF assessment:

Financial attractiveness: After buying the IP from the company, the remaining costs are controlled by the payer.

Equity impact and fairness: While the payer now controls cost, this is now seen to have a potentially limiting effect on gene therapy price.

Traceability: Not applicable.

Pros:

- Once the IP is bought, the costs are controlled by the payer hence this solution could be seen as potentially price-limiting.

Cons:

- Single country affordability to buy IPs with broader/international coverage.
- Does not reduce payer uncertainty on outcomes achieved.
- Neither attractive to manufacturers, nor to payers, as interest become reversed (payers become responsible for production, among others (Hanna et al., 2018). Quid innovative synthesis and production know-how needed for gene therapy to be implemented.
- Public bodies are unlikely to have capacity to run multiple treatment schemes and innovation-leading manufacturers are unlikely to be willing to devolve their interests to such an extent (Carr & Bradshaw, 2016).

Feasibility within the current framework:

- Very unlikely (see under Relevance).

Fit within the Belgian context:

- A solution coming close to compulsory licensing, which is not part of current Belgian pharmaceutical healthcare policy.
- Belgium or any country is unlikely to have capacity to run multiple treatment schemes and innovation-leading manufacturers are unlikely to be willing to devolve their interests to such an extent (Carr & Bradshaw, 2016).

Risks:

- All the risks (both ex-ante and ex-post risks) are transferred to the government, and hence ultimately the taxpayer.

Relevance:

- These schemes involve a paradigm shift in the current pharmaceutical-healthcare model. Public bodies are unlikely to have capacity to buy IP rights and manufacturing know how or to run multiple treatment schemes (Carr & Bradshaw, 2016).

13.b.2 Transversal / pooling budgets

The third building block covers the possibility of implementing a transversal integrated NIHDI Healthcare budget, instead of the actual silo NIHDI budgets (pharmaceutical specialties budget versus care budget). A transversal budget, for a breakthrough treatment, can only apply in case of significant savings in healthcare and societal costs. These indirect costs however need to be well-documented in order to demonstrate the savings and impact on the healthcare budget. Cost of illness with clearly documented local data is required to assess savings on the care budget and to justify transversal or pooling of budgets. However, documenting and estimating the indirect costs will be a challenge in complex diseases. Transversal or cross-silo pooled budget models can provide an opportunity in case potential curing therapies would generate significant reduction in healthcare cost. However, silo or transversal budget monitoring is required. A consensus with other stakeholders on the curing or significant savings potential has to be achieved. Even if significant savings in other health care silo budgets would be demonstrated/ proven in case of curing therapies it is expected to be challenging to justify any budget transfers to the medicines budgets and to achieve buy in from the other silo HC budget owners. Consequently, pharmaceutical industry must in that case also be willing to accept decrease of the pharmaceutical budget if significant savings in the pharmaceutical budgets can be made due to better care.

Moreover, a public-private fund for breakthrough pharmaceuticals could also be considered as a solution.

A. Combined budgets (within NIHDI)

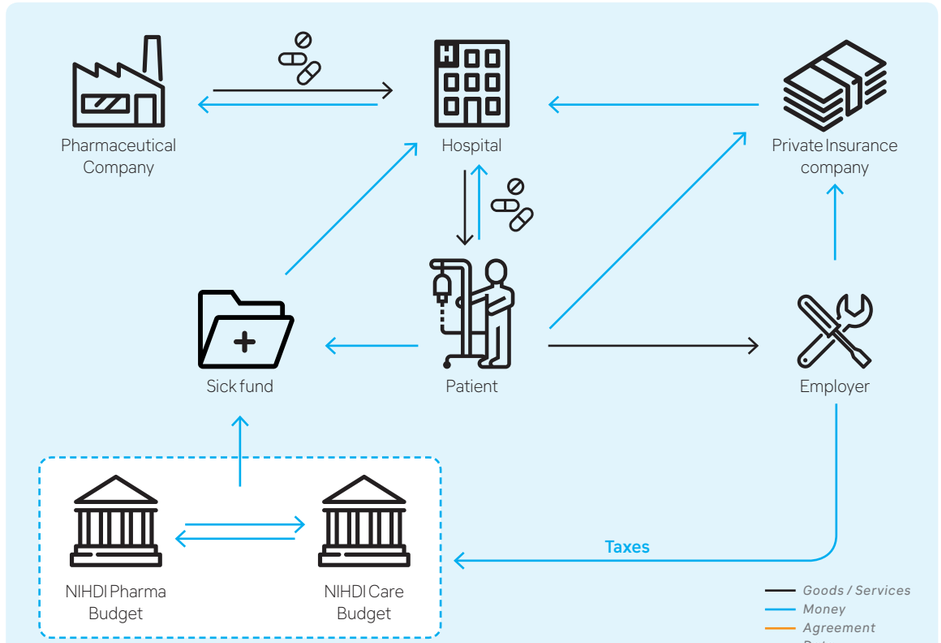

Figure 39

How does it work? (Detailed description)

NIHDI Pharma and NIHDI Care pool budgets for specific innovative products (e.g. ATMP's) or therapy area and bundle payment per episode of care or patient cured depending of the cost of illness.

How does it address funding challenges?

Cure reduces the cost of the illness and consequently health care cost.

Spread the pharmacological treatment cost over several budgets benefiting of the resulting savings of cure, rather than imposing an unreasonable financial burden on the pharma budget.

CSF assessment:

Financial attractiveness: Potential curative treatment can provide an opportunity to reconsider a cross-silo approach such as pooling or transfers of budget but strong evidence (e.g. through a cost of illness study) will be needed to justify possible transfers i.f.o savings outside medicines budget.

Only has potential if the cost of illness represents a substantial budget in comparison to the medicine budget part of the gene therapy (e.g. haemophilia).

Equity impact and fairness: will be strongly stakeholder-dependent.

Traceability: Needs transversal budget monitoring structures and curing therapy evidence-based case.

Pros:

- Healthcare costs avoided by gene therapies will free up budget for other care activities.

Cons:

- Need to document cost of illness.
- Needs transversal budget monitoring structures.
- Needs a strong evidence-based case for transversal budgeting to be believed in by various healthcare system stakeholders.

Feasibility within the current framework:

- Only worth the effort if the amount is high enough (range of millions).

Fit within the Belgian context:

- Needs transversal budget monitoring structures to determine the cost of illness, which are not in place for the moment.
- Non-pharmaceutical and/or indirect costs can be / are substantiated by the manufacturer in the access file and are taken into account for its access decision, but not further used in a transversal budgeting system.
- Can transversal budgeting be applied to the wider budgeting context with the aim to increase welfare?

Relevance:

- Transversal cost of illness study needed to further investigate for a detailed case such as haemophilia.
- Highly likely to be seen by care providers as an opportunity cost, not as a saved budget to be used for pharmaceutical specialties.

B. National silo fund: pooled budgets outside NIHDI

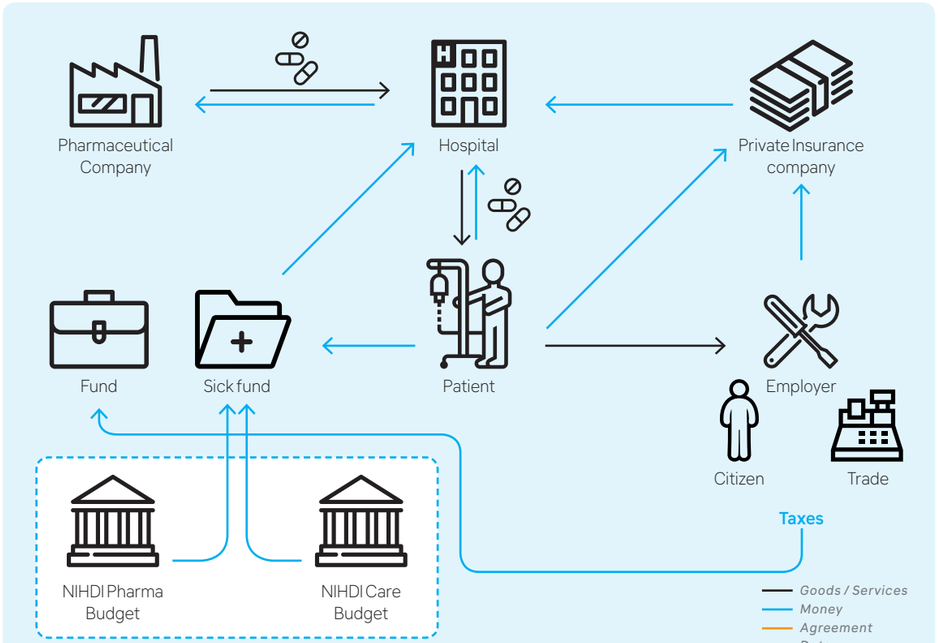

Figure 40

How does it work? (Detailed description)

NIHDI Pharma (and NIHDI Care?) put budgets into a dedicated condition-specific innovation fund (Hanna et al., 2018) based on horizon scanning feedback and depending on health care priorities.

How does it address funding challenges?

Financed through the government budget, i.e. taxes, on top of the health insurance budget. These funds allow circumventing affordability issues and the tight pricing regulations for pharmaceuticals, creating an exception, and may therefore represent an option to fund ATMPs (Hanna et al., 2018).

Examples, cases:

AIFA Fund (Italy), NMF, (Scotland), the Cancer Drug Fund (UK) (Hanna et al., 2018).

CSF assessment:

Financial attractiveness: The government will need to define a proportion of GDP allocated to this fund. Taxes on medicines or specific transactions could be considered to finance some innovative drugs procurements and supply.

Equity impact and fairness: Extra burden on society through extra taxes to raise money for the fund to benefit a small population.

Traceability: A robust and effective horizon scanning will be critical to allow strong forecasting of the resources necessary to fund ATMPs, and to ensure that prices of ATMPs are aligned with the budget.

Pros:

- Could be used to secure temporary funding for gene therapies representing non-parametric risk and hence for which insurance-based solutions are not feasible while outcome evidence is still lacking.

Cons:

- National healthcare providers and insurers are unlikely to risk such a high level of investment for unproven drugs.
- A possible misuse of the product is possible making it difficult to maintain costs (cfr. Cancer Drug Fund) (Carr and Bradshaw, 2016).

Feasibility within the current framework:

- Existence of Early Temporary Access budget for Unmet Medical Need drugs.
- Only for products for which risk is non-parametric. Needs to be complemented by a real-world evidence capturing system to understand the risk over time and hence eliminate its non-parametric nature.

Fit within the Belgian context:

- Depending on where the means for the fund come from, there might be societal and equity issues when raising new money to treat a small part of the population.

Risks:

- As the funds are then available, there is a risk of providing the therapy for patients even when the clinical effectiveness is unclear or the uncertainty about it, is too high.

Relevance:

- Can be used as managed access fund for gene therapies that cannot prove effectiveness, representing non-parametric risk and need a set period to allow for evidence generation.

13.b.3 Insurance-based budgets

A. Patient-based extra insurance

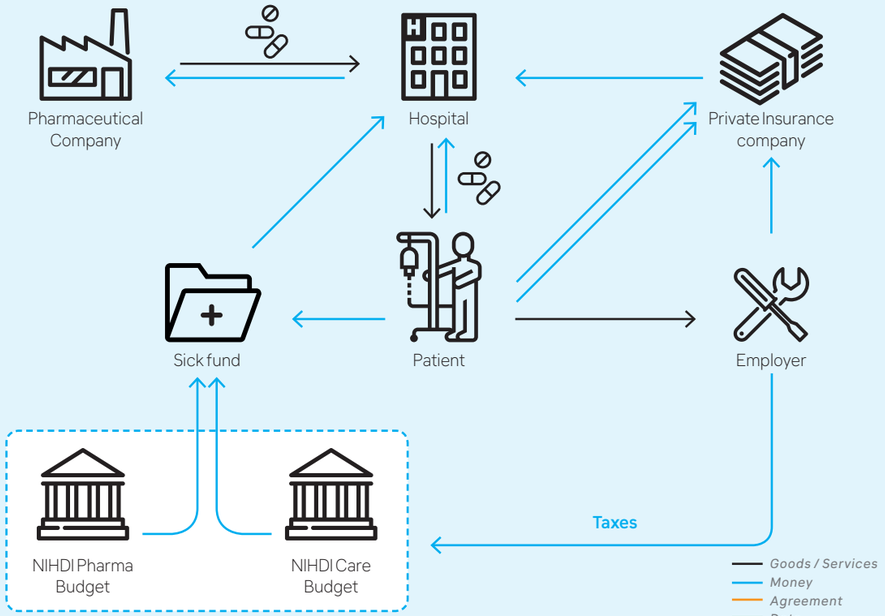

Figure 41

How does it work? (Detailed description)

Increase the co-payment of the patient for this treatment. This increased co-payment can be covered by an additional private health insurance. (Edlin et al., 2014; Montazerhodjat, Weinstock, & Lo, 2016).

How does it address funding challenges?

By increasing the co-payment of the patient the amount of budget that must be provided by the government is decreasing.

Examples, cases:

Mainly US-based.

CSF assessment:

The solution based on extra private patient insurance is not supported, because of its contradiction with the basic philosophy of the Belgian social security system: solidarity and equality (cfr conclusions 1st Round Table).

Financial attractiveness: Could lower the weight on pharma budget.

Equity impact and fairness: Considered to be extremely unfair to the patient in a EU health policy context.

Traceability: Not applicable.

Pros:

- Accessibility of drug to patients, which is still better than lack of coverage (Carr & Bradshaw, 2016).

Cons:

- Development of a healthcare system with 2 speeds. No more equal access for all patients.
- Adding a stakeholder, with potentially different objectives and interests, may overcomplicate payment and patient access (Carr & Bradshaw, 2016).

Fit within the Belgian context:

- Not feasible in a social welfare economy.

Risks:

- Risk of insurance companies refusing patients because of genetic predisposition.
- Insurance companies are not willing to cover this risk because they do not understand it (hence they cannot price it).

B. Hedge fund

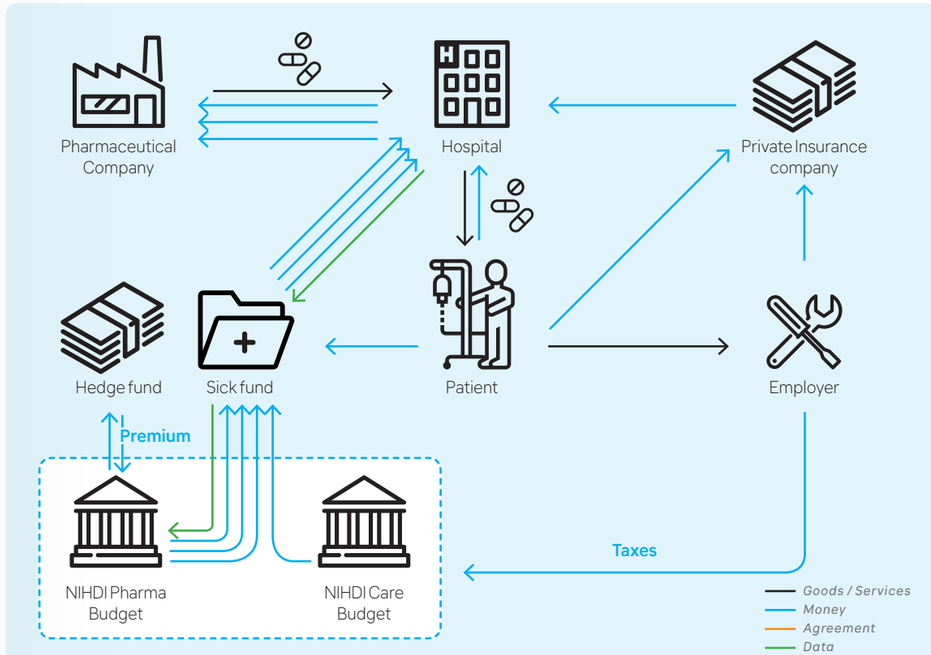

Figure 42

How does it work? (Detailed description)

A third-party Hedge Fund provides loans to NIHDI- and bears the risk if the payer stops repayment if the patient dies or the therapy stops working and build in a risk related premium (Marsden et al., 2017).

The therapy risk is taken on by the payer and covered by an investor.

How does it address funding challenges?

These funds allow circumventing affordability issues and the tight pricing regulations for pharmaceuticals, creating an exception, and may therefore represent an option to fund ATMPs (Hanna et al., 2018).

Examples, cases:

Common in industries outside of healthcare.

CSF assessment:

Financial attractiveness: The government can take a loan at favourable conditions. However, the Hedge fund will charge interest or a premium risk price depending on the risk provided by the gene therapy.

Equity impact and fairness: The premium risk price might be a challenge.

Traceability: A robust and effective horizon scanning will be critical to allow strong forecasting of the resources necessary to fund ATMPs.

Pros:

- It is a known loan-based funding solution taken by the government
- Accessibility of drug to patients, which is still better than lack of coverage (Carr & Bradshaw, 2016).

Cons:

- The premium price charged for the risk represented by the gene therapy
- Relieves short-term budget pressure. Spreads the risk, but does not solve the long-term sustainability issues (Marsden et al., 2017)
- An investor fund is poorly equipped to estimate therapy risk and hence is highly unlikely to accept such a contract.

Feasibility within the current framework:

- Feasible solution.

Fit within the Belgian context:

- Healthcare loans can be taken at present by the government.

C. Payer reinsurance

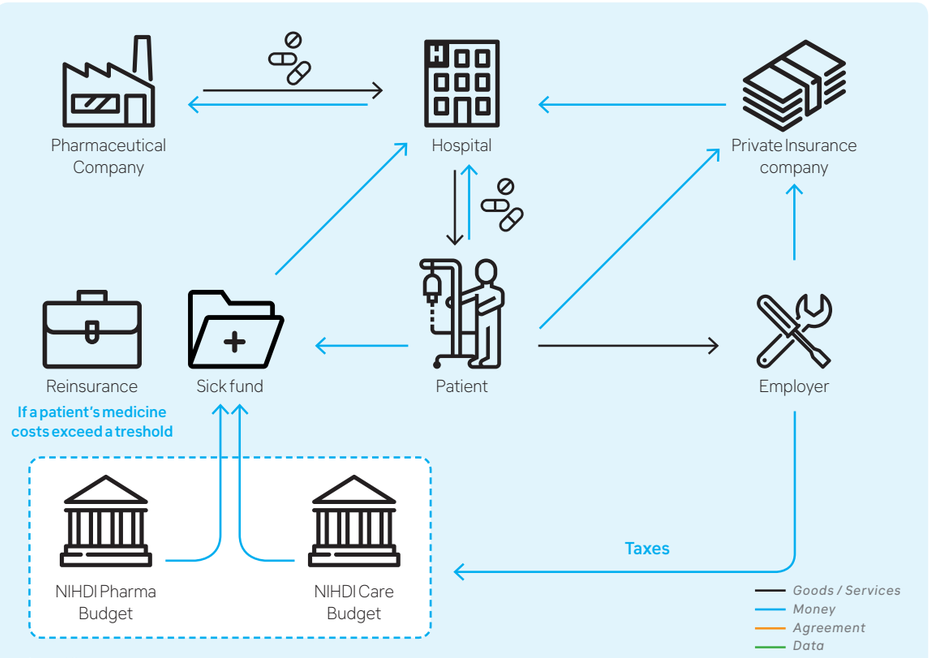

Figure 43

How does it work? (Detailed description)

(Re)insurance is an insurance policy that payers buy to protect against their ex-post risk of exceeding their budget (Zettler & Fuse Brown, 2017), in this case the budget foreseen for gene therapy. The reinsurance risk pool reimburses payers for the portion of claims incurred by high-cost patients, the same way.

The concept is not all that different from reinsurance today, but with a lower attachment point (i.e., the amount an insurer pays until supplemental insurance coverage comes into effect) for specific high-cost drugs, or an individual aggregate amount for patients with total drug costs past an attachment point, for example, $25,000, or some other breakpoint around which specialty pharmaceutical costs tend to cluster (Kleinke & McGee, 2015).

The therapy risk is taken on by the payer and covered by an insurer.

How does it address funding challenges?

Protects against adverse selection and consumers against destabilization of the insurance market and discriminatory health insurance practices (Zettler & Fuse Brown, 2017).

Relieves short term budget pressure. Spreads the risk but does not solve the long-term sustainability issues (Marsden et al., 2017).

Examples, cases :

Very high-cost healthcare claimants in US.

CSF assessment:

Financial attractiveness: Covers for unexpected (ex-post, not part of horizon scanning) healthcare costs. Attractiveness depending on how high the risk of high-cost patients and consequently how high the premium to cover this risk is (Marsden et al., 2017).

Equity impact and fairness: Makes health budgets robust against unexpected ex-post budget raises.

Traceability: Transparent overview of typical ex-post high patient costs needed to determine the amount the insurer has to cover.

Pros:

- Unexpected high-cost patients are covered by the insurance to keep the payer budget sustainable.
- Increases robustness of healthcare expenditures.

Cons:

- The requirements for reinsurance can be very specific (Marsden et al., 2017).
- Relieves short term budget pressure. Spreads the risk but does not solve the long term sustainability issues (Marsden et al., 2017).
- A premium must be paid by the payer to the insurer.
- Adding a stakeholder, with potentially different objectives and interests, may overcomplicate payment and patient access (Carr & Bradshaw, 2016).
- An insurer is equipped to estimate therapy risk but charges a high premium to cover this gene therapy related risk.

Feasibility within the current framework:

- Clear criteria are needed to determine what is a high-cost patient and which diseases need to be covered by the budget-exceeding risk premium.
- When assuming outcome-based amortization, the likelihood of exceeding the foreseen budget is small or even non-existing. With outcome-based amortization one might not pay back the full amount when the outcome is not met corresponding with a lower budget to be spend than forecasted.

Fit within the Belgian context:

- Healthcare loans can be taken at present by the government.

Risks:

- Commercial insurers may look to exclude high cost therapies (Hampson et al., 2018).
- Re-insurers do not accept risk that cannot price with a reasonable degree of accuracy. For this to happen, data is needed, which is largely missing at the moment.

Relevance:

- Only relevant if the risk of a high-cost patient and the cost when exceeding the budget is high enough to cover the premium that must be paid.

D. Social impact bonds

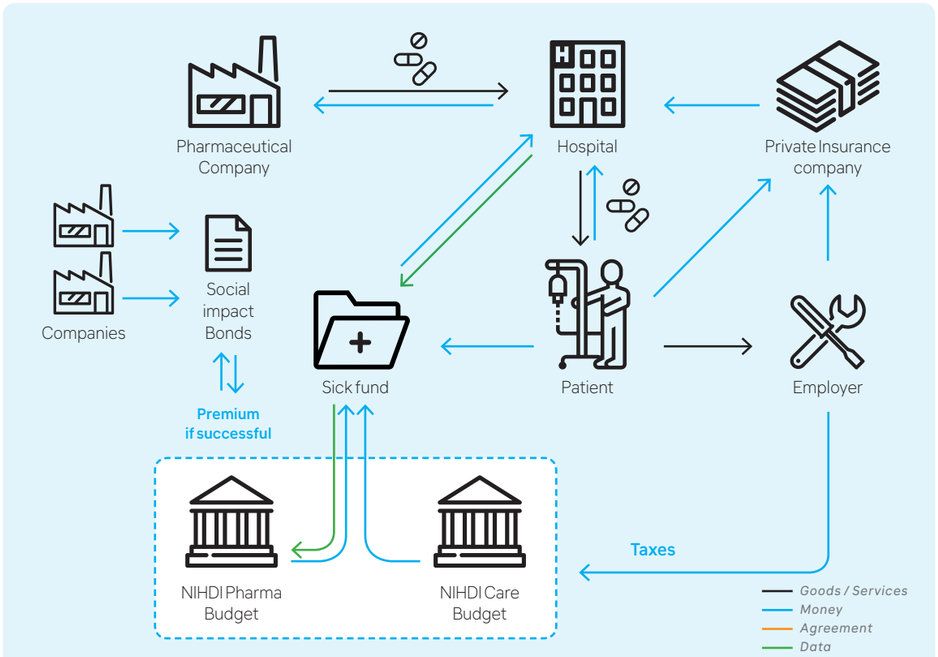

Figure 44

How does it work? (Detailed description)

Pay for success scheme (e.g. health benefits). Funders (e.g. private insurers) get a return when the public interest initiative achieves positive results. Could be paid from healthcare savings generated by the therapy.

The therapy risk is taken on by the payer and covered by the capital market. (Hanna et al., 2018; Katz, Brisbois, Zerger & Hwang, 2018).

How does it address funding challenges?

Use the social bond capital markets to address the raising budget issue for highly innovative curing therapies. (Hanna et al., 2018; Katz, Brisbois, Zerger & Hwang, 2018).

CSF assessment:

Financial attractiveness: Insures the payer against unexpectedly high budgets making use of the capital (bond) market.

Equity impact & fairness: The public capital (bond) market insures the payer for expensive therapies. However, the payer can still offload therapeutic risk to the innovative manufacturer through an outcome-based spread payment MEA.

Traceability: A Trusted Third Party monitoring therapeutic and mortality risk is a prerequisite for an insurer to step in to this bond scheme.

Pros:

- Social impact bonds have the capacity to fund innovative health and social programs while generating profits for investors and savings for governments.

Cons:

- Increased costs for governments through paying of surcharge for investors.
- Restricted Programme Scope as the success is tight to a limited number of metrics. A premium must be paid by the payer to the insurer.

Feasibility within the current framework:

- Predetermined criteria are needed for the scope of the bond solution.

Fit within the Belgian context:

- Unlikely for insurers to step into national payer-based plans given the too small scale.

Risks:

Will be more difficult if not impossible if risk seen to be non-parametric by the insurer e.g. if endpoints are more difficult to measure as in the case of Duchenne or Spinal Muscular Atrophy.

E. Manufacturer-based gene bonds

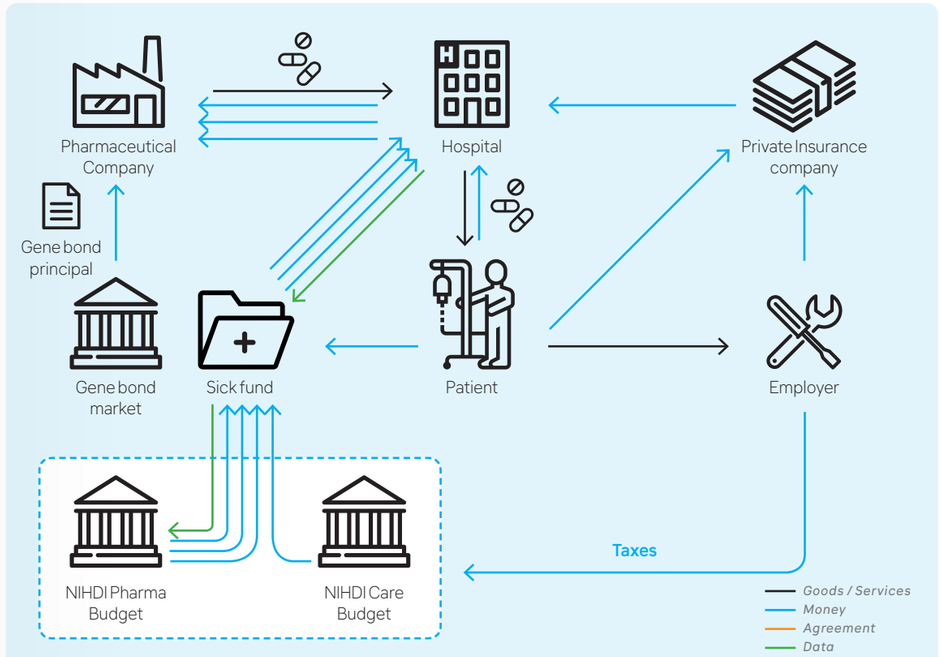

Figure 45

How does it work? (Detailed description)

Gene bonds are a financial market instrument available to innovative manufacturers to insure them against therapy risk i.e. against payers halting spread payments while the therapy is not (sufficiently) delivering promised outcome.

A preset limitation or index will be determined (e.g. a predefined set of patients for which the gene therapy doesn't (sufficiently) work or for which the effect only lasts a short period of time).

Gene bonds are issued on the financial obligation markets through an auction. They are bought by institutional investors (ex. Pension plans and asset managers). Gene bonds are attractive while being uncorrelated with other financial instruments (they are not related to the macroeconomic and economic and financial crises) and give a reasonable return (currently catastrophe bonds give a return between 2,5 and 3,5%). Gene bonds typically are set out for a specific period of time (3-5 years).

The money from the bonds (the principal) can be invested in safe investments or in pharmaceutical innovation.

Bond holders get the annual return and the principal if the limit is not reached. If the limit is reached, the principal is used to pay for the costs.

The therapy risk is taken on by the manufacturer and covered by the capital market.

How does it address funding challenges?

It covers the therapy and mortality risk the manufacturer has to take, while incentivizing the manufacturer to bring a good therapy to the market.

If the therapy does not work as expected, the preset limit or index is reached (see left column), and investors start losing a proportion of the principal of the bond. The manufacturer will then incur reputational costs on bond markets which they will try to avoid.

Examples, cases:

Pandemic bonds of the World Bank.

CSF assessment:

Financial attractiveness: Insures the manufacturer against poor therapy outcome.

Equity impact and fairness: The payer can still offload therapeutic risk to the innovative manufacturer while the latter will then face a lower principal to be invested (preferably) in future innovation.

Traceability: A Trusted Third Party monitoring therapeutic and mortality risk is a prerequisite for an insurer to step in to this bond scheme.

Pros:

- Covers innovative manufacturer for therapy and mortality risk whilst still incentivizing it to deliver the promised therapy outcome.
- Gene bonds are a solution for manufacturers accepting a spread payment MEA: streaming the payments over a much longer time period would increase the time-to-return on R&D investments, with implications for investments in developing future innovative technologies (Edlin et al., 2014).
- Principal could be used by the manufacturer to fund innovation at bond market rates as opposed to stock market rates i.e. ultimately having a downward effect on therapy development cost, and by extension on therapy price.
- Financing through capital markets is stimulated, which is in line with European Commission policy of increasing financing through capital markets.
- Big re-insurance companies who would issue the bonds for the manufacturer are larger and have less debt.

Cons:

- Need for a Trusted Third Party to monitor real world effectiveness, which incurs costs.

Feasibility within the current framework:

- Only possible with an ex-ante parametric (i.e. defined and understood by the insurer) risk: measurable endpoint biomarkers, toxicity, long term risks, epidemiology
- Only possible with sufficient scale: different diseases can be aggregated into one specific bond, or one can aggregate geographically (different countries).

Risks:

- Pricing can be difficult the first years due to lack of data, unless a European structure (similar to Healthdata.be) is put in place.

Relevance:

- This securitization of gene therapy is part of "Insurance-lined securities", which is a growing market.

13.c Round Table 2: Outcome stakeholder group break-out discussion of the preferred solutions

SOLUTION 1 **Outcome-based MEA**

Stakeholder Solution

	Authorities	Sick funds + private insurer	Academia + patient groups	Industry

PROS	• In line with EMA asking more evidence and outcomes data for accelerated authorization procedures
	• Allows for a tendering model for same type of therapy. However, tendering criteria should include quality criteria and not only price.
		Eligibility conditions:
		• Only for paradigm-shifting innovative therapies with either
		  • *impact exceeding 0.5% of the pharmaceutical budget at NIHDI (20 – 25 million €)*
		  • *cost over 100.000 € p.p. and p.a.*
		• Contracts must be disease-specific
			• Eligibility for reimbursement:
			  • *patient should have yearly/regular check-up to be eligible for reimbursement.*
			  • *In addition, both patient and doctor should register to ensure input from both.*
			• Registries:
			  • *Population-based registries is only an option if the group is large enough. For rare diseases, this is more difficult. European registries could therefore be a solution.*
			  • *Patient-based registries might be less feasible due to the high admin burden.*
				• Possibility of re-evaluation of the value of the therapy based on RWE
				• Allows for performance-based risk-sharing agreement between payer and manufacturer

CONS	• Outcomes data will not be immediately available because difficult to collect patient-centred data. Also, historical longitudinal data is missing. Healthdata.be can facilitate the data collection. • Lack of transparency of the MEA contracts			• RWE data collection will be difficult and costly for all stakeholders: HCPs, patients (PROM), company (register), payer (don't have the means to analyse the data) • Should be combined with solution 2 to avoid peak in expenses and costs for payer

CHALLENGES AND COMMENTS	• Defining good end points, will be easy for some diseases and complicated for others
	• How will we deal with partially achieved end-points?
	• Preference for determining a European starting price ("eenheidsprijs") using Value-Based assessment tools. Moreover, this price can be corrected for each country based on the economic reality.
	• Spread payment mechanism is only applicable for breakthrough/potentially curing therapies that generate sufficient healthcare savings to avoid a shift of the financial burden to next generations.
		• This solution should be combined with solution 2.		• Outcomes and endpoints should be discussed proactively:
				  • *early on, before start of reimbursement procedure*
				  • *in collaboration with HCPs and other stakeholders*
				• Registries:
				  • *Set-up of RWE register is demanding and requires time*
				  • *lack of incentives and adequate IT infrastructure*
				  • *Healthdata.be only collects data but does not analyse the data (EMA collects and analyses data)*
				  • *Preference for population-based registers for rare diseases at EU level, also covering patients that can't be followed (relocation,…) or therapy-unrelated deaths.*

SOLUTION 2 **Spread payments**

Stakeholder Solution

	Authorities	Sick funds + private insurer	Academia + patient groups	Industry

PROS	• Model is coupled to performance
	• Production cost could be reduced over time and should be included in the spread payment
	• Possibility to conduct longitudinal studies and collect data on long-term
		• Duration: 5 years payment, to confirm therapy is effective and preventing transfer of payment to future generations. Risk profiles need to be defined as they will affect the payment period. Spread payments should first cover the production cost, followed by value-based pricing.
		• If the therapy doesn't work:
		  • *Pay back: not preferred as a substantial amount of money will have to be paid back (P4P)*
		  • *Stop payment, which was the preferred solution (CED)*
			• Spread payment coverage:
			  • *Start with higher start-up fee (for production costs) followed by a lower amount spread over time (degressive spread payments).*
			  • *value health gain or work with a cost-based pricing.*
				• Ensure access for all patients, but payer funding could be limited to responders only.
				• This solution in combination with solution 1, provides more financial stability for payers and industry

CONS	• Administrative burden to keep track of data and payment system			• Shift of performance risk to innovator, depending on the duration of annuities and level of first payment.

CHALLENGES AND COMMENTS	• Duration should be limited in time: suggestion of fixed duration of 5 years (for all diseases) to avoid endless discussions and uncertainty for industry.
	• Definition of failure is needed + course of action in case of partly successful therapy: stop treatment.
	• Accountability for failure should be split over stakeholders, e.g. incentive to train HCP to avoid administration errors
	• The preferred model is a combination of solution 1 and 2 that moves towards a more individualized patient-based performance model
	• Suggestion to "lease" therapy to solve ESA restrictions
		• This solution should be combined with solution 1.	• Duration of spread payments should be disease specific and depends on the presence of comparator.
			  • *If reimbursed comparator available: payments until all costs of the new therapy is paid back*
			  • *If no comparator available: look for comparison with other therapies including surgery*
			• How to cover the risk of:
			  • *Lost patient due to therapy-unrelated issues (death, relocation,).*
			  • *Therapy-induced diseases (e.g. cancer)*
			• Possibility of stratification, cf. HepC where therapy was also expensive. But untreatable diseases this is difficult.
			• Possible alternative models:
			  • *Include as many patients as possible into clinical trials*
			  • *Hospital exemption (cf. Sheffield) where hospital produces the therapy. However, not applicable on a routine base for all patients*
				• This solution in combination with solution 1, increases affordability and financial predictability /stability for payers and industry.
				• Initial lump sum should be attractive enough for innovator. Degressive spread payments model is preferred

SOLUTION 4A: COMBINED BUDGETS WITHIN NIHDI

Stakeholder Solution

	Authorities	Sick funds + private insurer	Academia + patient groups	Industry
PROS				• Health care costs avoided by gene therapies might free up budget for other care activities
CONS	• Complex and can incur more costs than savings, definitely in case of non-ideal treatment • Other stakeholders funded by other silos, will disagree and not support this solution.			• Bundled "forfaitary" payments can lead to decrease and insufficient budget use, which can in turn lead to selectivity of patients (cherry-picking by hospitals) • How to deal with reimbursement if budget is spent before end of the year • Only worth the effort if the amount is high enough • Likely to be seen by care providers as an opportunity cost
CHALLENGES & COMMENTS	• Cost-of-illness study needed • Include patient preferences and accountability by letting the patient decide on how to spend his budget envelope • Examples in Scandinavia: local pooled budgets and local authorities decide on spending. In Denmark, savings generated by using generics is allocated to fund hospitals.	• Feasibility of this solution?		• Major challenge to align with the different HCPs • How to deal with potential productivity gains and savings that also impact the environment of the patient (family, caregivers,)

SOLUTION 4B: NATIONAL SILO FUND – POOLED BUDGETS OUTSIDE NIHDI

Stakeholder Solution

PROS	• Stimulation for pharma companies to invest in rare diseases, to open the field. For government way to promote and focus investments on new technologies/ therapeutic fields. • Easiest solution to sell to all stakeholder groups. • Can address underdeveloped products and motivate companies with accelerated procedure products, to generate long-term longitudinal data.			• Taxes are used for additional innovation budget • National health care providers and insurers only risk a high level of investment for proven drugs
CONS	• This is not really a solution for reimbursement, but rather stimulation for innovation in the field. In the end, the government is still funding the therapy.			
CHALLENGES & COMMENTS		• Feasibility of this solution?		

13.d Round Table 3: Outcome stakeholder group break-out discussion of the preferred building blocks

Outcomes

Stakeholder Building block

	Authorities	Sick funds + private insurer	Academia + patient groups	Industry
CLINICAL OUTCOMES / END-POINTS	• Should be agreed upfront, including partial response • Should be based on multi-stakeholder consensus (including HCP and patients/citizens) • Clinical outcomes need to be scientifically well founded and reliable and based on reasonable expectations • Have to be linked to patient HRQoL	• Always applicable and need to be taken into account • Do not have to be linked to annuities	• Consistent patient follow-up is needed • Expert group per disease group should be appointed to determine the disease-specific and general indicators	• Endpoints of RCT might be less relevant in case of gene therapy • Should be agreed upfront as early as possible, in collaboration with Belgian KOLs and patients before the CTG/CRM evaluation • Only use clinical outcomes/endpoints that are feasible in practice and measurable and relevant for KOL, patient and CTG/CRM • Outcomes need to be objective and verifiable
PATIENT QOL OUTCOMES	• Can be very subjective (depends on patient preferences) and therefore have to be linked to clinical outcomes • They also have to be agreed upfront (joint decision-making), case by case • Very disease dependent and patient dependent	• No specific remarks	• PROM: • Follow-up by HCP, 1 or 2 times per year • Patient can also use a log book	• Registration of QoL is very important but requires more attention and time of HCPs • Possibility to use QoL as sub-group of clinical end-point
OUTCOMES DATA COLLECTION IN PATIENT REGISTRIES BY HC PROVIDERS	• It has to be part of electronic patient/health records • Standardised system with single entry • It also has to be obligatory for individual reimbursement, HCP will have to follow his patients • Coordination by HCPs to have a joined opinion with patient about the outcomes and registry of it.	• Need for a registry that is acknowledged	• Incentive: Individual outcome and reimbursement should be linked. • Suggestion to record PROM in waiting room, where patients can fill in the questionnaire	• Registries: initiation, financing and filling in of the registries requires serious work to catch up to the rest of Europe • Incentive HCPs to fill in these registries could be the linked to the reimbursement of the consultation of the patient, instead of linking it to the reimbursement of the therapy in order to ensure the follow-up data • Registries need to be linked to electronic health record • Ideally, endpoints in Belgian registries should be the same as the endpoints used in EU
INDIVIDUAL PATIENT OR RW POPULATION BASED	• In favour of average population-based RW outcomes • Not in favour of individual patient-based RW outcomes: because of the risk of exclusion of patients based on economic reasons/ bias in selection of patients	• No specific remarks related to patient or population-based measurement	• Population-based outcomes should be used to demonstrate efficacy of the therapy	• Preference for average population-based outcomes to solve privacy issues and the possible loss of patients over time

Spread payments mechanism

Stakeholder Building block

	Authorities	Sick funds + private insurer	Academia + patient groups	Industry

BUDGET IMPACT EXCEEDING THRESHOLD	• Conditions:
	  • *Clear ROI has to be demonstrated*
	  • *Only for real breakthrough therapies (or therapies that positively impact the mechanism/course of the disease)*
	  • *In case of a unique and the best solution for a certain period of time (e.g. unique therapy for min. 5 years)*
	• Should be a possible option for the government, and not a standard solution and it is up to the government to decide
	• Transparency in the option with and without annuities and what the cost of annuities are
		• For eligibility, a flowchart should be constructed that starts from the whole therapy portfolio. Look at horizon scan and apply annuities on a portfolio of breakthrough therapies (instead of 1 therapy) and make a longlist based on the eligibility criteria. Then, conduct a number of tests to get to the list of treatment eligible for annuities
		  1. *Prioritisation of patients and therapies (~Hep C) is needed, ranking based on the high unmet need*
		  2. *Budget threshold is when the price is larger than 2x prices / NPV of current therapies – however, CTG/ CRM or Minister should decide*
		  3. *Look for need for immediate funding given disease burden the payer wants to tackle. If all other means are exhausted and Payer still wants to have access to the treatment in a given year, then annuities can be used so it fits the yearly budget*
			• Horizon scanning is necessary
			• Eligibility criteria: in case of curing the disease. However, "cure" needs to be defined and for how long (only during the spread payment period?)
			• Regarding the budget, prioritisation/ selection of treated patients is not desired
				• Spread payments is one of the flexible solutions that allows treatment of patients instead of postponing the treatments. It would be the CTG/CRMs decision to decide whether they need such a system or not.

DURATION	• Annuities not longer than 5 years per patient • But contracts can be longer (e.g.10 years) but then the payment is based on QALY	• Spread payment should be the exception – principle should be to only spend the money you have • Annuities term should be no longer than 5 years		• Strength of the evidence is inversely correlated with the spread payment duration: the stronger the evidence in the long-term, the lower the risk and therefore the shorter the duration of annuities
FOLLOWING TREATMENT RISK PROFILE	• No link to treatment risk profile, keep spread payments simple • Spread payments are only a payment mechanism and should not be value-linked (spread payment is only economical, value is linked to outcomes)	• Agree, spread payments should follow the treatment risk profile		• Yes, has to be linked but negotiated case per case
LINKED TO OUTCOME / PERFORMANCE	• Annuities should not be considered as a standalone solution, but should be linked with outcome-based solution	• Determine risk (profile) upfront and split up full amount in annuities if needed. No patient-based yearly RWE correction.	• HTA to demonstrate efficacy of the treatment and clarity about long-term effect is also needed	• Logical reasoning in case of outcome-based approach

Transversal budgets

Stakeholder Building block

	Authorities	Sick funds + private insurer	Academia + patient groups	Industry
COST OF ILLNESS	• Required but needs to be a local study	• To be considered only if substantial enough to be relevant		
SIGNIFICANT SAVINGS IN HC	• Cost of illness study used as rationale and clearly documented with local data • Savings can also be used for other areas, based on multi-stakeholder / society consensus			
CONSENSUS WITH OTHER STAKEHOLDERS ON CURING POTENTIAL	• Yes, consensus is needed.	• Yes, but this will be difficult		
SILO OR TRANSVERSAL BUDGET MONITORING	• Monitoring should be done on a population level.			
PUBLIC PRIVATE INNOVATION FUND	• Currently, there is already a public-private fund for the "vergrijzing" • Maybe we should think about a separate dedicated public-private fund for breakthrough therapies and medical devices (the private party should be a representative of the whole pharma) • Mapping of all existing innovation funds is required (and also streamlining them) before deciding if extra funding is necessary • Agreement from all stakeholders is needed			

Used abbreviations list

RWE	Real-World Evidence
MEA	Managed Entry Agreement
ESA	European System of Accounts
TTP	Trusted Third Party
ABR	Annual Bleeding Rate
MIT	Massachusets Institute of Technology
HRQoL	Health-Related Quality of Life
SOC	Standard of Care
WTP	Willingness to Pay
P4P	Pay-for-performance
IP	Intellectual Property
RR	Result Rate
HCP	Health Care Professional
RT	Round Table
ATMP	Advanced Therapy Medicinal Products
RCT	Randomized Clinical Trial
HA	Haemophilia A
HB	Haemophilia B
CSF	Critical Success Factors

References list

- Berggren R. et al. (2018). R&D in the 'age of agile', McKinsey, October 2018
- Carr, D. R., & Bradshaw, S. E. (2016). Gene therapies: the challenge of super-high-cost treatments and how to pay for them. Regen Med, 11(4): 381-393.
- "Commentary: Novartis CEO: Gene therapies offers hope of cures in one treatment, but US needs new pricing and payment model", CNBC, 17 May 2019, tinyurl.com/y3tod72r.
- Danzon, P. M. (2018). Affordability challenges to Value-Based Pricing: Mass diseases, orphan diseases, and cures Value In Health, 21(March): 252-257.
- Edlin, R., Hall, P., Wallner, K., & McCabe, C. (2014). Sharing risk between payer and provider by leasing health technologies: an affordable and effective reimbursement strategy for innovative technologies? Value In Health, 17: 438-444.
- ESA 95 manual on government deficit and debt, Eurostat European Commission, 2002, tinyurl.com/y4abcqfn.
- "EU budget headings and ceilings", European Commission, tinyurl.com/yyvnxf2t.
- European System of Accounts ESA 2010, Eurostat European Commission, 2013, tinyurl.com/y2utcygn.
- Foundation, K. B. (2011). Fund for rare diseases and orphan drugs. www.archipelkbs.org/fund.
- Hampson, G. et al. (2018). Gene therapy: evidence, value and affordability in the US health care system. J Comp Eff Res, 7(1): 15-28.
- Hanna, E. et al. (2018). Funding breakthrough therapies: A systematic review and recommendation. Health Policy, 122(3): 217-229.
- Hettle, R. et al. (2017). The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. Health Technol Assess, 21(7): 1-204.
- Jaroslawski, S., & Toumi, M. (2011). Market Access Agreements for pharmaceuticals in Europe: diversity of approaches and underlying concepts. BMC Health Serv Res, 11: 259.
- Katz, A. S. et al. (2018). Social Impact Bonds as a Funding Method for Health and Social Programs: Potential Areas of Concern. Am J Public Health, 108(2): 210-215.
- Kleinke, J. D., & McGee, N. (2015). Breaking the Bank: Three Financing Models for Addressing the Drug Innovation Cost Crisis. Am Health Drug Benefits, 8(3): 118-126.
- Marsden, G. et al. (2017). Gene Therapy: Understanding the Science, Assessing the Evidence, and Paying for Value. London: ICER - Office of Health Economics Research.
- Matthijs, H. (2015), Overheidsbegrotingen, p. 79-80.
- Micklus, A. (2018), "Gene Therapy: A Paradigm Shift in Medicine", Pharma Intelligence, November 2018.
- MIT NEWDIGS FoCUS (2019). White Paper 2019F201-v023 Precision Financing Solutions for Durable / Potentially Curative Therapies. Retrieved from Massachusetts Institute of Technology.
- Montazerhodjat, V., Weinstock, D. M., & Lo, A. W. (2016). Buying cures versus renting health: Financing health care with consumer loans. Sci Transl Med, 8(327): 327ps326.
- Rosenberg-Wohl S. et al. (2017). Private Payer Participation In Coverage With Evidence Development: A Case Study. Health Affairs Blog.
- Towse, A., & Garrison, L. P. (2010). Can't get no satisfaction? Will pay for performance help? Toward an economic framework for understanding performance-based risk-sharing agreements for innovative medical products. Pharmacoeconomics, 28(2): 93-102.
- Zettler, P. J., & Fuse Brown, E. C. (2017). The challenge of paying for cost-effective cures. Am J Manag Care, 23(1): 62-64.