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Integrated roadmap to narrow evidence gaps and uncertainties to support access and reimbursement decisions for valuable innovative medicines

A Multistakeholder engagement approach, from concept to implementation in Belgium

Colophon

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Preface by Jo De Cock

For many years health authorities and social health insurers are trying to make a fair balance between valuable innovation and affordable access for pharmaceuticals.
Since more and more novel treatments for different pathologies are coming to the market, such as immunotherapies and cell- and gene therapies, often for small patient groups, it is necessary for health authorities to create preparedness with regard to the challenges which are coming ahead. Although many discussions and solutions take place at the international scene (European Pharmaceutical Strategy, HTA regulation…) it is necessary that Belgium is preparing its homework too.

In order to support Belgian decisionmakers, a multi- stakeholder group was set up to explore some possible solutions for a number of challenges health authorities and social health insurers are struggling with.

Two major challenges were identified.
The first one is related to the evidence base. Indeed, more and more therapies come to the market with a conditional approval or as a result of fast lane procedures trying to provide early access for patients with unmet needs and without alternative treatments available. Those products are launched with a limited evidence base and many uncertainties with regard to clinical benefits and the cost-benefit balance. This is often due to the fact that classical ways of evidence generation don't apply for ethical reasons or as a consequence of the rarity of the disease. Logically this results in the question which initiatives could be taken to narrow the uncertainty gap so that access can be provided.
The multi-stakeholder group explored this issue in depth emphasising the need for appropriate evidence generation plans and the importance of good data collection.

A second point is related to the reimbursement issues. It should be recognized that sometimes a catch-22 situation is occurring when pharmaceutical companies are proposing pricing expectations which are considered as unrealistic by payers whilst pricing and reimbursement authorities and payers who are not accepting these proposals are considered by the companies to be reluctant to give access to innovation for patients in need. Such situations are leading often to emotional discussions on public fora.
In order to avoid this catch-22 it seems clear that a more appropriate way must be found for the traditional approach in which at the start of the reimbursement a fixed price or amount is approved. Therefore, we discussed a pathway in which a certain form of flexible pricing is applied that is aligned with the evolution of the evidence base.

This report contains a number of concrete and practical recommendations and solutions to support good decision making.

It was for me an honour and a pleasure to chair this multistakeholder group. In this group a lot of stakeholders from different backgrounds – authorities, academics, pharmacists, patients and patient associations, health insurance funds, companies – have exchanged their experiences and

their concerns. The different round tables which were organised have contributed to better mutual understanding. Moreover, it is important to notice that all the stakeholders share the fundamental principles of affordable access, therapeutic benefits and solidarity. On this basis we have co-identified, co-created and co-designed essential building blocks and topics of a roadmap which should be brought on board at the policy level. Of course, not all problems have been solved. Nevertheless, in my opinion, important steps were set, and useful progress was made.

This report also wants to contribute to the "spearheads process", co-ordinated by RIZIV-INAMI, that wants to, among others, modernize reimbursement procedures. Finding the right balance between a more rapid access to innovative medecines with sometimes limited evidence on the one hand and pricing and reimbursement modalities that are acceptable for all partners, is a particular point of interest in the spearheads process. It's our wish that this report can inspire policy-makers.

This report is fully in line with the pathway with regard to innovation and solidarity Belgium is following since 2010 when the report "A call to make valuable innovative medicines accessible in the European Union" was published..

Jo De Cock
Chairman of the multi-stakeholder ATMP initiative
Former Administrator General NIHDI
Chairman of the National Commission for Doctors of Health Insurance Funds and the National Joint Commission Doctors and Hospitals

January 2023

Executive Summary

The current price and reimbursement procedural pathway in Belgium are not yet suitable to cell and gene therapies, or any advanced therapy medicinal products (ATMP). Several challenges specific to one-time treatments (opposed to medicines intended for chronic intake) and irreversible treatments, have been identified. Especially the limited evidence and clinical uncertainties at launch are an issue for market authorisation and access for patients in high medical need, and also for reimbursement decisions on those therapies. To make the Belgian system future-proof, and prepare the way for these medicines, each challenge has to be met.

To co-develop a solution in multistakeholder engagement, multiple roundtable meetings were organised in 2022. This multi-stakeholder dialogues were following earlier multistakeholder roundtables held in 2018-2019 on funding solutions for ATMPs in Belgium (summarised in a policy report published in November 2019[1]). It proposes outcome-based managed entry agreements (OB-MEA) as a potential innovative funding solution. The complexity of preparing such outcome-based agreements (OBA) has however been identified by all stakeholders as a major roadblock hampering its implementation.

It Is however important to mention that not all ATMP therapies address high unmet medical needs, and that evidence should primordially be demonstrated in randomised clinical trials (RCTs).

RWE or Real-World evidence is the clinical evidence regarding the usage and potential benefits, or risks of a medical product derived from analysis of real world data. *(Source: FDA)*

RWD or real world data are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources (other than traditional clinical trials) *(Source: FDA)*

Waiting until evidence is obtained is not ethical towards patients with high medical need and no one can predict the outcomes. Therefore, specific attention must go to collecting real world data (RWD), while evidence is key to support evaluation for access and reimbursement decisions. Collecting real-world data and generating real-world evidence, can only be applied as far as classical (via RCTs) evidence cannot be generated in another way and when there is no alternative. Early dialog will be important to have this discussion and proactively prepare.

The proposed integrated pathway, based on four solution elements, aims at providing inspiration on the common ground and main elements to find a solution, with fundamentals to build on and reform our current system. It is not just for ATMP therapies but should be considered as a metaphor for all breakthrough medicines targeting unmet medical needs. We do not suggest a separate or exceptional procedure, but a solution integrated in our current and future procedure.

Proposal of solution strategy containing four elements

The proposed strategy addresses the main challenges and consists of four key solution elements. These elements together form an integrated roadmap, with each of them described in further detail below.

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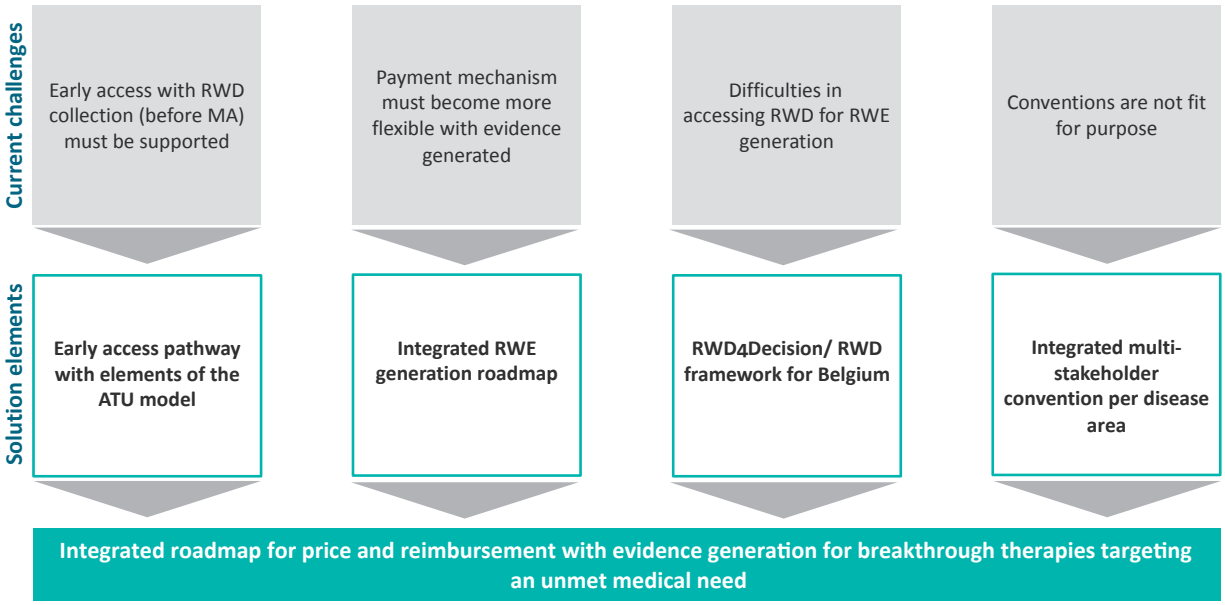
[1] Maes, I. Boufraioua, H. Van Dyck, W. Schoonaert, L. (2019). *Innovative solutions for paradigm changing new therapies. https://www.inovigate.com/media/filer_public/e8/9c/e89ca2b0-1dcf-48fb-9afc-9e911ddcef84/innovative_funding_solutions_-_short_version_without_appendix_vs09.pdf*



1. Adapted early access model with RWD collection (before market access for high-impact medicines targeting unmet medical needs (UMN)

The current Early Temporary Reimbursement (ETR) procedure in Belgium is not fit for purpose and is barely used to provide Belgian patients in high need early access to advanced medicines, before EMA and local regular reimbursement approval. The actual ETR procedure is considered overly complex and takes too long.

The actual flat-rate compensation for innovator pharmaceutical companies is not incentivising companies to provide Belgian patients suffering from serious, rare, or disabling diseases, with early access to these breakthrough medicines. These patients typically cannot wait for a product to be approved and are generally unable to take part in a clinical trial. The actual closed budget is very limited and can only allow early access for a very limited number of patients with high medical need. New elements are proposed to improve the actual Belgian ETR procedure based on the successful French ATU (Temporary Authorization for Use) model.

Clear criteria for early access, with requirement for RWD collection are proposed:

- The ETR would be limited to “presumed” innovative medicines for which there exist no alternatives. If it is not approved, the product’s safety and efficacy must be demonstrated based on clinical trial results.
- Eligibility criteria: early access is limited to a cohort of patients with a serious, rare, or disabling disease for which treatment cannot be postponed.
- A utilisation protocol is defined, including the hospital reference/expert centres as well as the responsibilities for real-world data collection.
- A more substantial early access compensation is recommended with the discount increasing in function of the costs (cfr. The French ATU discount table).
- Flexible funding with win-win guarantee, based on retrospective adjustment of preliminary early access compensation, depending on the negotiated reimbursed price.

2. Integrated (real-world) evidence generation roadmap

The proposed integrated evidence generation roadmap allows an increase in proactiveness and preparedness in five steps.

1. **Horizon scanning** to identify high impact products + **UMN list and approach to prioritise** disease areas
2. **Request for early dialogue** to early dialog platform
3. Early dialogue meeting to **define and agree on the RWE plan** depending on clinical uncertainties **+ potential early access scheme** for high medical need (cfr. new ATU/ETR)
4. Management of the **enabling foundation (governance, conventions), management of the execution** of the RWD & Evidence generation plan supported by **Belgian Health Data Institute**
5. **Reference centers** take the lead in **data collection and analysis, pool the knowledge and update treatment guidelines** based on emerging evidence
6. **Critical assessment of RWE & implementation in OBAs** by RIZIV.

The International Horizon Scanning Initiative (IHSI) (https://ihsi-health.org) will allow health authorities to identify which high-impact medicines are coming up, based on public information. The UMN list, initiated by the National Institute for Health and Disability Insurance (NIHDI) system should be complemented with input from clinicians and patients. The UMN list defines priorities and can help NIHDI to identify for which high-impact medicines it wants to prioritize early access for patients with high UMN.

The IHSI will enable a more proactive identification of medicines for which cross-country collaboration (e.g., BeneluxAiRe) can be considered to align on early access conditions, real-world data collection and health technology assessment (HTA).

In the second and third step, an early dialogue must be initiated on a Belgian and European level. In such dialogue, it will be possible to discuss and agree proactively on the additional needed evidence (via clinical trials and real-world data). This should result in an evidence generation plan, based on the clinical study program and the remaining clinical uncertainties of the therapy. NIHDI has to set up a Belgian pre-submission platform for early dialogue, consisting of reference centres and key opinion leaders involved in clinical trials (the European reference centres and Belgian reference centre are already regularly involved in clinical trials), patient representatives, HTA- bodies, the Federal Agency for Medicines and Health Products (FAMHP), the company, and data experts. In this step, alignment of the appropriate outcomes to support possible outcomes-based agreements (OBA), must be discussed as well. A potential early access scheme for high medical needs can start in this step if the medicinal product is meeting the eligibility criteria (see point 1 earlier).

In a fourth step, management of the enabling foundation (governance, conventions), and of the execution of the real-world data and evidence generation plan, supported by a dedicated Belgian Health Data Institute (that pools and build expertise and experience and goes beyond the current Belgian Health Data Agency role), must be discussed and set up. This should result in an integrated multistakeholder convention between NIHDI, companies and expertise centres, that outlines roles and responsibilities, including funding aspects.

In step five, the reference centres take the lead in data collection and analysis, pool the knowledge and update treatment guidelines based on emerging evidence.

In the sixth and last step, critical assessment of the RWE and implementation in OBAs by NIHDI takes place. The generated evidence must be available to the payer, and HTA body, who can use this evidence to adapt the price

of the therapy. A flexible pricing model addresses the clinical uncertainty over time, by providing proven evidence through RWD. This is needed because of the often-small target population for gene therapies, short clinical trials, or lacking understanding of the long-term effect of the gene therapy. Setting a fixed price for the whole contract is therefore difficult. A flexible price amenable to fluctuations, according to proven evidence through RWD represents an efficient solution.

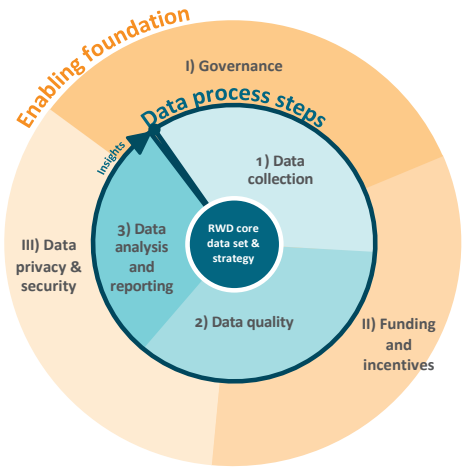
The proposed solution should be implemented on a flexible learn-and-adapt basis. Adjustments to the proposed procedure, based on new insights and learnings, should be made in a continuous improvement approach.

3. Approach to organize access to RWD for evidence generation, including automated data registration ('harvesting') and a clear enabling governance and funding framework

To organize access to data and generate evidence, an RWD/E framework for Belgium with roles and responsibilities has been developed. This framework is the result of the European RWD4Decision initiative translated to a Belgian context.

Today, there are different data registries for different disease areas. These registries should be harmonised. Although a lot of data might be interesting for research purposes, a core data set containing information on treatment should be the starting point to support OBAs. This data set should represent the real-life situation and should support long-term follow-up. It also needs to be flexible and adjustable over time, based on increasing insights, starting from the current registries where possible, with the option to align internationally. To achieve international harmonisation and alignment with the EMA data collection requirements, standardized data types and terminology are essential. This is also required to be able to combine data from various countries and have statistically sufficient data for analysis.

RWD4Decission translated to Belgian RWD (re-use) framework + stakeholder roles



Data collection and quality control can only be done by clinicians at the source where data is generated. They are best placed to evaluate the data on their relevance and accuracy. A joint team may perform the independent data analysis for the reference centres.

To reduce additional burden for patients and extra workload for clinicians, an automated data harvesting solution is needed to feed the local and international registries. Such solution preferably collects data from the electronic patient directories (EPD) in each of the hospitals and feeds the various registries through the e-health platform. An "only once data registry" principle, based on one time data collection at the source and feeding the registries (local and international) from this source, should be applied. Such a solution has been developed for multiple myeloma Car-T treatments in co-creation with the four Belgian reference centres and four pharmaceutical companies, represented by pharma.be. Through a Data Providers Interface and the eHealth platform various registries could be populated. A Health Data Analytical Interface, with specific interfaces for each stakeholder group, supports data analysis.

In order to succeed, there needs to be a willingness and incentive to collect data. Collecting RWD is considered a significant hurdle. To address this, there must be a willingness amongst all stakeholders to contribute resources and investment (i.e., to update infrastructure to enable this and make it sustainable). Clinicians and data managers that perform data management tasks (data collection, data analysis) should be financially compensated,. Hospitals should develop a data strategy and should be rewarded for their efforts (e.g., via hospital financing). To address the lack of funding and knowledge at the hospitals, inspiration can be drawn from Switzerland and many other countries. A SWAT team, consisting of experts on data science, data collection and infrastructure, was set up by the government. This SWAT team travels from hospital to hospital to support the set-up of the data infrastructure and to transfer know-how. This team could serve as a knowledge pool that can be reused per hospital. This is a more cost-effective way to share the experience and know-how. Such a team could house in a specific to be set up "Health Data Institute" consisting of data science experts, to pool the knowledge and experience and make it available to support future RWD/E requests by all stakeholders.
Funding for building and maintaining the RWE infrastructure and automated data harvesting, should be based on a collective model, representing funding from government, clinical societies, and companies, to assure sustainability. Such a specific collective fund could support building and maintaining RWD infrastructure and RWE generation tasks on a fee-for-service basis for industry.
Also, on the governmental side (NIHDI, FAMHP, KCE) sufficient resources and funding is needed to support data and evidence reviews for OBA models. This will require identification of the importance of RWD for evidence generation, through prioritization of investments and resources. To do so, RWD should be recognised as an important asset for Belgium, available for decision-making.

An executive RWD/E infrastructure is also a requirement for keeping Belgium attractive for clinical trials, to support the identification of patients eligible for clinical trials, but also to support pragmatic trials.

4. Integrated multistakeholder conventions per disease area outlining the roles, responsibilities as well as financing model

Agreements on RWD collection, analysis, and reporting, including data infrastructure, but also funding and governance aspects, can be outlined and organised on the disease domain level (complementary to conventions on product level) in an integrated multistakeholder convention or contract between NIHDI, the company and reference centres. These agreements on evidence to be generated include commitments to be provided by the applicant (type of RWD, source of data, architecture, timeline, etc.), on the roles and responsibilities, on funding for RWD collection analysis and reporting. Such an approach on the disease level will reduce lengthy case-by-case discussions and reduce ad hoc solutions, leading to consistent and harmonised RWD/E solutions across disease areas in Belgium.

Proof-of-concept on a practical case

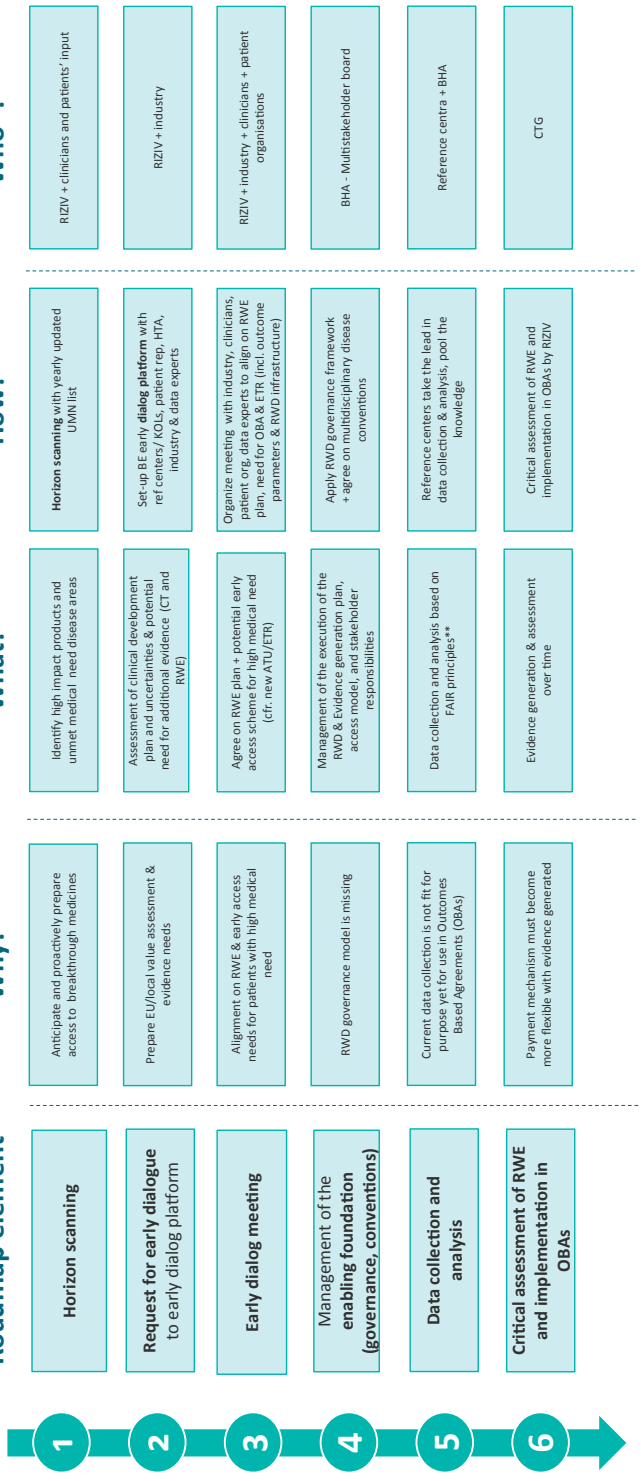
To make this solution more concrete, the proposed integrated implementation roadmap has been applied on a real-life case. The Duchenne muscular dystrophy gene therapy case was selected as a proof-of-concept, to assess practical applicability and discuss the roles and responsibilities needed to put the roadmap in practice.

Recommendations for implementation

Based on these proposed solution elements, recommendations have been formulated for building a future-proof access and reimbursement pathway with integrated evidence generation for breakthrough therapies with an UMN in Belgium.

Overall solution and integrated roadmap:

Integrated roadmap with the elements addressing the main challenges (the why) and with key recommendations (what has to be done, how it has to be done and by who / who has to take the initiative)



*Who will take the initiative?
** Findable, accessible, interoperable, and reusable

MNP: Medical Need Program, RWE: Real World Evidence, OBA: Outcome-Based Agreements, CT: Clinical Trials, ATU: Early Temporary Authorisation, ETR: Early Temporary Reimbursement, KOLs: Key Opinion Leaders, CTG: Commission for Reimbursement of Medicines

Recommendation 1: Complement horizon scanning with a yearly updated UMN list, based on input from clinicians and patients to define priorities and to enable proactive preparation based on dialogue and collaboration with the innovator company (e.g. possible early access conditions, RWD collection protocol, etc.).

Recommendation 2: Implement an RWD/E framework for Belgium, supported by an ethical overarching governance framework, common interpretation of GDPR, legislative adaptation for data re-use in price & reimbursement (cfr. Law in Finland) to eliminate case-by-case decisions and inconsistencies, and to make Belgium an attractive country for data use and re-use (to maintain and complement our clinical trial leading position).

Recommendation 3: Improve the Belgian ETR model to enable early access and local RWD collection of breakthrough medicines for Belgian patients with high UMN. The new French early access (ATU) best practice can be considered as inspiration.

Recommendation 4: Develop disease registries and multi-stakeholder conventions detailing the responsibilities of all concerned parties (based on the RWD4Decision publication).

Recommendation 5: Set up a joint fund for RWD infrastructure, data collection, and analysis, and establish a Health Data Institute to assure pooling of expertise and experience to make it available to all stakeholders and become more cost-effective.

The proposed Belgian Health data Institute (BHI) has a broader role compared to the current Belgian Healthdata Agency. It extends it role in data related knowledge building and dissemination as a center of excellence on health data-related topics (a.o. in data science, data infrastructure, legislation, etc.)

Context and objective

Why do we need a solution for cell and gene therapies /ATMPs in Belgium?

An increasing number of paradigm-shifting therapies are being developed. These have the potential to offer life-changing solutions for patients with few or no alternative treatments available. Among these new therapies, advanced technology medicinal products (ATMP) including gene and cell therapies, play an important part. Despite the enormous potential these therapies hold, some challenges arise, such as funding of those therapies, but also lack of sufficient evidence at launch, on clinical uncertainty and long-term efficacy and safety. Following multi-stakeholder roundtables held in 2018-2019 on "Innovative funding solutions for paradigm-changing advanced therapy medicinal products (ATMP) in Belgium, a multistakeholder consensus on gene therapy funding solutions", a policy report published in November 2019[2] proposed outcome-based managed entry agreements (MEA) as a potential innovative funding solution. The complexity of preparing such outcome-based agreements (OBA) has however been identified by all stakeholders as a major roadblock hampering its implementation. Moreover, the actual early access procedure to provide early access to Belgian patients with high unmet medical need (UMN) and the Early Temporary Reimbursement (ETR) procedure are not suitable for one-time treatments which require higher upfront investments. Therefore, an initiative was set up to prepare a roadmap enabling implementation of early access and RWD solutions, as well as outcome-based MEA for ATMPs in Belgium.

The current early access and reimbursement procedural pathway in Belgium is not suitable for cell and gene therapies or other ATMPs. Several challenges specific to one-time treatments (opposed to medicines intended for chronic intake) have been identified. To make our procedures and systems future-proof, each challenge has to be met. The current health system focuses mainly on treating conditions with proven therapies being administered on a regular basis (for example by taking a daily medication). However, for cell and gene therapies administration of the therapy can be reduced to a single dose with a potential lifelong effect. The differences between conventional therapies and cell and gene therapy, has a disruptive impact on our health system. Most of the authorized cell and gene therapies are based on adaptive, small, open-label, single arm trials, leading to challenges, such as insufficient or limited evidence and remaining uncertainties (a.o. on durability of the treatment) at market launch. Because of the uncertainty on product benefits and the risk balance at market launch, these treatments require an adaptation to the access and reimbursement procedure. Our system is currently not adapted to these breakthrough therapies for high UMN, with limited evidence.

We need to define the health outcomes of personalised medicines like cell and gene therapies and find a right balance between access for all, affordability, and stimulation of innovation. To be able to provide the patient-in-need with the required medicine, we must bring together clinical and observational information, or in other words merge clinical evidence and real-world evidence.

[2] Maes, I. Boufraioua, H. Van Dyck, W. Schoonaert, L. (2019). *Innovative solutions for paradigm changing new therapies. https://www.inovigate.com/media/filer_public/e8/9c/e89ca2b0-1dcf-48fb-9afc-9e911ddcef84/innovative_funding_solutions_-_short_version_without_appendix_vs09.pdf*

A multistakeholder engagement approach

When developing new solutions, we must avoid assessing cases on an emotional basis (e.g., the baby Pia and Victor case). We must develop balanced solutions taking into account the specificities and uncertainties of cell and gene therapies, while exploiting opportunities for international cooperation (e.g. BeneluxAIRe, International Horizon Scanning, etc.). We also need to engage in dialogue with all stakeholders involved, in order to assure a solution that provides access to cell and gene therapies for patients. And finally, we must develop a solution that is implementable in Belgium on the short term.

The aim of this project was to create a coalition-of-action that enables reimbursement decisions and patient access to cell and gene therapies / ATMPs in Belgium. By developing a practical roadmap, it can bring solutions from concept to implementation. To co-create proposals that are supported by all stakeholders, we applied a multistakeholder engagement approach, involving clinicians and reference centres, academia, patient organisations, authorities, pharma companies, and sick funds. The advantage of this multistakeholder dialogue is that a common language has been developed enabling reflections. Building on the joint intelligence of the multistakeholder community, this strategy supports the development of solutions.

To support multistakeholder engagement and solution co-creation, we organised several multistakeholder roundtable meetings between January and October 2022. The roundtables were chaired by Jo De Cock, former CEO of NIHDI. Each roundtable was prepared in a steering committee with representatives of all key stakeholders.

The roundtables were preceded by an extensive literature study on cell and gene therapy reimbursement and RWD solutions in other countries as well as interviews with representatives of all involved stakeholders in Belgium. In the first roundtable, the challenges that needed to be addressed were discussed and prioritized, supporting a focused discussion. During the second roundtable meeting, the list of potential solution elements was discussed and evaluated in terms of acceptability and feasibility within the Belgian context. During a side track meeting, the RWD and evidence generation framework was detailed further. The third roundtable meeting focused on the proposed integrated roadmap. During the fourth roundtable, we studied the proposed key solution elements and developed them in further detail. After the roundtables, the solution elements were further developed in detail with key experts.

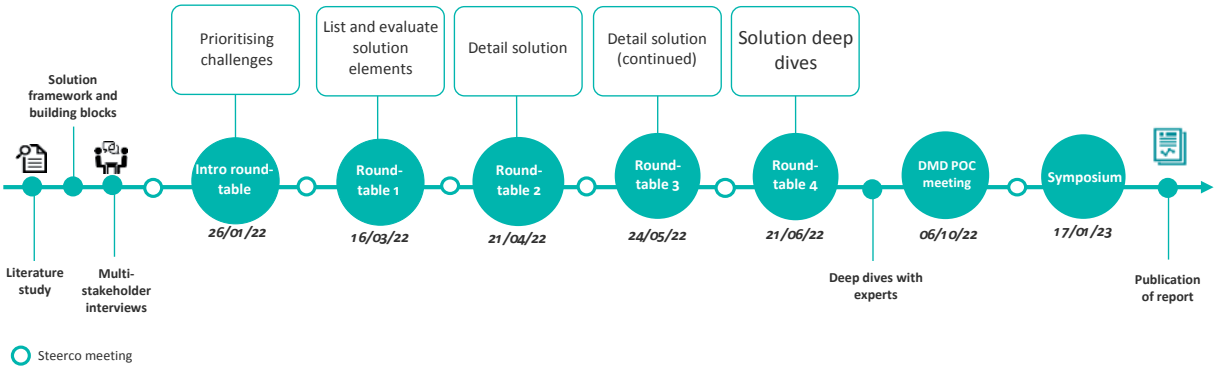


Figure 1: Chronological overview of multistakeholder engagement initiatives in 2022

To assess practical applicability of the proposed integrated roadmap and discuss the roles and responsibilities, the practical case of Duchenne muscular dystrophy (DMD) gene therapy was selected as a proof-of-concept.

The challenges of implementing cell and gene therapies

To find a suitable solution for implementation of cell and gene therapies in current models, the challenges specific to these ATMPs were first identified and prioritised. A list of challenges was assembled based on literature review, input stakeholder representatives during interviews, and experience gained from the first cell and gene therapies in Belgium. Thirteen challenges and barriers for the implementation of cell and gene therapy in Belgium were listed (see figure 2).

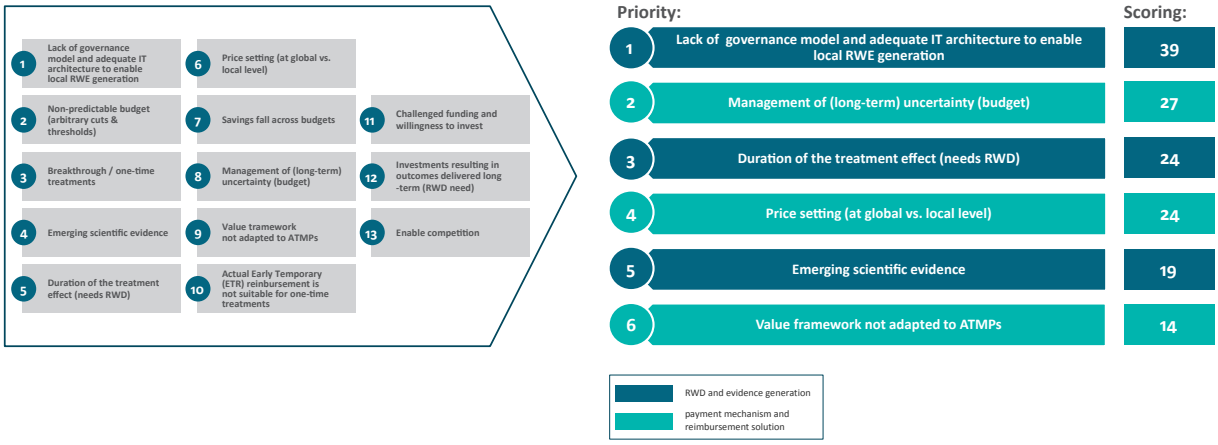


Figure 2: Priority challenges and barriers for implementation of cell and gene therapy as selected by stakeholders in roundtable meetings

In the first roundtable, participants were asked to prioritise the challenges and barriers that needed to be addressed. They were asked to select their top six priority challenges and barriers from the list to overcome the practical implementation of cell and gene therapy and select the ones that can be implemented on the short term in Belgium.

The following six priorities were selected (figure 2) based on a scoring system. The other challenges have been deprioritised, because they do not allow short-term implementation, need to be addressed outside Belgium/internationally or were considered outside the scope of this project.

The six selected priorities can be grouped into two overarching categories (figure 3). A first category focusses on RDW/E generation. A second area focusses on the payment mechanism and reimbursement solution. Both categories should be complemented by an adapted early access mechanism and optimized conventions, with the current ones being not fit for purpose. Solutions for each of these four areas have been developed in parallel, even informing each other, to result in an integrated solution addressing all prioritised challenges.

Figure 3: Overarching challenges for implementation of cell and gene therapy

The proposed solution

Based on the prioritized challenges for cell and gene therapies, four solution elements were co-developed in several multi-stakeholder roundtables (figure 4), to define a pathway for early access and reimbursement with integrated RWE generation.

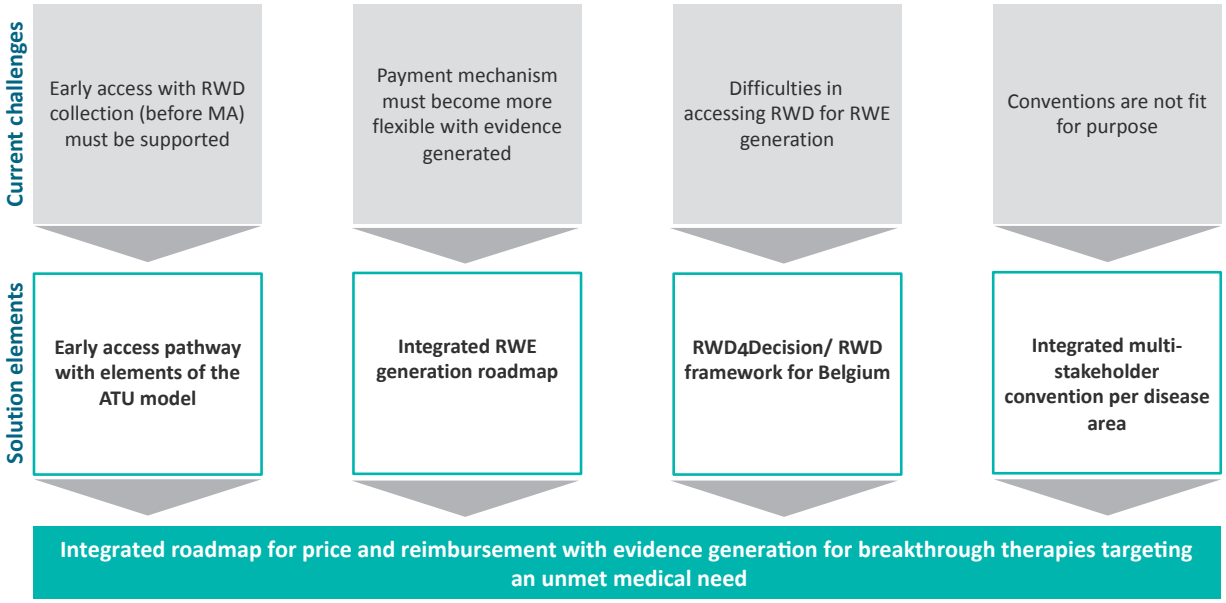


Figure 4: Current challenges for implementation of cell and gene therapy and accompanying solution elements

The proposed integrated roadmap for cell and gene therapies can be considered as a metaphor for all breakthrough and high-impact medicines with unmet medical need and can be applied beyond cell and gene therapies.

The main benefit of the proposed integrated procedure (displayed in figure 6), is that it allows proactiveness and timely preparedness. Horizon scanning and the UMN priorities list, allows to identify high-impact medicines with an UMN, as possible candidates for early access. Changes to the Belgian unmet medical need procedure, have been proposed to provide quick access to unapproved or non-reimbursed medicines with no therapeutic alternative for patients with serious, rare or disabling diseases These patients are unable to wait for a product to be approved and are unable to take part in clinical trials.

Five criteria for a product to be “presumed innovative” and eligible for the early access process, have been outlined, based on the French Temporary Authorization for Use (ATU) model:

1. If it is not approved, the product’s safety and efficacy must be “strongly presumed”, based on clinical trial results.
2. It is indicated for a serious, rare, or disabling disease
3. There is no appropriate treatment available (the availability of an appropriate treatment for a disease is one factor that can lead to the Haute Autorité de Santé (HAS) to refuse early access to a new unapproved product)*.
4. Treatment cannot be deferred.
5. The product is “presumed to be innovative”, in particular with regard to any relevant comparator.

After the assessment of compliance to these criteria the price and reimbursement pathway follows. The integrated evidence generation can be used to address uncertainties and provide a flexible pricing mechanism based on proven evidence.

Roadmap for outcome-based agreements with integrated RWE generation

To enable outcome-based reimbursement and patient access a six-step integrated roadmap with RWE generation, has been developed (figure 5).

1. **Horizon scanning** to identify high impact products + **UMN list and approach to prioritise** disease areas
2. **Request for early dialogue** to early dialogue platform
3. Early dialogue meeting to **define and agree on the RWE plan** depending on clinical uncertainties **+ potential early access scheme** for high medical need (cfr. new ATU/ETR)
4. Management of the **enabling foundation (governance, conventions), management of the execution** of the RWD & Evidence generation plan supported by **Belgian Health Data Institute**
5. **Reference centers** take the lead in **data collection and analysis, pool the knowledge and update treatment guidelines** based on emerging evidence
6. **Critical assessment of RWE & implementation in OBAs** by RIZIV.

Figure 5: Belgian integrated roadmap to enable reimbursement decision and patient access

Each of the steps were further elaborated in multistakeholder dialogues. The result of this discussion is described below.

Step 1: Horizon scanning to identify high-impact products combined with healthcare practitioners and patients input to define the UMN priority list

Through horizon scanning, of public data sources, one can outline what is coming (figure 6). As such upcoming high-impact products can be identified. NIHDI is the initiator of horizon scanning, but input should also be provided by health-care providers, patients and patient organizations, academia and insurers.

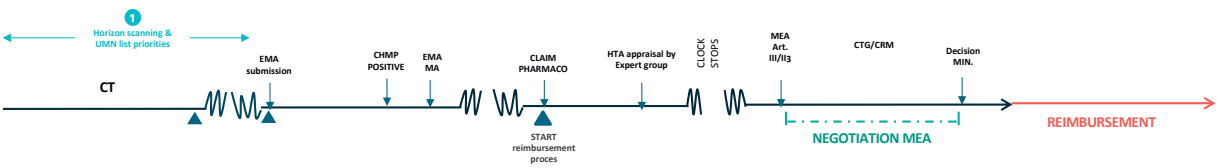


Figure 6: Management entry agreement pathway – Horizon scanning

Horizon scanning needs to be complemented with the input from healthcare practitioners and patients to build an UMN list. The UMN list is currently being compiled by NIHDI. Input from health care practitioners and patient organisations should be added to determine priorities of these UMNs. Input from these parties creates a list that reflects societal needs.

We need a framework that will be used during horizon scanning and which reflects societal willingness to pay. This framework should provide a rationale, enable authorities to explain why a certain decision is taken, be transparent on the decision-making process, and be dynamic (adaptable over time). The political and social support determines the social willingness to pay/invest and defines the affordability. Therefore, we must agree on what we want to achieve as a society and what is not a priority, as well as which criteria and conditions to use in the decision process. Priority setting should be based on the list of key criteria defined by the Belgian Health Care Knowledge Centre (KCE), the seven principles of the King Baudouin foundation mentioned below; and the citizen's opinion as determined through regular citizen surveys. Sciensano has such a citizen survey platform which could potentially be used for this purpose. The KCE conducted a large survey in 2014, asking 4.500 people to evaluate decision criteria used today by experts and NIHDI-commissions. The goal was to make Belgian health care more transparent and socially acceptable. Based on a survey the most important criteria for reimbursement were defined: Quality of life comes first, followed by diseases for which current treatments cause a lot of discomfort, and then impact on life expectancy. The King Baudouin Foundation conducted a guided discussion referred to as "citizens lab", which resulted in seven criteria for therapy reimbursement, listed in figure 7.

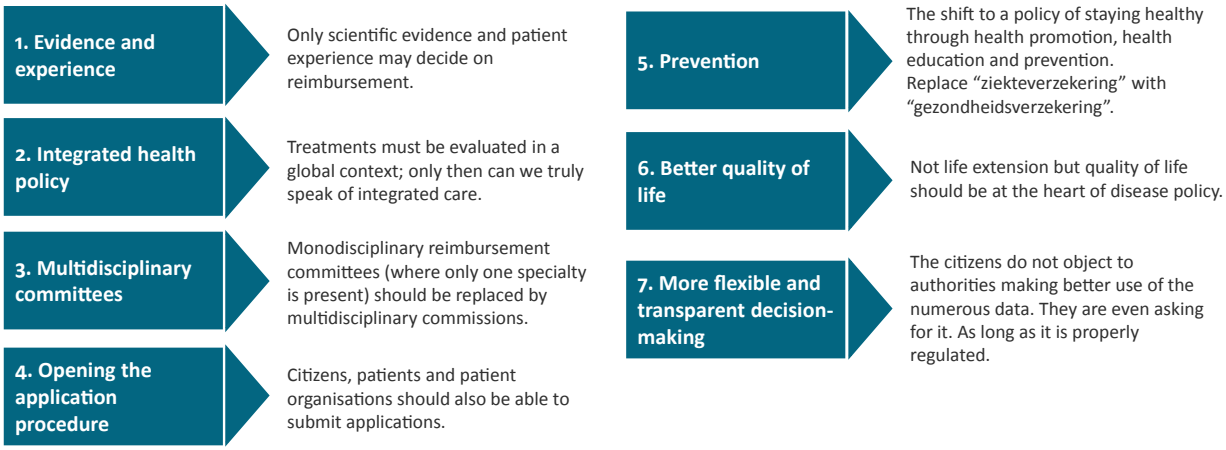


Figure 7: Seven criteria for therapy reimbursement, as put forward during the citizens' lab of King Baudouin Foundation

The UMN list sets priorities and will allow NIHDI to identify the most interesting "high-impact" therapies. This will allow to proactively decide which medicines, for which indications it wants to "buy" and be considered for early access/UMN procedure and reimbursement (within an OBA with RWD collection).

Thanks to the Horizon Scanning Initiative, NIHDI will proactively know what is coming up and which medicines, for which indications, the payer will want to "buy" or will be eligible for reimbursement. In this case the payer may act as a buyer and can co-create the decision.

The International Horizon Scanning Initiative will also enable a more proactive identification of medicines for which cross-country collaboration (e.g., BeneluxAiRe) can be considered, to align on early access /medical need conditions, RWD collection and HTA assessments.

Step 2: Request for early dialogue

Horizon scanning and early dialogue will allow payers to proactively assess medicines they want to "buy" and should be considered for (potential outcome-based) reimbursement and early access (figure 8).

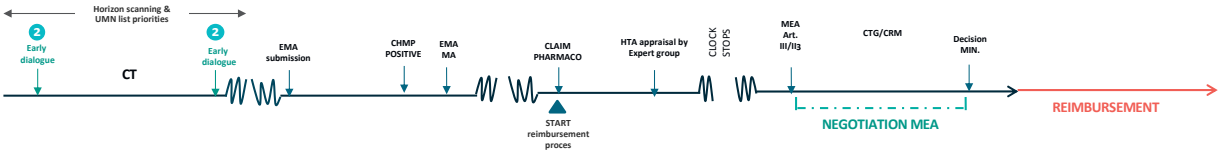


Figure 8: Management entry agreement pathway – Request for early dialogue

High-impact products and HTA needs should be discussed proactively and early-on by the innovator companies, HTA authorities and payers to help prepare for assessment of the clinical value and to address potential uncertainties (cfr. early scientific consultation with EMA and the recently created EU HTA coordination group). The goal is to prepare in time and make it feasible for authorities to proactively prepare Belgian local RWE generation, early access plans (for patients with high medical need), as well as the MEA using additional evidence collection. NIHDI will be responsible to set up a Belgian pre-submission early dialogue platform consisting of reference centres, and key opinion leaders involved in clinical trials (European reference networks (ERNs) and Belgian reference centres are often already involved in clinical trials), patient representatives, HTA bodies, companies, and data experts.

It is also important that Belgian HTA authorities play an active role in aligning with other EU colleagues within the EMA and the recently created EU HTA coordination group. As of 2025, the newly created EU HTA coordination group will provide consolidated EU scientific advice and a EU scientific assessment report for ATMPs.

Step 3: Early dialogue meeting to agree on evidence generation plan

Early dialogue at the EU and local Belgian level, will allow to proactively agree on the evidence generation plan (figure 9). In the early dialogue meeting, local RWE needs must be discussed, leading to an evidence generation plan (based on randomized controlled trials (RCT) and RWD) focussing on major clinical uncertainties. RWD and evidence generation is key to reduce uncertainties, given that out of the 19 ATMPs that are approved (status sept 2021), not one was involved in RCTs. This means there are still important clinical uncertainties at the moment of launch.

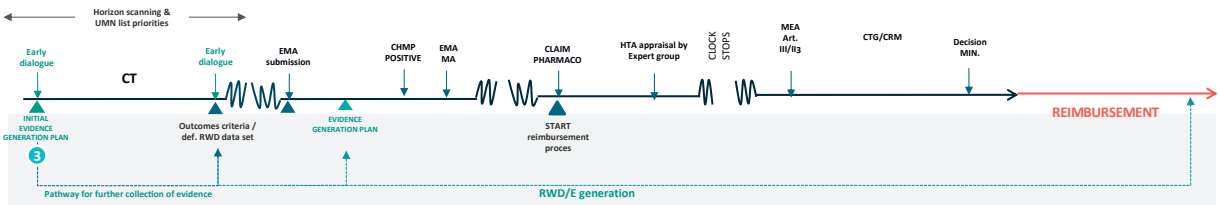


Figure 9: Management entry agreement pathway – Early dialogue meeting to agree on evidence generation plan

The early dialogue platform will facilitate alignment on data needs for OBAs and additional evidence to be generated based on the most important clinical uncertainties. This includes answers on which type of data should be collected, and how this should be done (the process for RWE generation). The result of such an early dialogue meeting is an agreed RWE generation plan, including roles and responsibilities for all concerned stakeholders. This meeting needs to be organized by NIHDI and needs to include industry, clinicians, and patient organisations.
The Belgian pre-submission early dialogue platform should consist of the reference centres and key opinion leaders involved in clinical trials, patient representatives, HTA bodies, FAMHP, companies, data experts (potentially provided by a new Health Data Institute acting as a centre of excellence on data science and pools all available expertise and know-how), and the RWD infrastructure holder.

Both EMA and NIHDI need the same data to address clinical uncertainties. EMA and the national HTA authorities should be more aligned. The evidence plan should be the starting point for collecting evidence (via RCTs and RWD) at the international and Belgian level. This will enable Belgian authorities to provide European-aligned HTA advice to innovator companies which will facilitate integration into global clinical development plans of companies. (After 2025, via newly created EU HTA coordination group for ATMPs)

RWD/E framework for Belgium

To support the development of the RWE generation plan, including commitments to be provided by the applicant, an RWD/E framework for Belgium has been developed. It is the result of literature review, recommendations specified in the RWE4Decision project[3] translated to the Belgian context, and interviews with all stakeholder representatives (figure 10). It provides answers to questions such as:

- What type of data should be collected for gene therapy follow-up?
- How should this data be collected?
- What would be the appropriate governance and funding model for such an RWD infrastructure?

Main objectives are to support well-founded decisions on pricing and reimbursement, to facilitate post-marketing surveillance, and to fulfil post-marketing obligations. To fulfil these objectives, RWD infrastructure should be created based on (existing) disease registries and adapted towards future treatments such as cell and gene therapies. This framework summarises the recommendations regarding a governance model and action plan to facilitate the collection of RWD for future cell and gene therapies. In this respect, requirements as well as roles and responsibilities for Belgian stakeholders have been clarified.

The developed RWD/E framework for Belgium consists of:

- A data process steps to (1) collect and process the data, (2) perform data quality and verification, and finally (3) perform data analysis and reporting (blue circle in figure 10).
- An enabling foundation: providing the necessary conditions to make this work (the yellow circle in figure 10). It contains (I) governance aspects, (II) funding and incentives, and (III) data privacy and security aspects.

In figure 10 each element of the data process steps, and the enabling foundation is outlined. For all elements of this framework, roles and responsibilities have been defined and an action plan created to facilitate access to RWD, (secondary) use of RWD and generation of RWE.

Two reports[4] on the RWD/E framework for Belgium have been published earlier this year and provide a detailed overview of the key elements and the roles and responsibilities for all involved stakeholders.

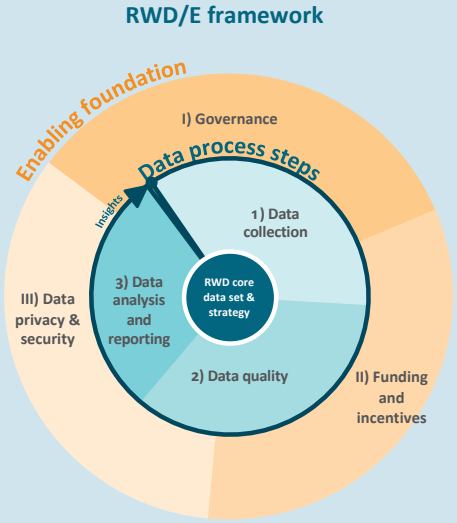


Figure 10: RWD/E framework with data process steps and the elements of the enabling foundation

Data use is integral to the future of health care, which is why stakeholders from across the ecosystem must come together to support data collection. By joining forces, we will be able to make a real difference to the patient's experience and quality of care, while also supporting outcome-based reimbursement agreements. It has been recommended to pursue some pilot use cases to test practical implementation (e.g. the forthcoming gene therapies for Duchene Muscular Disease, described later in this report).

[3] De Cock, J., & Kurz, X. (2021). *Co-Creating Real-World Evidence Excellence for Decision-Making: Meeting Regulatory and HTA/ Payer needs. RWE4Decisions.*

[4] Maes I., Kok E., Dewulf G., *Recommendations on a Real-World Data Strategy for Belgium, a multi-stakeholder initiative on reuse of routine care health data, 2022*

Maes I., Kok E., Dewulf G., *The Use of Real-world data for Personalized Medicine, multi-stakeholder roundtable outcomes on the use and reuse of routine care health data (in the context of project ATHENA), 2022*

Adapted early access model for UMN products / Belgian ATU model with integrated RWD collection

The current early access /UMN procedure in Belgium is not fit for purpose and is barely being used. It is considered as overly complex and takes too long. The closed budget is very limited and will only allow early access for a very limited number of patients. Compensation of innovator companies is, moreover, not incentivising early access for Belgian patients. The current Belgian early access procedure should become an early access and restricted UMN procedure. It must be simplified and have clearer eligibility criteria. The collection of RWD (including efficacy) should be facilitated and a more attractive compensation should be implemented for pharmaceutical companies. Providing early access for ATMPs by the concerned companies is mostly challenging because of complex and expensive manufacturing, and very limited supplies at that early phase of the life cycle. Moreover, inadequately funded early access is generally not viable from a commercial point of view.

The new International Horizon Scanning Initiative will allow to readily identify upcoming innovative high-impact medicines for Belgian patients with high medical needs, and for which early dialogue and early access before marketing authorization /reimbursement approval needs to be considered. The actual early access process must be simplified to make it easier and applicable for these breakthrough medicines. Moreover, patients should be part of this decision-making process. The legal framework in Belgium for collecting efficiency data needs to be updated to support OB-MEA.

Early access of such innovative therapies should be restricted to Belgian reference centres, as knowledge and experience on those therapies can be pooled. Consequently, an important element that must be put in place to facilitate early access are the appointment and implementation of reference centres (cfr. also, the national plan for rare disease and recommendations of the King Baudouin Foundation). National reference centres should also be assessed and validated to enable them to remain part and contribute to the EU reference network in a sustainable way.

At this moment the national early access schemes in the European countries are very different, resulting in significant variability in early access for patients with high UMN, even in neighbouring countries. Ideally, harmonization of country early access schemes within Europe should be considered, but this is not foreseen yet.

As a best practice in Europe, the French ATU system has been proposed, as inspiration. It provides early access to unapproved or non-reimbursed medicines with no therapeutic alternatives for patients who cannot wait for a product to be approved and are unable to take part in clinical trials. This new French ATU process already provided early access to 40 new breakthrough medicines for French patients with high medical needs within its first year of implementation. This is considered a success, especially when compared with the Belgian early access procedure which has only been used three times over the previous six years. The early access “indemnity” compensation foreseen in France will allow early access to ATMPs for those patients with high UMN. It foresees standard rebates which increase in function of the number of patients involved. It also involves a retrospective correction in case the final reimbursed price approved by the French authorities would be different, even in case no final market authorization or reimbursement would be reached. It also foresees provisions to guarantee continuation of care for the patients enrolled during another 12 months.

The French ATU system offers a couple of interesting elements for consideration to improve the Belgian early temporary access (ETA) process. Inspired by this system, six elements were identified, considered to improve the Belgian early access system:

- A utilisation protocol with eligibility criteria for quick access to unapproved or non-reimbursed medicines with no therapeutic alternative for patients with serious, rare, or disabling diseases, who cannot wait for a product to be approved and are unable to take part in clinical trials.
- Local RWD collection in reference centres (a responsibility of the pharmaceutical company and reference centres).
- More substantial early access compensation based on a fixed discount table.
- Flexible funding with win-win guarantee, based on retrospective adjustment of preliminary early access compensation based on the negotiated reimbursed price.
- Conventions or contracts between payer, pharmaceutical company and reference centres.
- Based on a flexible learn-and-adapt model, with adjustments based on new insights and learnings or through continuous improvement.

Moreover, clear eligibility criteria for early access are needed in order to provide a more explicit definition of "therapeutic alternatives", and to determine whether an "appropriate treatment" is already available and who can have early access for which therapy. The following 5 conditions were proposed:

1. If the medicine is not approved, its safety and efficacy must be "strongly presumed", based on clinical trial results. It is indicated for a serious, rare, or disabling disease.
2. There is no appropriate treatment available.
3. Treatment cannot be deferred.
4. The product is "presumed to be innovative," regarding any clinically relevant comparator.

Step 4: Management of the enabling foundation for RWD collection and RWE generation

The enabling foundation has to be set up in order for it to start supervising data collection and access, updating infrastructure, and ensuring data quality, accessibility, and sustainability (figure 11). Management of the enabling foundation includes (I) governance, (II) funding and incentives, and (III) data privacy and security to support the execution of the RWD and evidence generation plan. Management of the enabling foundation (governance, conventions), management of the execution of the RWD/E generation plan should be supported by the Belgian Health Data Institute.

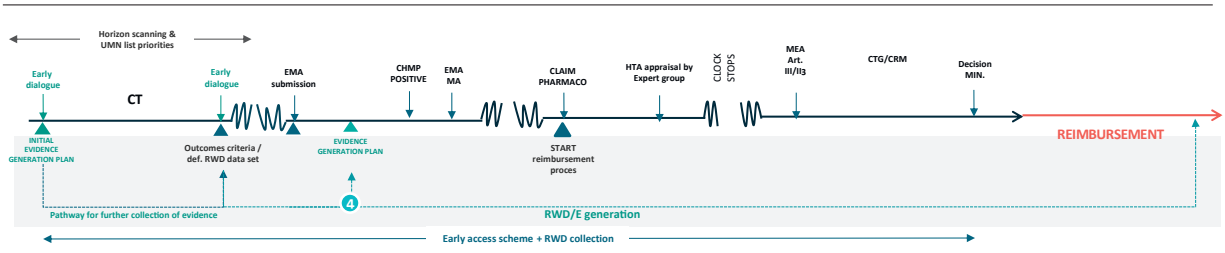


Figure 11: Management entry agreement pathway – Management of the enabling foundation for RWD collection

Two major tasks have to be performed:

- Set up a (I) governance, (II) funding and incentives, and (III) data privacy and security model, to update infrastructure and ensure data quality, accessibility, and sustainability. A multistakeholder governance board with representatives of all involved stakeholders (registry holder, clinicians, patient organizations, authorities, industry) is preferred, to balance interests of all.
- Update actual conventions and set up multistakeholder integrated conventions per disease area, that outline roles and responsibilities as well as the financing model.

(I) Governance

There is a distinction between data from clinical trials and RWD. Their purpose differs and therefore a different type of governance framework is needed. Currently, governances for primary and secondary use of data have been developed separately. For example, in the governance model for secondary use, where very complex and unstructured data comes together, OMOP common data model (standardized vocabulary) is used, which is not applicable to primary use. These two should be properly aligned to ensure appropriate data use at both the primary and secondary level.

A governance board with representatives of all involved stakeholders is preferred to balance the interests of all. To create a good governance model, patients, similar to other stakeholder representatives (registry holder, clinicians, patient organizations, authorities, industry), must be included, to agree and set up the enabling foundation.

To build a strong and sustainable health data governance framework, four concepts have been elaborated. These concepts have been based on proven best practices.

- The way we look at health data and its use is crucial for the implementation of health data frameworks. A "being-relationship" must be created with the data rather than an ownership. This means that phrases like "guardian of the data" and "access to data" better encompass the perspective of how one should look at data compared to being the "owner of data".
- The creation of an ethical values framework is essential to answer questions that cannot be answered by a legal framework alone. This ethical values framework should be built using basic principles and can be communicated to the citizens through a charter. This way, transparency can be guaranteed, and citizen support can be set up by communication campaigns.
- The ethical values framework is mainly active at the overarching level. At this level, it is important not to set up a governance board but a governance process. This implies that parliamentary review and citizen consultation have to be set up.
- To have a broadly supported vision for the use of health data, we need to work bottom up. For this purpose, a citizens' platform can be set up and revised every seven years, like in France with its "Etats généraux de la bioéthique"[5]. This allows the value framework to be revisited regularly, as times are continuously changing and updating will be necessary. In addition to the opinion of the citizens themselves, it is also essential that experts review and interpret the outcomes of this platform. For this purpose, the Sciensano cohort or King Baudouin Foundation could be engaged.

These four concepts have been considered while setting up the proposed health data governance model (figure 12). This model includes three levels:

- **Level (0)** is an overarching level including the Belgian ethical values and principles framework outlining the basic ethical principles and values for health data. This is based on input from societal surveys and citizen platforms organized by ScienSano or the King Baudouin Foundation and should be revised every seven years to follow societal evolution (cfr. France).
- **Level (1)** represents the health data institutionalisation, including the information security committee (under Parliamentary oversight) which provides approvals on information security aspects and surveillance of individual/fundamental rights (not only health data related). This committee has a normative authority and acts on matters that cannot be covered by a Royal Decree. It has a role in setting standards and carrying out preventive checks. The committee carries out generic deliberations to validate standard working methods and specific deliberations on data exchanges. Accountability of the data retrievers will be ensured through announced and unannounced inspections to maintain trust. The board consists of representatives of all stakeholders. This board could also act as a board of sages ("groep van wijzen"/group of senior experts) to translate the ethical values and principles framework into legislative proposals, evaluate the legislative framework and propose

[5] Rapport de synthèse du comité consultatif national d'éthique, opinions du comité citoyen ; Juin 2018

adaptations, based on the learn-and-adapt principle. However, we must be aware that ethical committees will provide approvals on ethical aspects only.

- **Level (2)** contains the health data operationalization level, where the Belgian HDA will play three strategic roles. The first role is to support, facilitate, create, and improve the processes for health data re-use on a strategic level. It will supervise data standardization, propose automation options for recurring data queries, and provide client-oriented services (at fee for service) to answer data-related questions from clients. Next, it should integrate KCE and IMA activities. Second, it will set up the platform and execute the operational tasks independently from patients, based on the decisions of the ethical framework and level 1. In the execution, no direct stakeholders should be involved, but the group has to have deep knowledge in the areas of data science, data privacy, and medical/disease. Third and last, the overview should be ensured by a "neutral" chairman and board with multidisciplinary expert representatives of all stakeholder groups (medical-scientific, ICT technical, information security, ethical-legal, etc.) to build confidence and buy-in towards implementation. Next to this, the Belgian Health Data Academy will inform, create awareness, and provide services on a self-service basis.

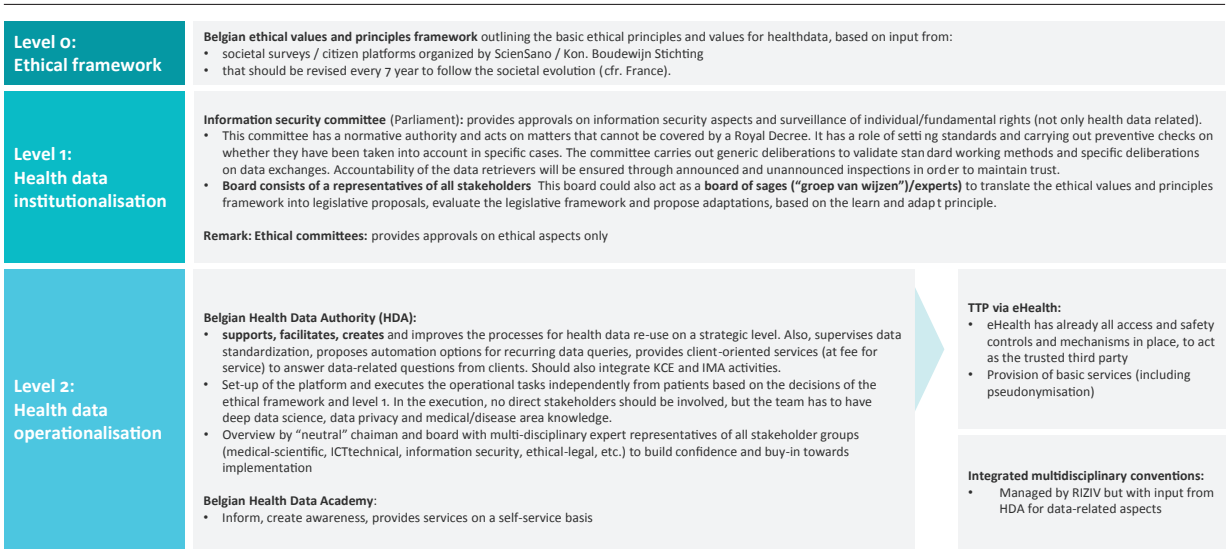


Figure 12: Health data governance model for Belgium

The eHealth platform will take the role of trusted third party. eHealth has already all access and safety controls and mechanisms in place, to take this role and have provision of basic services (including pseudonymisation).

(II) Funding and incentives

Structural funding and clear incentives for clinicians to collect data are needed. Clinicians are being paid for consultations with patients, not for time spent on collection of data. The current financing system (based on payment per consult) does not fit the data collection needs and must be adapted. General practitioners are already remunerated for the implementation of electronic patient directories (EPD), this could potentially be expanded. Additionally, incentives for clinicians must not jeopardize the time a doctor spends with their patients.

Incentives should not only be monetary. Monitoring dashboards and benchmarking between hospitals/reference centres to improve quality of care, is also a motivating factor for data collection. Being rewarded for performing research and advancing science are other important incentives.
Patient organizations have limited resources, while they are often involved and considered partners (always for free). Pharma companies and governments should support them by creating funding baskets. Clinicians and patient associations can be funded by these baskets to support data collection (and provide input to EMA and pharma companies).

Data collection of a specific therapy or product needs to be funded by the innovator company. Data collection on the disease level can also be financially supported by pharma companies coordinated by pharma.be in an "RWD fund". The fund consists of money from involved companies and NIHDI. Funding by the companies can be based on project funding and or a fee-for-service funding mechanism.

(III) Data privacy and security

The GDPR is perceived as a limiting factor for clinical research and care. GDPR is necessary for the protection of sensitive health data. Correct implementation is, however, lacking, due to deficient health data literacy and each stakeholder interpreting GDPR differently. Is it overlooked that the collection of anonymised data is based on informed consent? Use and reasonable re-use of data is out of the scope of GDPR, whereas GDPR fundamentalists plead the contrary. Some health data, such as genetic data, are harder to keep anonymized, but researchers would hardly have access to sufficient data to link back to patients. Therefore, a better understanding of the legal issues and an alignment on the basics of GDPR is required.

Nowadays, patients are often asked to fill out informed consent forms (ICF) they do not understand, not knowing what they are agreeing to. Patients should be well informed by their clinician and the rest should be simple, lean and clean. There was a clear consensus by the stakeholders on the importance of informing and involving patients to share data to the benefit of themselves as well as public health-policy. It is important to inform patients on the need for donation of data. Patients need to be made aware on the need for better insight in their treatment as well as the public character of funding of their treatment, the importance of data sharing, and what will be done with their data. Patients know a great deal about their illness, are experts in their disease and should be seen as partners. If they can help others, almost all of them will agree to share data voluntarily. This should become a societal trust aspect, independent of individual perceptions. A question of information, education and trust building.

Multistakeholder-integrated conventions per disease area

Today's convention structure is bilateral, including NIHDI and a pharma company, or NIHDI and the expertise centres, or NIHDI and Sciensano (figure 13). This has been established historically. Some conventions are already 20 years old, such as those representing haemophilia, neuromuscular diseases, etc. For many diseases, conventions are missing, or data collection is not included. Integrated multistakeholder conventions on the disease level between NIHDI, reference centres, Sciensano, and pharma companies could organize RWD collection and evidence generation better amongst parties. Separate complementary conventions between NIHDI and pharma company will remain necessary on the product level.

These integrated multistakeholder conventions could be based on a standardized template with key elements of the convention, such as the RWD infrastructure, governance model, roles and responsibilities, funding for RWD collection, penalties, incentives, etc. Disease-level agreements on RWD collection, analysis, and reporting, including data infrastructure and funding and governance aspects can be outlined and organised in an integrated multistakeholder convention/contract between NIHDI, companies, and reference centres (complementary to conventions on the product level). These agreements on the evidence to be generated include commitments to be provided by the applicant (which type of RWD, source of data, architecture, timeline, etc.), on roles and responsibilities, and on funding for RWD collection, analysis, and reporting.

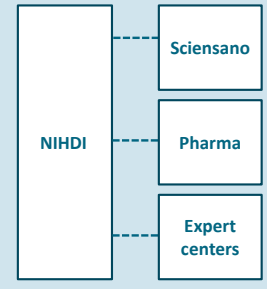


Figure 13: Current conventions structure in Belgium

Conventions can become more complex when linked to care as well. To reduce complexity of the conventions, care must be separated from the medicine and data collection integrated multistakeholder convention.

Making such integrated multistakeholder conventions will require resources. They should also be set up in a pro-active manner during early dialogue.

Step 5: Initiation of data collection process by reference centres

Local RWE generation has to be initiated by NIHDI and driven by the reference centres, supported by BHI (Belgian Health Data Institute, the BHI has a broader role than the Belgian Health Data Agency and supports data related knowledge building and insemination as a centre of excellence on data topics) and partly funded by industry (on a fee-for-service basis). Reference centres will take the lead in data collection and analysis, pool the knowledge, and update treatment guidelines based on emerging evidence (figure 14). Expert centres are needed for collecting data, generating evidence and the application of this emerging evidence in decision-making on price and reimbursement. Given their crucial role, they need to be selected and supported for this role. The centres need to be defined by the government based on their merits and objective criteria related to knowledge, research capability, and performance. they also need to work together. This is essential and a precondition for incentives. Because of the societal role of university hospitals and their role as expert centres, they can be responsible for initiating proof-of-concepts.

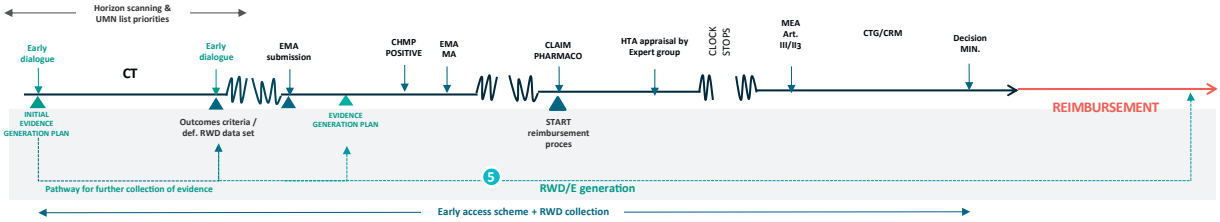


Figure 14: Management entry agreement – Initiation of the data collection process by reference centres

The expert centres will be responsible for three aspects:

1) Data collection

- Support high quality collection and generation of RWD useful and informative to decision making at individual and population level, to create RWE.
- Responsible: Reference centres should engage and commit, together with patients. BHI will support the execution of the Belgian evidence plan to make sure that data sources are identified, and the right data will be collected.

2) Data quality

- Review and apply quality standards for registries issued by EMA and EUnetHTA.
- Follow the FAIR data principles and provide “privacy by design”.
- Use the unique patient ID to enable linkage with other health data sources.
- Responsible: BHI (Belgian Health Data Institute)

3) Data analysis & reporting

- Analysis with commitment to transparency, replicability, and principled database epidemiology
- Responsible: Clinicians and analytic group, BHI must support the execution of the Belgian evidence plan to make sure that data will be translated in evidence.

Solution for automated data registration (' harvesting')

There is a need for an automated data registration solution to feed registries, without creating an additional burden for clinicians and patients (figure 15). Data should preferably be collected from the EPDs in each of the hospitals and via the e-health platform. An "only once" data registry principle should be applied, which means data collection happens at the source and automatically feeds into the registries (local and international). This will simplify data submission. Manual entry of already digitalized data, duplications, manual validation/verification of field values, and manual/subjective interpretations will be minimized or even avoided.

A solution for automated data harvesting from the EPD has been developed in the context of the multiple myeloma Car-T project with four reference centres and four pharma companies represented by pharma.be.

Through a Data Providers Interface and the eHealth platform, various registers could be fed. For the data analysis a Health Data Analytical interface, with a specific interface for each stakeholder group with a different purpose, will be foreseen.

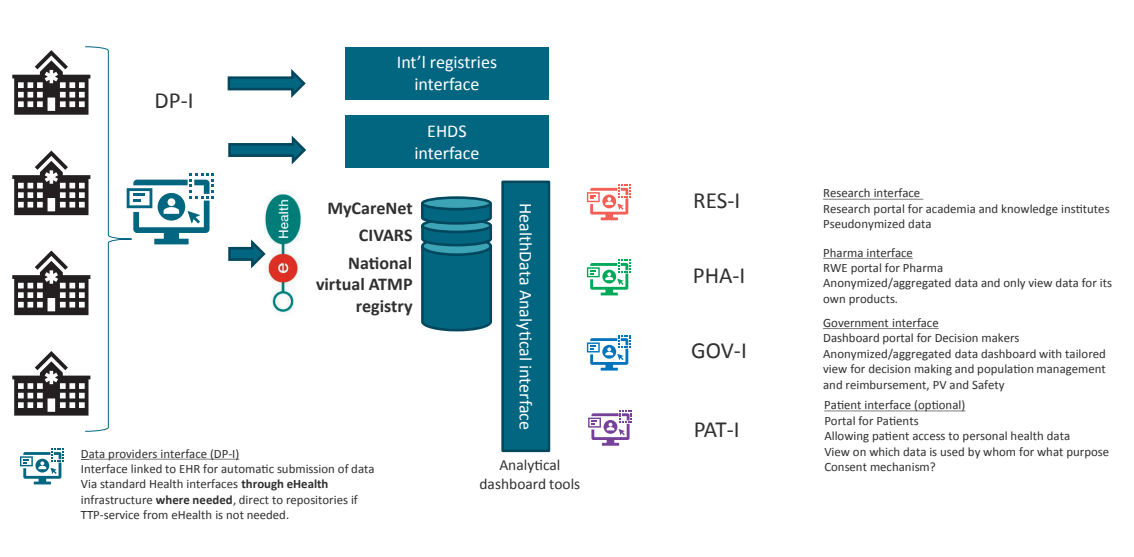


Figure 15: Future automated data registration solution: Proposal for future solution that supports 'only once' data registration, via the Belgian eHealth solution to feed National ATMP registry, CIVARS for reimbursement, but also for European Health Data Space and international registries

This solution makes RWD/RWE retrieval possible, compliant with GDPR, trusted third party enabled, with an appropriate governance model. It supports the generation of aggregated reports, provides an interface for all stakeholders, and is funded on a pay-per-use/fund for pharma companies.

The reference centres should facilitate data collection by making it as simple as possible to enter and gather data. It should ideally be based on standardized automated data harvesting from the electronic health record (see separate text box).

To determine which data must be collected, a small group of experts should select a maximum of two to three parameters (to avoid an overload of data collection that is not necessary for price and reimbursement). The data collection itself can be a task performed by health scientists (people with a background in physiotherapy, nursing, biomedical sciences, etc.). The data interpretation is an import step and needs to be performed by experts in the field and patient organisations. It is important that data is analysed in a correct way.

Among the different stakeholders participating to the roundtables, the consensus was reached that qualitative data collection is a priority. It is the cornerstone of qualitative evidence generation and of improvement of the quality of care. There is a need and willingness of all stakeholders to work together, and this is also necessary to achieve qualitative data and resulting evidence. Analysis of the data is key, but this is impossible if data quality is lacking. To ensure quality, the entire care environment and all disease areas need to be involved.
A minimal data set should be collected to support OBAs, and on top, specific research data can be collected. Data are often being collected without this insight, which hinders later research projects.
Data should be collected as quickly as possible, preferably directly after diagnosis, so we can prepare the use data for prevention purposes. To avoid collection in different silos and systems, it was suggested to collect data across disease and therapies areas, in broad (virtual) registries, eventually beyond Belgian borders, on a European level. Certainly, for rare diseases, broader data sets will provide more reliable and robust insights.

Every hospital should organize themselves to collect data, but it should be clear what data is expected to be collected and how much funding is given. Involvement of several stakeholders would be preferred but this requires good governance and an agreement on funding. A governance board with all stakeholders is necessary to determine which type of data is collected, what the quality of data should be, and how it will be collected.

Evidence generation is a collective responsibility. The payer should be the initiator and needs to assess valuable and less valuable medicines. Patients have a role, as well as the insurance funds. In the end, pharma expects to be paid for the real value of the product.

Today, there are different registries for different disease domains. These registries should be harmonised. A minimal core data set on treatment is needed for harmonisation. A lot of data might be interesting for research purposes, but a core data set on the treatment should be the starting point to support OBAs. This data set should be flexible and adjustable over time, based on increased insights.

The core data set for cell and gene therapies should represent real life and support long-term follow-up (at least 20 years), but we should start from what is easy to capture. We should start from current registries, when possible, adapt these to cell and gene therapies, and align internationally. To harmonise data on an international/EU level, we need standardized data types and terminology. The Belgian registry should be aligned with the EU registry and EMA data collection requirements should be integrated. Also, to have sufficient data for analysis, alignment with international registries is required.

Data analysis is a joint responsibility. Data collection and quality control can only be done by clinicians. Data quality checks should be done by the clinicians, as they are best placed for this. Data analysis is a broader task and should become the responsibility of different parties. A joint team may perform the data analysis for the reference centres. Funding can be provided by industry and government. A “Health data institute” consisting of data science experts, that pools knowledge and makes it available, could support this endeavour. On the governmental side (NIHDI, FAMHP, KCE), sufficient resources and funding is needed to support data and evidence reviews for OBA models.

In order to succeed, there needs to be a willingness and incentive to collect data. Collecting RWD is considered a big challenge. To address this, there must be a willingness amongst stakeholders to contribute to resources and investment (e.g. to update infrastructure enabling this and to make it sustainable). Clinicians and data managers that perform data management tasks (data collection, data analysis) should be financially compensated. Hospitals should develop a data strategy and should be rewarded for their efforts (e.g., via hospital financing). Through priority setting, resources should be made available to make this important asset available for decision-making.
To address the lack of funding and knowledge, inspiration can be drawn from the Swiss system. A SWAT team was

set up by the government including experts on data science, data collection, and infrastructure. This SWAT team travels from hospital to hospital to support set-up of the data infrastructure and to transfer the know-how. This team could serve as a knowledge pool that can be reused per hospital. This is a more cost-effective way to share the experience and know-how.

Funding for the registry infrastructure and automated data harvesting should be based on a mixed model, guided by funding from government, clinical society, and companies. (In the SMA case, this has been funded by Biogen per patient for 3 years. In the Tardis case it was initially funded by NIHDI and the clinician society.) To assure sustainability, a model of mixed funding will be required. A performant RWD/E infrastructure is also required to keep Belgium attractive for clinical trials.

Step 6: Critical assessment of RWE and implementation in OBAs

The final step of the roadmap is a post hoc critical assessment of the generated RWE (figure 16). This assessment will influence the price, in OBAs. The evidence must be provided to the payer/ HTA body and company, who can use this to model the price of the therapy.

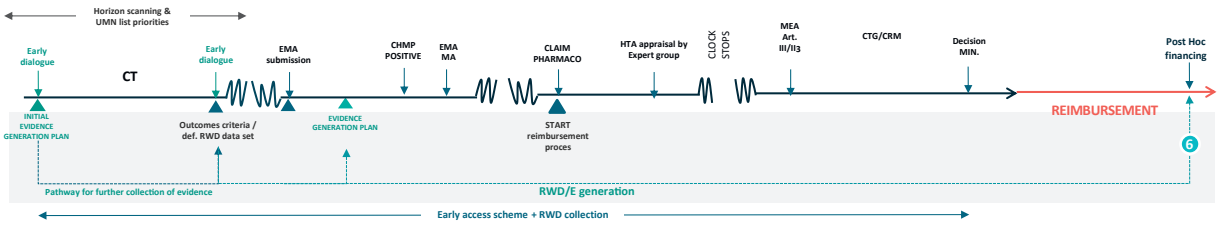


Figure 16: Management entry agreement – Post hoc critical assessment of the RWE

The pricing and payment mechanisms agreed in an OBA should be flexible and in line with the generated evidence. The price modulation mechanism should be agreed upfront based on the evidence being generated over time.

For the funding mechanism specific case-by-case solutions are being recommended whenever needed, like more flexible spread payments, outcome-based MEA and transversal “gain sharing budgeting”. (See also ATMP Vlerick-Inovigate multistakeholder consensus report, 2018.)

Critical assessment of RWE and implementation in OBAs should be the role of NIHDI. Evidence generation over time should be provided by the pharmaceutical company, supported by the reference centres and the Belgian Health Data Institute.

Overview of the integrated pathway

The overview of the whole proposed price and reimbursement pathway with integrated RWE generation and early access for UMN, and timelines is provided as a summary on the next page (figure 17).

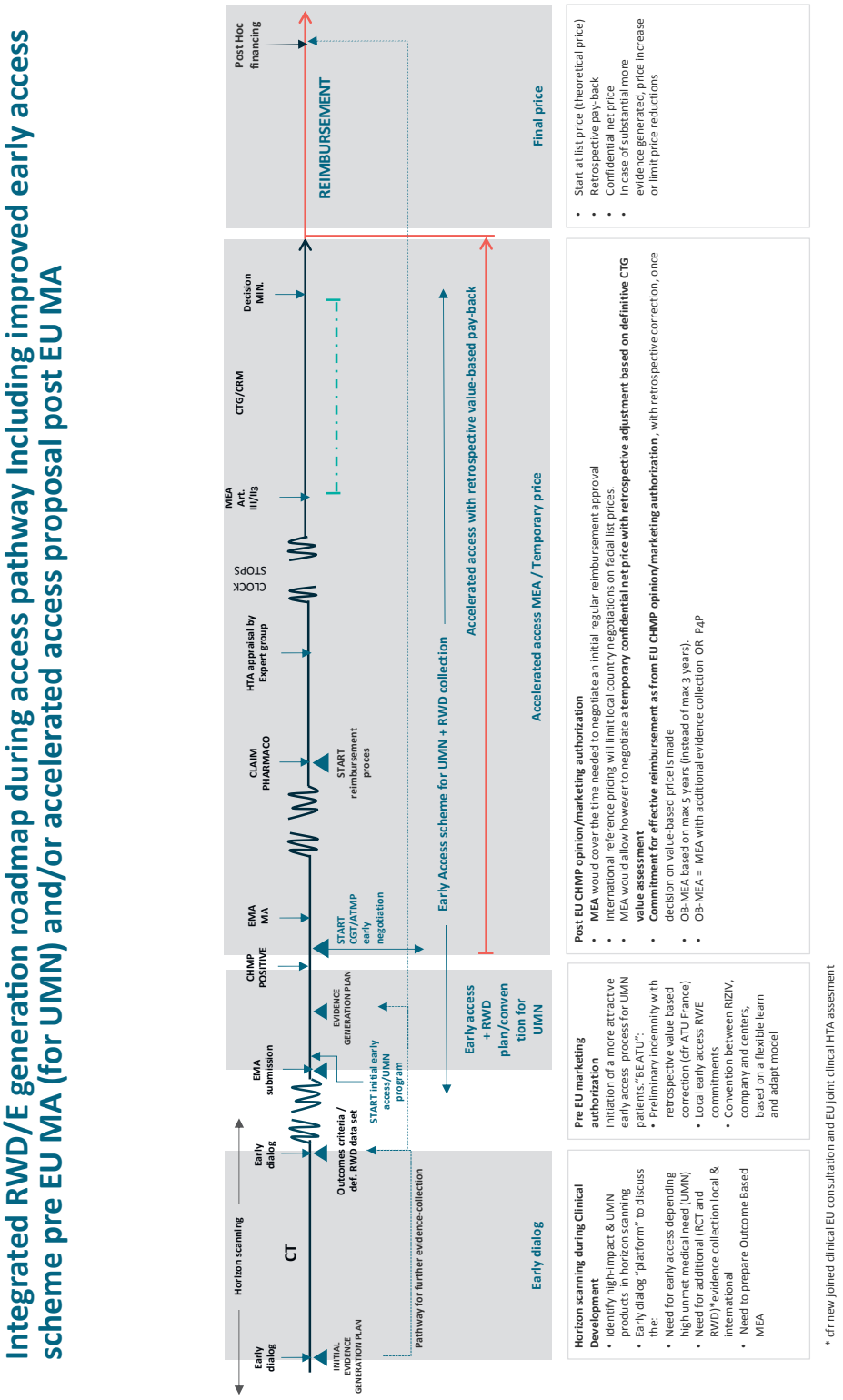


Figure 17

Proof-of-concept of a real-life case

The case of Duchenne muscular dystrophy (DMD) gene therapy was selected as a proof-of-concept, to assess practical applicability of the proposed integrated implementation roadmap and discuss the roles and responsibilities to put this roadmap into practice. For this purpose, a roundtable with clinical experts, project managers from the Belgian Neuromuscular Disease Registry (BNMDR), and patient representatives was organised. During this meeting the RWD/E framework for Belgium was applied to the DMD situation.

RWD collection on gene therapies allows for evaluation of long-term efficacy and safety. The advisory board indicated that a DMD RWD infrastructure should ideally fulfil a broad spectrum of objectives and serve all stakeholders involved:

- Long-term follow-up of patients after clinical trials;
- Support physicians in medical decision making;
- Support well-founded decisions on pricing and reimbursement;
- Facilitate post-marketing surveillance and fulfilment of post-marketing obligations.

To fulfil the above-mentioned objectives, a DMD infrastructure should be created based on the BNMDR disease registry and adapted towards future treatments, including gene therapy. Through a pre-meeting survey, the major hurdle to set up such a DMD infrastructure was identified to be the general lack of resources and time, especially relating to data entry and collection.
The specific Belgian core data set for DMD should be in line with the international core data set, i.e. the TREAT-NMD core data set. This data set can act as a starting point and can be adjusted in a later stage. Quality of life (QoL) data were especially valued by patient representatives. Disease-specific QoL measures are preferred. ACTIVLIM, a QoL measure specific for DMD, is recommended as a good starting point. Use of the new DMD QoL could be explored. Data types should represent real-life needs and support long-term follow-up. To ensure feasibility, a start should be made with data that is easy to capture. In summary, the BNMDR should be upgraded to a future proof RWD infrastructure that is more flexible and less burdensome.

During the meeting the following questions were discussed:

Question 1: Which types of data (core data set) should be collected in a DMD RWD infrastructure for gene therapy follow-up?
Before a core data set can be defined, alignment on the purpose of the RWD infrastructure should be reached. The following recommendations need to be considered:

- A minimal required data set should align with the international/EU core data sets to maximize harmonization (especially in rare diseases it is important that data can come together on an international level, such as in a federated network or registry);
- It should reflect the needs of all stakeholders involved;
- It should ensure flexibility so that additional datapoints can be added over time;
- It has to include appropriate QoL measures, preferring disease specific QoL measures with a limited burden on patients;
- Parameters should:
  - Be easy to capture;
  - Provide sufficient data granularity;
  - Focus on long-term disease progression in real life.
- The frequency of data collection should range between once or twice a year and could differ between parameters;

- Duration of follow-up should be decided by the clinician, but lifelong data collection for certain parameters is desirable to evaluate disease progression;
- The data sets per patient need to be as complete as possible with room for data enrichment;
- All data should be standardized to facilitate data sharing.

Question 2. How should this data be collected?

The following recommendations were made to transform the current registries, such as BNMDR, to a RWD infrastructure that is future-proof and compatible for gene therapy:

- The burden on patients and physicians should be as low as possible and automated data harvesting from the EPD was considered as a solution. A well-structured EPD at hospital level is needed to facilitate automated harvesting. Web-based QoL questionnaires are preferred, and clinical routine should be optimized to limit patient burden;
- The data collection must be flexible and adjustable;
- Quality checks and validation at data entry are required to ensure high quality data;
- One joined analysis support group should be set up to perform analysis of the data.

Question 3: What would be the appropriate governance model for such a RWD infrastructure?

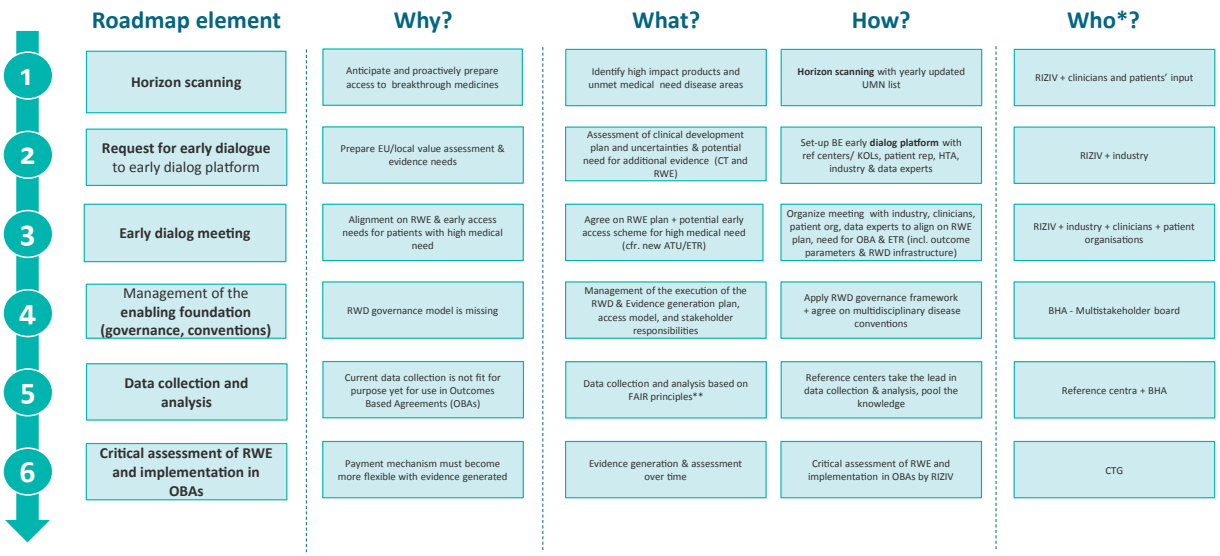
Once data is collected, an appropriate governance is essential to be agreed on:

- Clinicians were considered as initiators of the data infrastructure with support of companies. The voice of patients should always be considered, and payers should also be involved in an early multistakeholder dialogue;
- The government and industry will be essential to assure sustainability of the data infrastructure;
- Collaboration among different companies is strongly preferred;
- Data inclusion could be based on a common consent model as is currently done in the BNMDR, or through an opt-out model;
- Transparency is key to establish trust: a web-based tool for patients to consult their data will support this;
- Implementation of a data validation group for data analysis, consisting of clinicians;
- A web-based interface for patients to consult their data was proposed;
- A specific working group is needed per disease/subgroup (paediatric, spinal muscular atrophy and DMD) to take subgroup-specific decisions on the RWD infrastructure;
- Appropriate data access and reuse rules are required;
- A reform of current conventions into one overarching convention between NIHDI, the BNMDR and the Neuromuscular Reference Centres is needed to make it workable and sustainable, as well as to get recognition for the work done on RWD collection.[6]

[6] Maes I., Rey S., Mertens E., *Towards an implementation roadbook for real world data collection on ATMPs in Belgium (A pilot in DMD gene therapy); March 2022 (https://ap.lc/OvJr2)*

Conclusion and call to action

Cell and gene therapy is not yet business as usual, therefore a consistent and adapted integrated procedural pathway is required, including clear decisions on who should do what. In Belgium, compared to other countries, we are not prepared optimally. To catch up, we have to take action. This multi-stakeholder dialogue has contributed to the development of a future-proof price and reimbursement pathway with integrated evidence generation to support implementation of ATMPs in Belgium.



*Who will take the initiative?
** Findable, accessible, interoperable, and reusable

Figure 18: Integrated roadmap with the elements addressing the main challenges (the why) and with key recommendations (what has to be done, how it has to be done and by who / who has to take the initiative)

Today, the price and reimbursement, evidence generation, early access, etc. processes are sequential (mainly adapted for chronic treatments) but they should be integrated and adapted for breakthrough treatments for high UMN as well. We have identified the different steps of one integrated approach and defined what the roles for all stakeholders (clinicians, reference centres, patients, authorities, etc.) should be. To tackle the key issues and take action, key solution elements have been proposed for implementation. These solutions include an:

- Early access mechanism combined with RWD/E collection for patients with high UMN inspired by elements of the French ATU model;
- Integrated price and reimbursement pathway with integrated evidence generation, with flexible pricing modulation mechanism, based on proven patient outcomes;
- RWD framework for Belgium, including the data process steps and the enabling framework for the governance, funding and privacy aspects;
- Integrated multistakeholder conventions per disease area to complement separate product specific conventions.

It is clear that it should be a multistakeholder effort (clinicians, universities, patient organizations, authorities, industry, and sick funds).

Being prepared means we need an investment to make this integrated pathway possible, to set up a RWD infrastructure, to automate the data collection process and perform data analysis to generate evidence. We have to set up structures and build health systems which are responding to these challenges by for example setting up the Belgian Health Data Agency as a trusted third party. In addition, the role of reference centres is a very important element which needs to be further implemented.

As stated by H.G. Eichler we have to learn and adapt our system on a continuous base. It has to be general enough to include enough products, detailed enough to be concrete, and flexible enough to adapt while learning.

Recommendations

Based on these proposed solution elements, five recommendations have been formulated for building a future-proof access and reimbursement decision pathway with integrated evidence generation for breakthrough therapies for high UMN in Belgium.

Recommendation 1: Complement horizon scanning with a yearly updated UMN list, based on input from clinicians and patients to define priorities and to enable proactive preparation based on dialogue and collaboration with the innovator company (e.g. possible early access conditions, RWD collection protocol, etc.).

Recommendation 2: Implement an RWD/E framework for Belgium, supported by an ethical overarching governance framework, leading to common interpretation of GDPR, legal adaptation of data collection for re-use in price and reimbursement (cfr. Law in Finland) to eliminate case-by-case decisions and inconsistencies, and to make Belgium an attractive country for data use and re-use (to maintain and complement our clinical trial leading position).
Several conditions will have to be met to create a successful RWD infrastructure. To fulfil these conditions and to implement a RWD framework for ATMPs in Belgium supported by all stakeholders, several actions are recommended based on a combined top-down and bottom-up approach.

- Multistakeholder collaboration will be necessary to set up a RWD framework. Data collection is a joint responsibility of clinicians / expertise centres, and patients;
- NIHDI has a key role as payer and largest requester of data, and therefore should take the lead in setting up the required framework;
- Data collection should start as early as possible in the product life cycle and should be agreed upon in an early dialogue platform in Belgium, resulting in the evidence plan of the ATMP;
- A generic solution model for conventions outlining the basics for data collection to generate evidence defines the foundation;
- Good legal guidelines on data collection and RWD (incl. one GDPR interpretation) for every stakeholder, incl. a national 'charter' (inspired by Finnish law). Alignment is needed between the governance for primary use and governance for secondary use of health data;
- Start with a minimal required data set preferably aligned to international data sets and add additional data points over time when setting up the RWD framework;
- Set-up of well-structured data, via EPD, in the hospitals, allowing automated data extraction for further analysis and reporting;
- A flexible RWD framework which is easily adapted to other registries (a.o. international registries) or new needs;
- A dashboard/web-interface with an overview of the collected data for patients;
- Local RWE generation initiated by NIHDI and driven by the expertise centres;
- Clinicians, Belgian expertise centres and ERNs have a key role to play in collecting data and generating evidence;
- Data collection based on automated data harvesting from electronic health records to populate (virtual) registries;
- Set up a multistakeholder governance board with representatives of all involved stakeholders within the Belgian Health Data Agency;

- A combined public and private fund and incentives for the collection and analysis of data is needed. Funding baskets have to be provided based on collective / joint public and private funding (based on a fee-for-service model) for infrastructure, data collection and analysis;
- Patients must become equal partners as they have a key role to enable access to (re-use) data, and should be properly informed, but also involved in the decision process. Proper funding for patient representatives in the governance board and for involvement in the price and reimbursement process, should be foreseen;
- Patient representatives need to be involved along the roadmap to assure a patient-centric solution, which will also require education and training;
- Reach out to Union of the University Hospitals and the Belgian Association of Hospital Managers to initiate proof-of-concepts, pilot projects and initiatives;
- Educational programs to generate sufficient data science and ICT experts for the future.

Recommendation 3: Improve the Belgian ETR model to enable early access and local RWD collection of breakthrough medicines for Belgian patients with high UMN. The new French early access (ATU) best practice can be considered as inspiration.

Recommendation 4: Develop disease registries and conventions detailing the responsibilities of all concerned parties (based on the RWD4Decision publication).

Recommendation 5: Set up a joint fund for RWD infrastructure and data collection and analysis, and establish a Health Data Institute to assure pooling of expertise and experience to make it available to all stakeholders and become more cost-effective.

Finally, it was recommended to further test the practical implementation of above-mentioned recommendations based on a concrete pilot use cases (such as the ongoing CAR-T project and the Duchene disease case, etc.).

Recommendations for stakeholders

Based on the discussions during the roundtables, recommendations were formulated for each of the stakeholders to enable the implementation of cell and gene therapies in Belgium.

Recommendations for the government

The government will have to take the following top-down actions:

- Impose data standards, including interoperability standards for hospital EPD (e.g. OMOP, preferably EU);
- Reform conventions to assure sustainable financing of data infrastructure, collection, and analysis. Sustainable funding requires collaboration with the industry;
- Update the HealthData.be architecture to support automated data harvesting and quality checks;
- Provide clear guidance on legal requirements for (re-)use of RWD (e.g. possibility of opt-out system);
- Harmonize data infrastructures across diseases and international initiatives;
- Set up a governance model for RWD infrastructures, i.e. local translation of RWE4Decision.

Recommendations for hospitals and clinicians

Bottom-up, hospitals and clinicians will have to take the following actions:

- Hospitals have to work on restructuring the EPD to be compatible with different RWD infrastructures;
- Clinicians need to define core data sets per disease including clinical outcomes, patient-reported outcome measures (PROM), QoL, etc.;
- Clinicians need to define the necessary frequency and duration of data collection;
- Clinicians need to optimize their clinical routine based on data collection needs and adapt clinical guidelines to reflect these needs.

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List of abbreviations

ATMP	Advanced therapy medicinal products
ATU	Temporary Authorization for Use
BHI	Belgium Health Data Institute
BNMDR	Belgian Neuromuscular Disease Registry
CGTx	Cell & gene therapy
CT	Clinical trial
CTG	Commissie Tegemoetkoming geneesmiddelen (Commision for Reimbursement of Medicines)
DMD	Duchenne muscular dystrophy
EMA	European Medicines Agency
EPD	Electronic patient directories
ETA	Early Temporary Authorization
ETR	Early Temporary Reimbursement
ERN	European reference networks
EU	European Union
FAIR	Findability, Accessibility, Interoperability, and Reuse
FAMHP	Federal Agency for Medicines and Health Products
FOD	Federaal overheidsdienst (federal government department)
GDPR	General Data Protection Regulation
HDA	Health Data Agency
HTA	Health Technology Assessment
IHSI	International Horizon Scanning Initiative
KCE	Federaal kenniscentrum voor de gezondheidszorg (Federal knowledge centre for health care)
MA	Market Access
MEA	Management entry agreement
MNP	Medical need program
NIHDI	National Institute for Health and Disability Insurance (RIZIV)
OBA	Outcome-based agreement
OB-MEA	Outcome-based management entry agreement
OMOP	Observational Medical Outcomes Partnership data model
PROM	Patient-reported outcome measure
QoL	Quality of life
RCT	Randomized controlled trial
NIHDI / RIZIV	National Institute for Health and Disability Insurance / Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (RIZIV)
RWD	Real-world data
RWE	Real-world evidence
SWAT	special weapons and tactics, originally special weapons assault team
AUMN	Unmet medical need

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