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 4

2. Executive Summary 5

Problem statement and ambition of the multi-stakeholder round tables 5

Consensus for new innovative sustainable funding and reimbursement solutions 6

3. Recommendations 9

4. Background 12

4.a The problem we need to solve to finance game-changing gene therapies 13

4.b A comprehensive approach to define consensus solutions for gene therapy financing 13

5. Possible innovative funding solutions, summary of the literature review 16

6. Preferred success factors to evaluate the innovative funding solutions 19

7. Assessment of the funding solutions, summary of the multi-stakeholder discussions 20

7.a Multi-stakeholder analysis of the three preferred solutions illustrates a preference for combination solutions 21

7.b Building block principles and conditions for optimal solution selection 21

8. Multi-stakeholder consensus on preferred solutions 22

8.a Assessment of preferred solutions 22

8.b The basic principles per preferred solution 24

9. Decision-tree to enable assessment of the most optimal solution for each novel breakthrough therapy 26

9.a Outcome-based building block of the decision tree 27

9.b Spread payment building block of the decision tree 28

9.c Combination of outcome-based and spread payment building block of the decision tree 29

9.d Virtual transversal budget building block of the decision tree 30

9.e Additional modalities were discussed in the final round table regarding 3 specific topics 31

9.f Decision tree 32

9.g Final scoring of the decision tree illustrates multi-stakeholder consensus 33

10. Specific solutions for the European Accounting Rules and NIHDI accounting rules are required 34

10.a ESA rules 34

10.b NIHDI accounting rules 36

11. Application to a practical case: haemophilia A and B gene therapy 37

11.a Application of outcome-based MEA solution for haemophilia gene therapy 39

11.b Application of spread payment solution for haemophilia gene therapy 40

11.c Application of transversal budgets for haemophilia gene therapy 44

12. Conclusions 45

Used abbreviations list 46

References list 46

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:

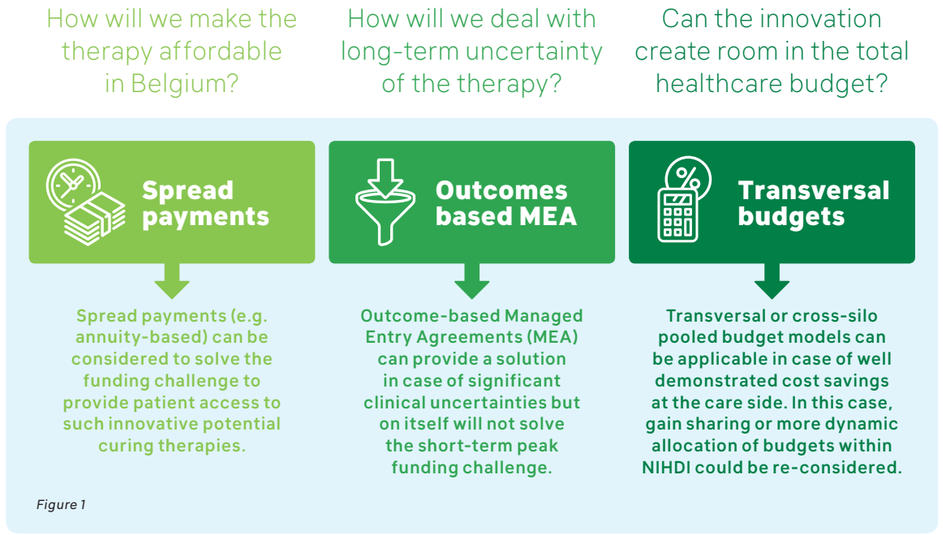

Figure 1

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.

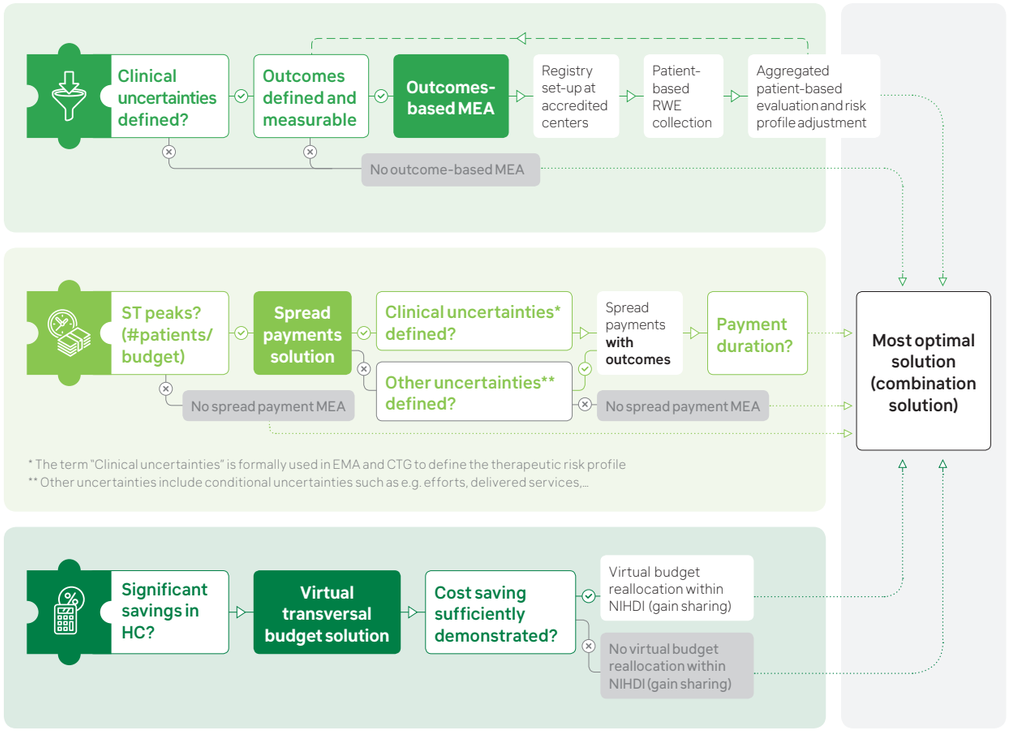

Figure 2

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.

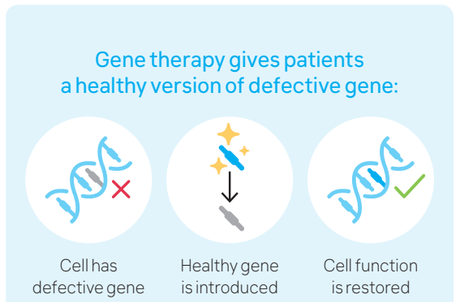

Figure 3 – What is Gene Therapy?
Source: St Jude Children's research Hospital

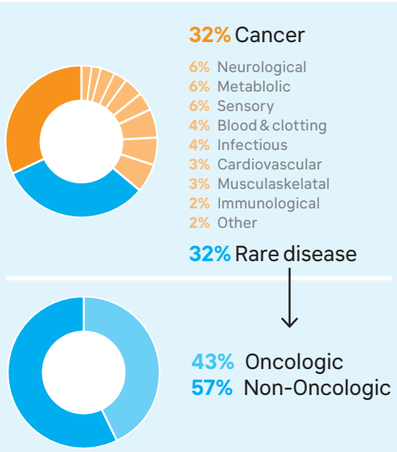

Figure 4 – Percentage of rare disease, percentage of Oncologic / Non-oncologic among rare disease.

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

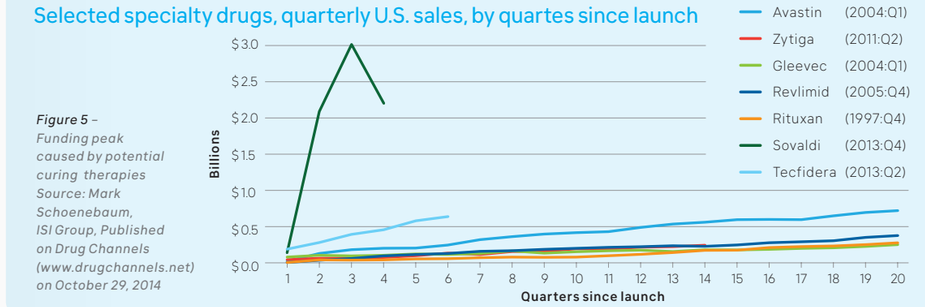

Figure 5 – Funding peak caused by potential curing therapies Source: Mark Schoenebaum, ISI Group, Published on Drug Channels (www.drugchannels.net) on October 29, 2014

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.

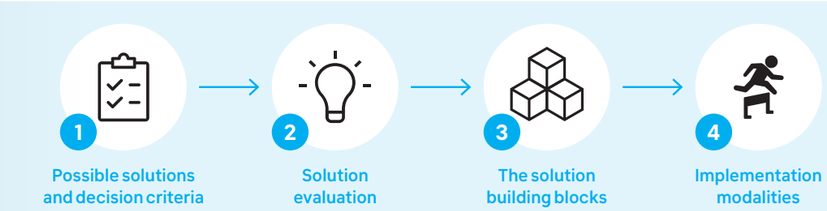

Figure 6 – Clear step-wise process comprising 4 steps

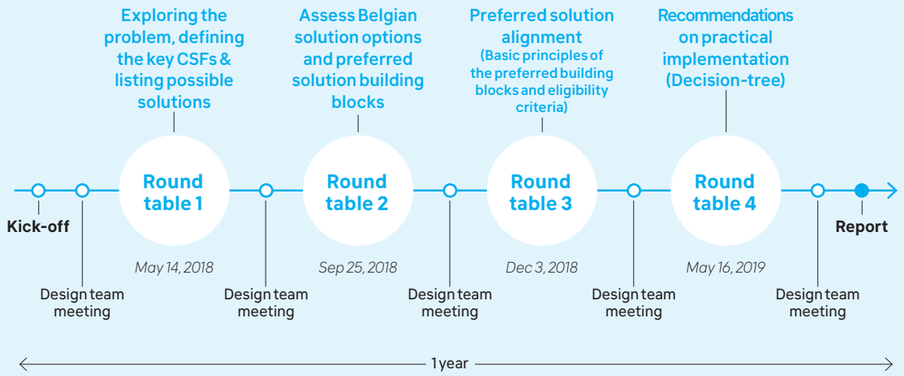

Figure 7 – Process for multi-stakeholder engagement

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.

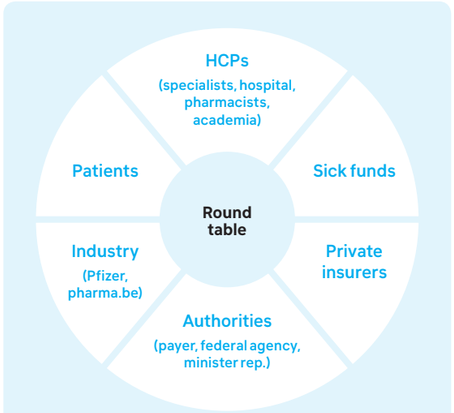

Figure 8 – Belgian healthcare stakeholder representaOon

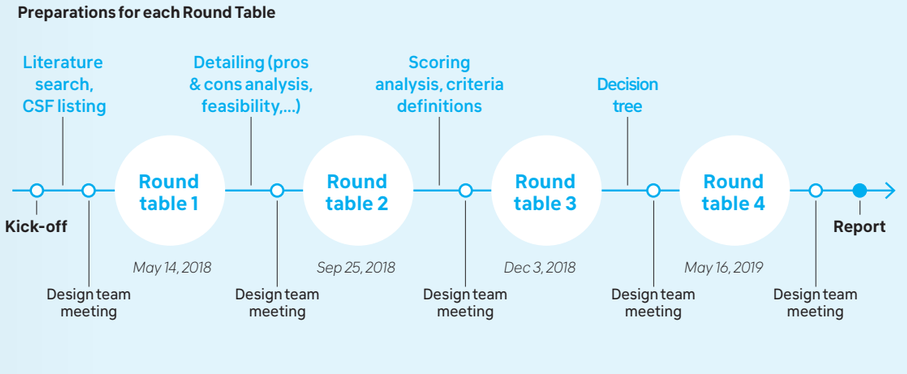

Figure 9 – Preparatory research, pre-reads and minutes were made for each Round Table

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.

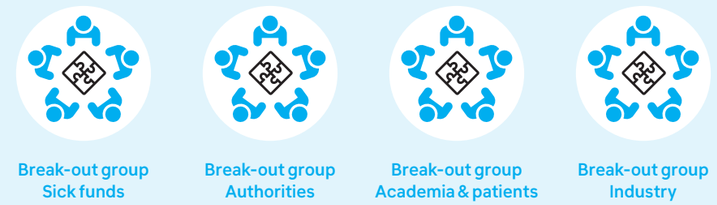

Figure 10 – Four stakeholder break-out groups during the break-out sessions

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:

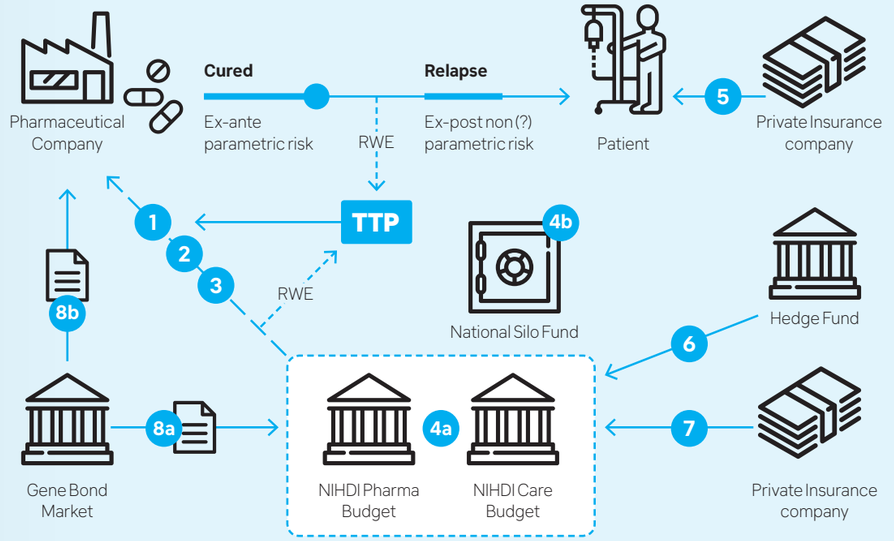

Figure 11 – Overview of funding solutions based on international literature

- *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.

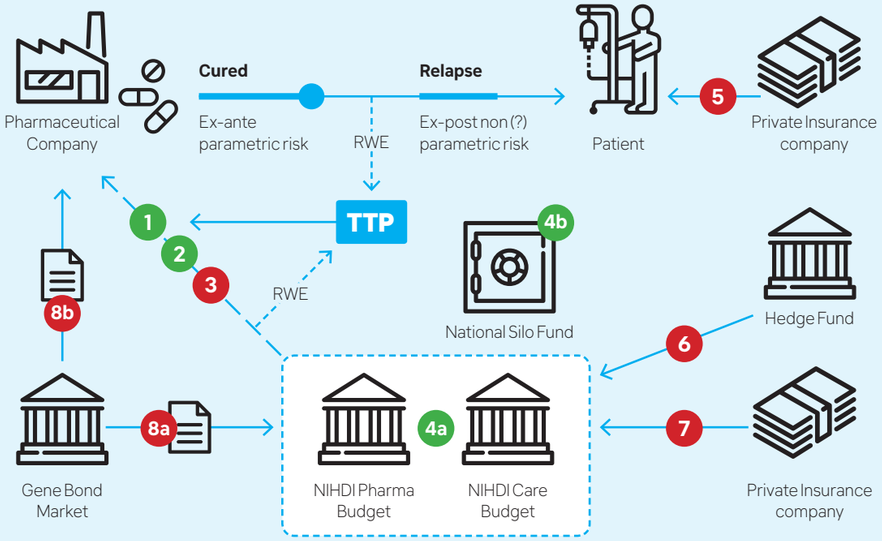

Figure 12 — Preferred solutions by the stakeholders, not including the private insurance based solutions

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.

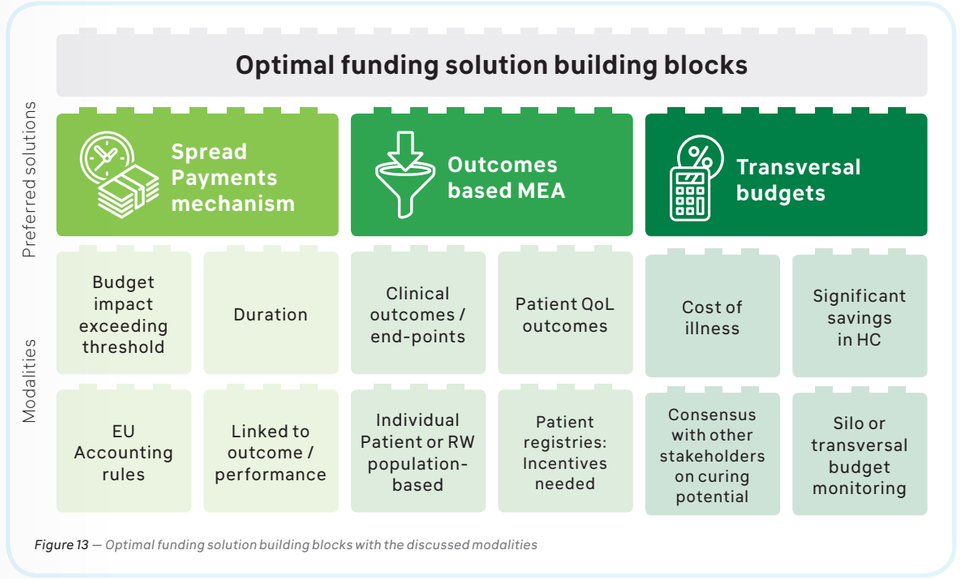

Figure 13 — Optimal funding solution building blocks with the discussed modalities

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.

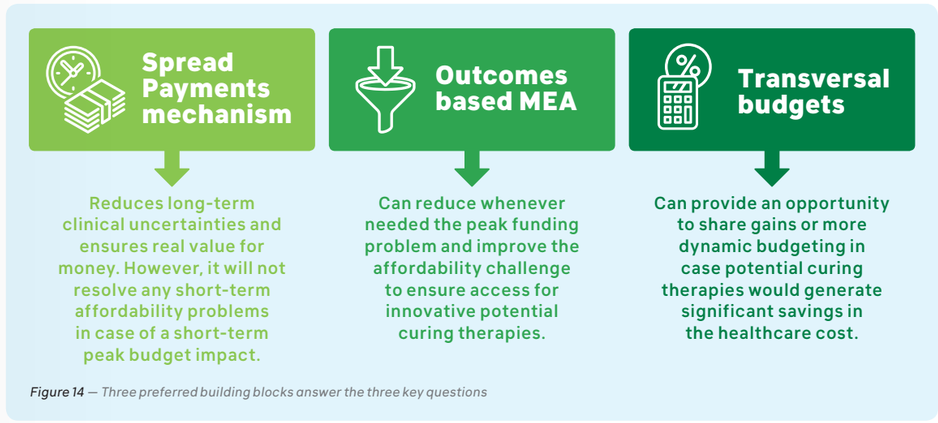

Figure 14 — Three preferred building blocks answer the three key questions

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.

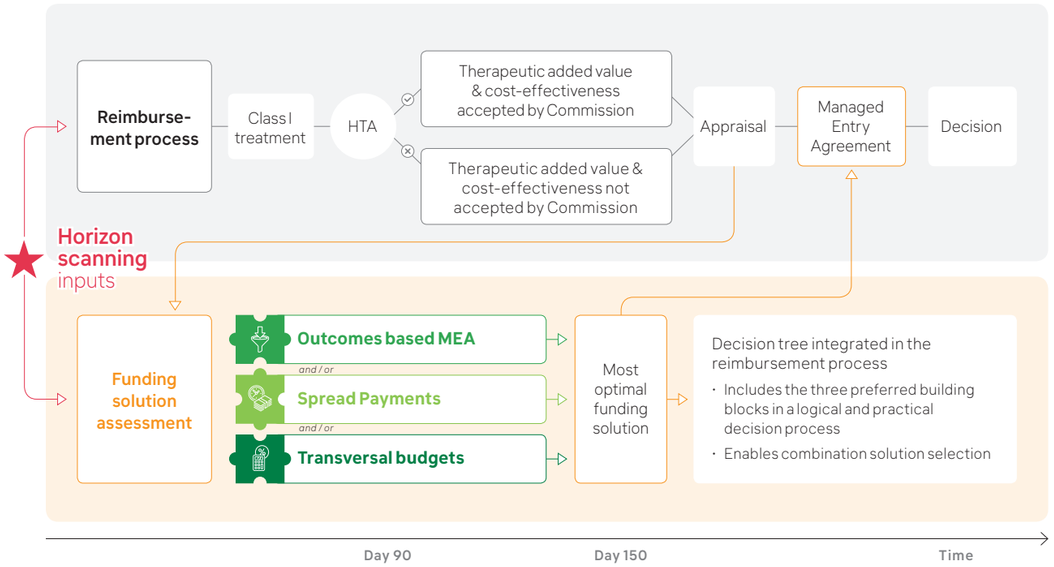

Figure 16 — The alternative funding solution assessment integrated in the current reimbursement process

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

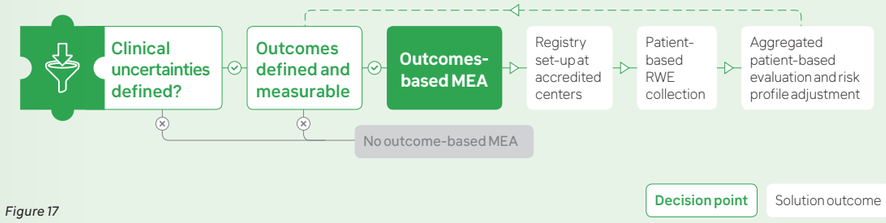

Figure 17

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.

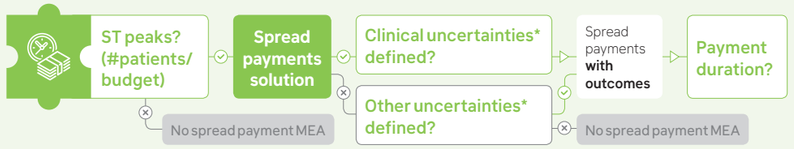

Figure 18

** 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

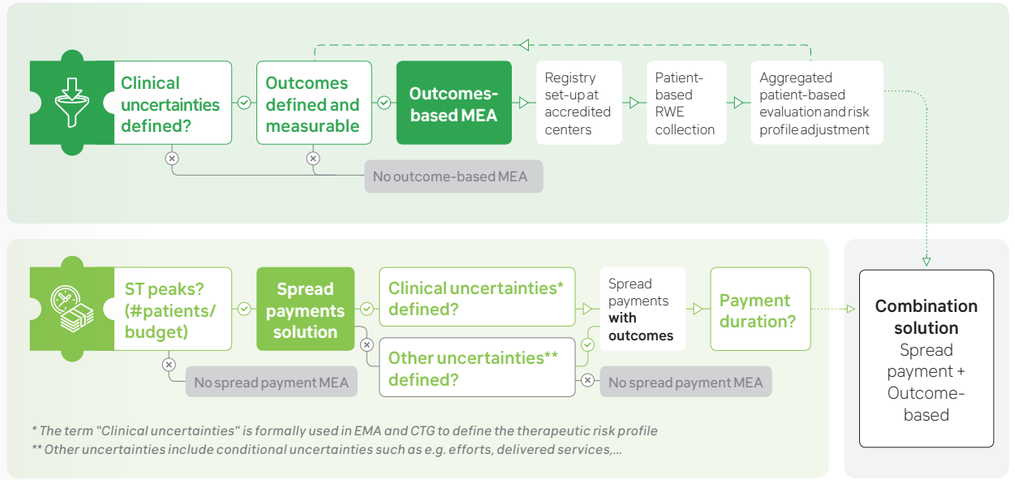

Figure 19

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

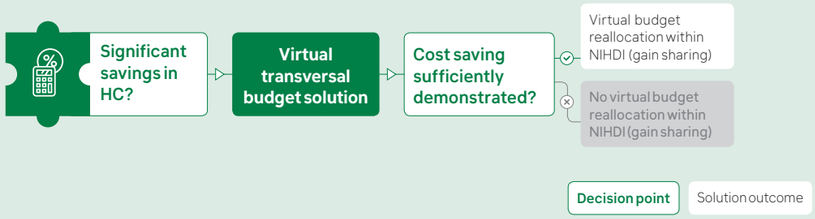

Figure 20

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.

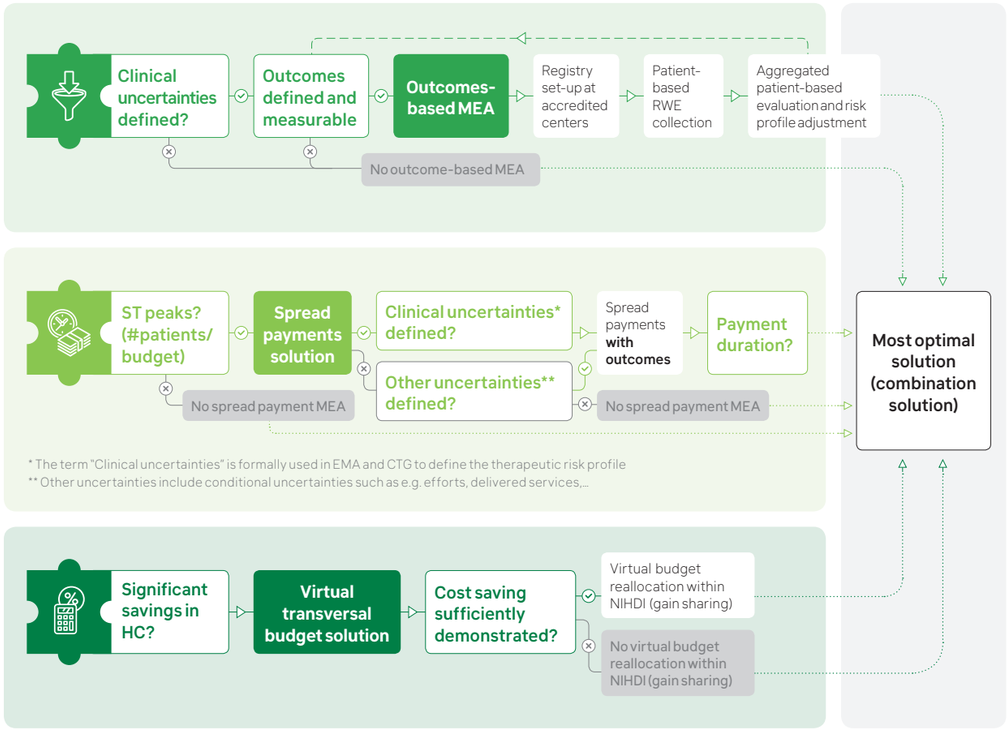

Figure 21

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:

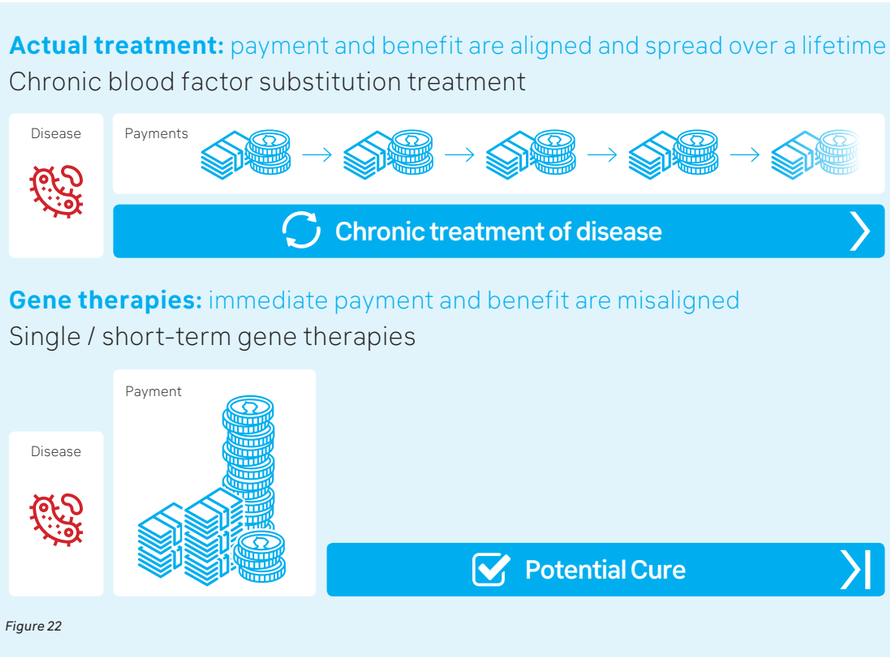

Figure 22

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.

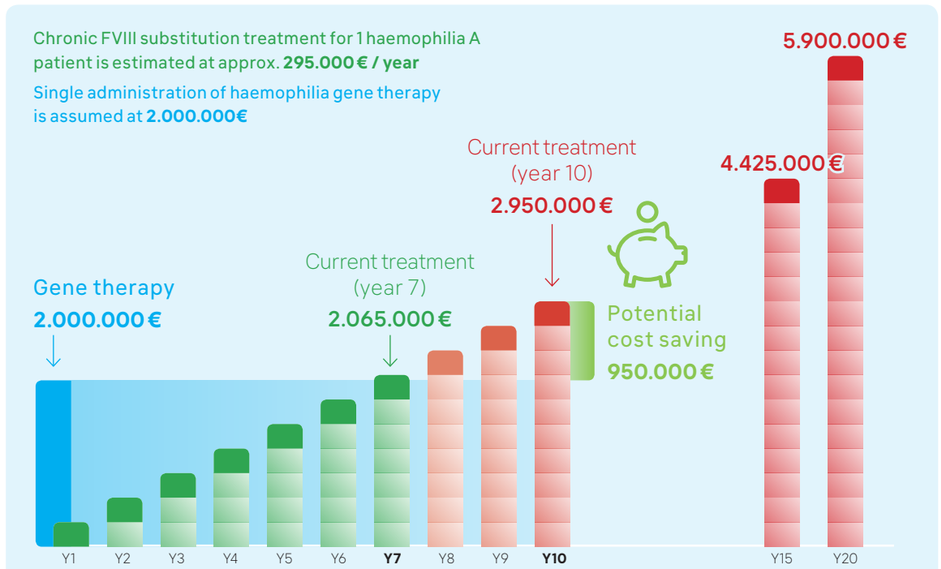

Figure 23 — Cost comparison over time for 1 patient on gene therapy vs current treatment

Number of eligible haemophilia A patients in Belgium

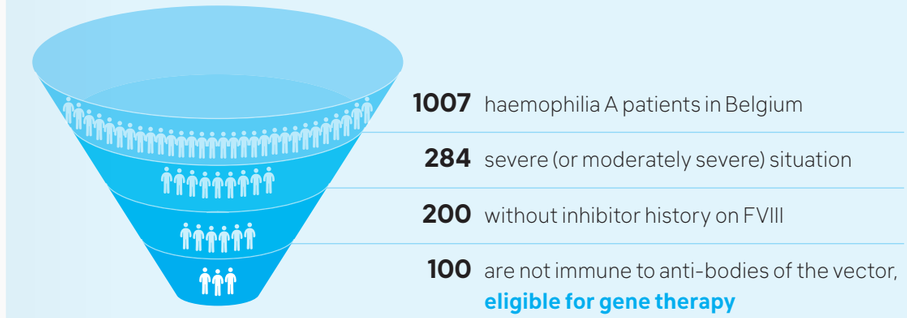

Figure 24 — Number of eligible Haemophilia A patients in Belgium
(Not taking into account: patients with active hep B & C / patients preferring to stayon current treatment.)

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

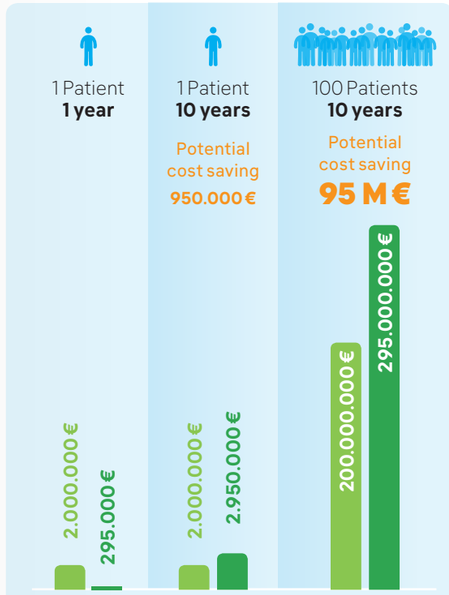

Figure 25 — Cost comparison over a period of 10 years illustrates cost savings generated by the gene therapy

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.

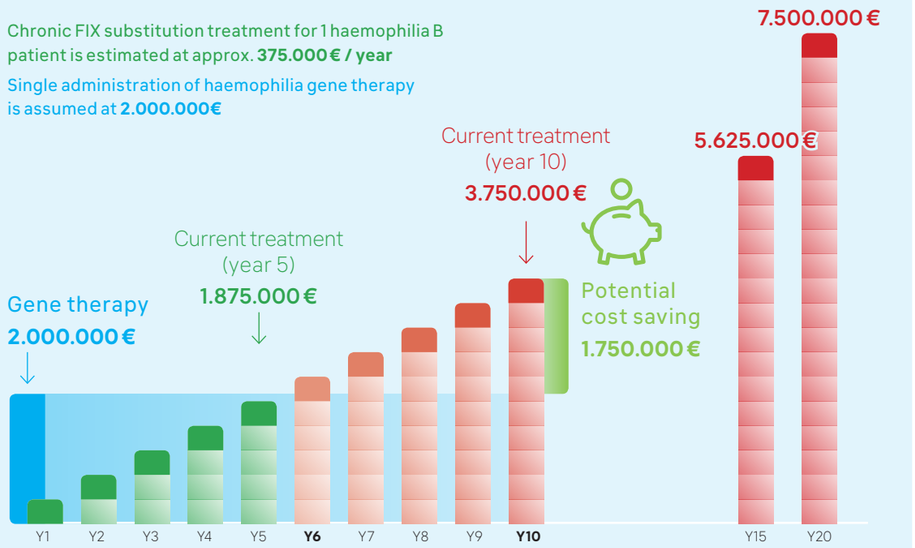

Figure 26 — Cost comparison over time for 1 patient on gene therapy vs current treatment

Number of eligible haemophilia B patients in Belgium

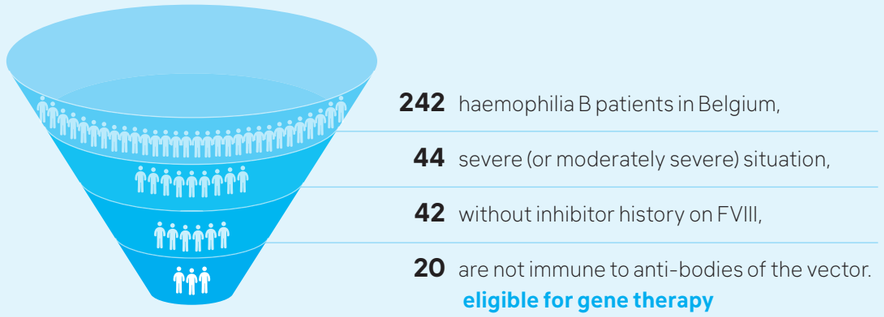

Figure 27 — Estimation of haemophilia B patients eligible for gene therapy
(Not taking into account: patients with active hep B & C / patients preferring to stayon current treatment).

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

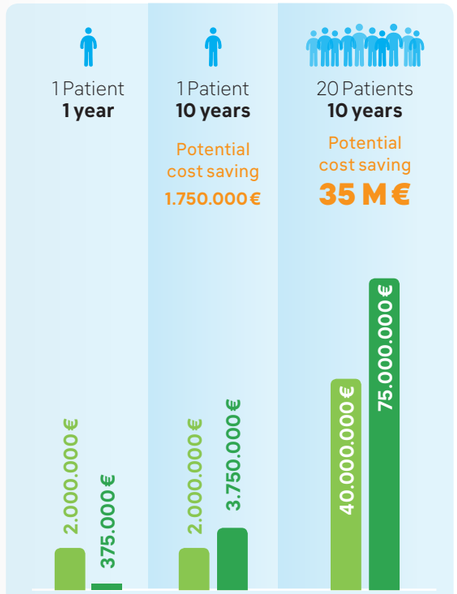

Figure 28 — Cost comparison over a period of 10 years illustrates cost savings generated by the gene therapy

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.

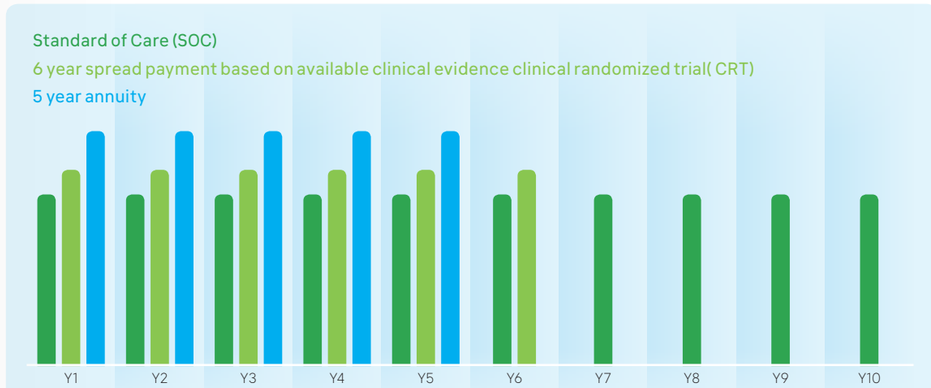

Figure 29 — Comparative yearly budget impact for type B patients in Belgium (illustrative, r=2%)

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

Notes