

White Paper

Together for Access to Advanced Therapies
and New Innovative Medicines for Patients
with Rare and Severe Diseases in Sweden

*An implementation
and payer perspective
from Swedish
health care*



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Recommendation Area 1: A regulatory system that secures availability of both well established and new, safe, effective, and cost-effective treatment options to patients.

Recommendation Area 2: An adaptive pricing and reimbursement system for new therapies for rare and severe diseases that reduces barriers to early adoption and implementation in clinical practice and thereby facilitating patient access.

Recommendation Area 3: A governmental funding mechanism for new medicinal therapies targeting unmet medical needs of patients with rare and severe diseases, stimulating early adoption, implementation in clinical practice and evidence generation from real-world settings.

Recommendation Area 4: A national commitment to strengthen the possibilities of data collection, storage, management and use as well as sharing of reliable and relevant health, care, and cost data from clinical use of new medicinal therapies.

Recommendation Area 5: A joint commitment between national and regional stakeholders to horizontal priorities in Swedish health care, including the role of early adoption and implementation of new medicinal therapies targeting unmet medical needs.

Sweden as a REAL WORLD LAB for early adoption and implementation of new therapies in clinical practice

White Paper

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Foreword

As the governor of Västerbotten, I am deeply impressed by the efforts undertaken by Region Västerbotten in the development of this white paper proposing a system for the introduction of new therapies for rare and severe diseases in Sweden.

The complex societal challenges of today require a new type of governance based on a horizontal approach where multiple stakeholders innovate and collaborate towards a joint goal, often called mission driven innovation. With this white paper, Region Västerbotten has presented a mission and a goal as well as areas of recommendation for joint action. Now is the time to support this mission and let the journey begin. The goal is to secure equal access to new treatments for patients with rare disease, and the right to a life in good health. As a result, we secure a better and equitable health care and strengthen Sweden as a life science nation. This creates jobs, growth and welfare. Let us now make the impossible possible. Let us put a man on the moon.

Helene Hellmark Knutsson,
Governor, County of Västerbotten

Together we turn possibilities into realities

The regions in Sweden aim to create best possible opportunities for life in good health, today and in the future. Patients living with rare and severe diseases has up until now had few effective treatment options. This is changing now.

We see these new possibilities as a result of successful research, development and innovation in health care. At the same time, we also acknowledge that we are facing challenges in terms of patient access to new therapies in Sweden.

In 2019, Region Västerbotten had to face these challenges first hand, when new innovative medicines where approved for hereditary TTR amyloidosis, the rare disease we commonly refer to as "Skelleftesjukan" due to its endemic nature in our northern regions.

This white paper is therefore developed with the intention to raise awareness about the challenges identified and propose action for a sustainable introduction of new therapies for rare and severe diseases in Sweden. We believe that challenges need to be addressed with a systemic approach, jointly by all key stakeholders and hope that the recommendations presented can serve as a contribution towards this task. We believe that we – together – can enhance access to advanced therapies and innovative medicines for patients living with rare and severe diseases in Sweden.

Anna-Lena Danielsson (S), Regional Council
and Chariman of the Health and Medical Care Committee
Brita Winsa, Health Care Director, Region Västerbotten

Background and Purpose

The health care sector is standing before an era of change as scientific breakthroughs are spurring drug discovery and development in the pharmaceutical industry. Advanced therapy medicinal products (ATMP) and innovative medicines create new possibilities to treat and cure rare diseases and severe medical conditions for patients with unmet medical needs. The first clinical trials have also been initiated with the Nobel Prize awarded genome editing technology, CRISPR/Cas9, discovered at Umeå University in 2012. This is only the beginning of a paradigm shift towards more precise and potentially curative treatments.

Yet, barriers to implementation of new therapies and patient access remains a challenge in Sweden. In an international context, countries are facing similar challenges. Region Västerbotten, responsible for health care in the county of Västerbotten, was confronted with these challenges in 2019 at the time of introduction of newly authorized orphan drugs for the

rare, progressive, and fatal disease hereditary transthyretin amyloidosis (hATTR). Since then, a systemic approach to the challenges with patient access to new therapies was initiated in Västerbotten, with a goal to contribute to a system that is sustainable for the Swedish health care sector over the long term.

In this white paper, the region presents an implementation and payer perspective on the challenges with patient access where Region Västerbotten elaborates on the current system in Sweden, what challenges that have been identified and ideas of how Sweden can become a forerunner for patient access to new, safe, effective, and cost-effective therapies targeting unmet medical needs. The recommendations presented include areas for action in the short and medium term. Region Västerbotten also proposes a more comprehensive concept for patient access to new therapies where Sweden can offer a REAL WORLD LAB for early adoption and implementation of new therapies in clinical practice.



Region Västerbotten and the Case with the Genetic Disease "Skelleftesjukan"

Hereditary transthyretin amyloidosis (hATTR) is a rare, life threatening disease due to mutations in the transthyretin gene. It is characterized by multisystem extracellular deposition of amyloid and rapidly progressing polyneuropathy, including sensory, motor, and autonomic impairments leading to dysfunctions of different organs and tissues. The disease can progress quickly, and some patients become wheelchair bound or bedridden only a few years after the disease onset. The average age of symptom onset is, in Sweden, around 60 years. Untreated, the average survival is between nine and thirteen years. hATTR is endemic in nature and in Sweden it is estimated that 70-80% of the approximately 400 patients are concentrated in the northern regions Norrbotten and Västerbotten. Therefore, the disease is commonly referred to as "Skelleftesjukan".

The Amyloidosis Center at Norrland University Hospital is responsible for hATTR diagnosis and treatment of patients since the 1980s. The center manages preclinical and clinical research about the disease mechanisms, diagnostics as well as treatment. Amyloidosis Center has for example participated in the development of some of the new therapies recently approved for the European market. Due to research, development and innovation the treatment options for patients with hATTR have improved in recent years. Before the market authorized therapies, early liver transplant was the main treatment option. The anti inflammatory drug Diflunisal has also proven to have a stabilizing effect on patients. Diflunisal has up until 2020 been prescribed as a medicinal product with special permission (license) based on the needs of patients. As of 2020, the possibility to obtain this permission from the Swedish Medical Product Agency (Läkemedelsverket) is greatly reduced, to patients in late stage of the disease (wheelchair bound), with reference to the newly market authorized therapies. Available treatment options are now restricted to the orphan drugs Vyndaquel 20mg (tafamidis), Onpattro (patisiran) och Tegsedi (inotersen). To have three orphan medicines approved for the same rare disease is possible based on the clinical indication of the orphan designation as well as the expectation that all therapies contribute a significant benefit to those affected by the condition.

New treatment options are also under development. In November 2020, the first "first in human" phase I clinical trial for a single-course, potentially curative, therapy for hATTR patients with polyneuropathy was initiated using the CRISPR/Cas9 gene editing technology.

The cost of treatment for available options range, based on non-negotiated official list prices, between 1.2 million Swedish Krona and 4.4 million Swedish Krona – per patient per year, for supposedly lifelong treatments. This applies to the new therapies Vyndaquel, Tegsedi and Onpattro. The economic consequences are posing great challenges. Particularly when these costs are compared with the annual cost of treatment of Diflunisal, 15 000 Swedish Krona per patient. Hypothetically, treating 100 hATTR patients in Region Västerbotten, average treatment costs between one and three million Swedish Krona per patient, would thus amount to approximately 13-27 percent of the total pharmaceutical costs of the region (1.1 billion Swedish Krona). This poses great risk of displacement of funds for other patients and other health care interventions, potentially resulting in loss of health in other patient populations. This can be derived from the fact that official list prices for these types of new therapies are far above the threshold of what is commonly defined as the willingness to pay. In addition, the health economic evaluation undertaken prior to the introduction of new therapies, in Sweden based on a value-based approach, express cost effectiveness from a societal perspective. This stands in stark contrast to the actual ability to pay and the affordability of treatments for the regions, being the payers and having to bear the costs.

The challenges illustrated by the case of Skelleftesjukan presents a first symptom of a malfunctioning system for effective patient access to new therapies which is not sustainable over the long term. Now is the time to act. The case from Region Västerbotten can serve as a lesson learned for Sweden in the quest of enhancing the health care for all, and strengthening the position as a leading Life science nation.



Advanced Therapies and Innovative Medicines for Rare and Severe Diseases

Over the past decades, scientific breakthroughs have paved the way for new advanced therapies ("advanced therapy medicinal products", ATMP) as well as other innovative medicines. Advanced therapies are innovative biological medicinal products for human use. Advanced therapies include cell and gene therapy medicinal products as well as tissue engineered products. They can also be combined with medical devices. As advanced therapies are new, complex and technologically specific products, they are partially managed through special regulations. It is still a novel field with limited

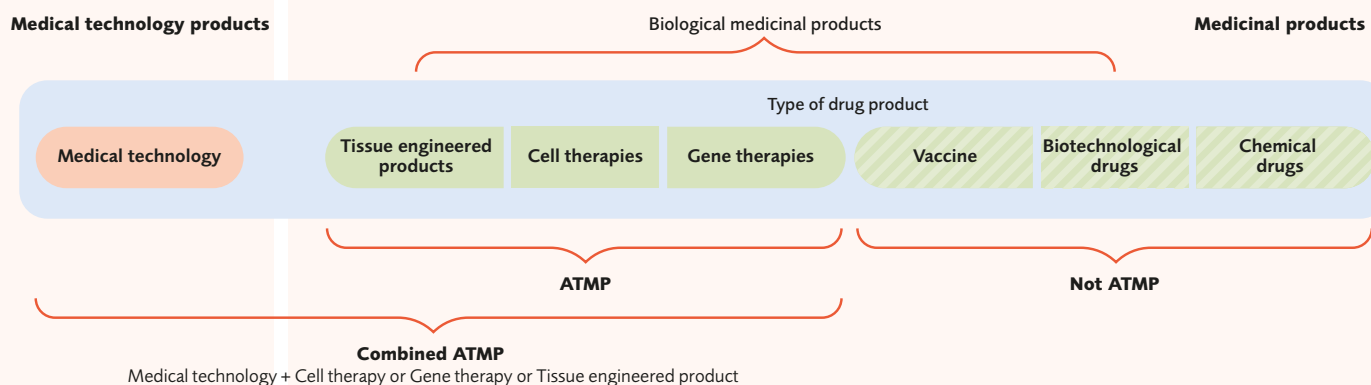
evidence and very little experience from clinical practice as countries are yet to turn scientific breakthrough into actual patient access in a bigger scale. This also applies to a range of innovative medicines, not always per definition advanced therapies, targeting rare and severe diseases (orphan medicines).

The pace of development is high. Approximately 1000 advanced therapies are expected to be under different stages of development. It is projected that between 20-30 market authorization applications will be submit-

What defines an innovative medicine?

A medicine that contains an active substance or combination of substances that has not been authorized before

What defines advanced therapies?



What defines an Orphan drug?

- Medicinal product targeting rare and severe disease where no satisfactory treatment option has been authorized, or medicinal product that adds significant benefit to patients.
- Medicinal product which is unlikely to generate sufficient returns to justify the investment needed for its development.

Adjusted version from Schnitger, A (2014) och O'Meara, S (2012) and Directive 2001/83/EG, Regulation (EG) Nr 1394/2007, Directive 2009/120/EG, Regulation (EG) No 726/2004

ted to the European Medicines Agency (EMA) in the coming five years. In the US, approximately 60 cell and gene therapies are expected to have reached the market by 2030. Clinical trials for new treatment based on the Nobel Prize awarded CRISPR/Cas9 have also been initiated for cancer, neurodegenerative diseases as well as severe blood disorders. CRISPR/Cas9 was only discovered in 2012. In addition, over the past 20 years, regulatory and economic incentives have been introduced to support the development of these therapies. E.g. flexibility in clinical trial design and adjustments in evidence criteria, adaptive pathways and iterative development through approval in stages or conditional approvals based on early data and surrogate endpoints. In 2009 the first market authorization for an advanced therapy was granted for the European market. Since then, a total of 15 advanced therapies have received market authorization in Europe, five of which have been withdrawn. Of the approved advanced therapies, ten have received an orphan designation. The orphan designation grants an additional 10-year market exclusivity. These therapies are commonly associated with high prices.

With the regulatory processes for these new therapies – some undergoing the so called adaptive pathways of market authorization – approval can be granted despite uncertainties of medium to long-term safety, efficacy as well as cost-effectiveness. As health care providers can expect many more advanced therapies and innovative medicines to be approved in a near future, patient access must reach beyond sporadic introduction of just a few therapies. The main challenge posed is how early adoption, implementation and patient access can be secured in a bigger scale, over the coming years. It is also important to account for the parallel development of precision medicine, particularly precision diagnostics, which presents increasing opportunities to diagnose rare diseases as well as targeting diagnosis to smaller subpopulations of otherwise common diseases. The need for more tailored treatments is therefore likely to increase with time.

The Current System for Introduction of New Therapies in Sweden

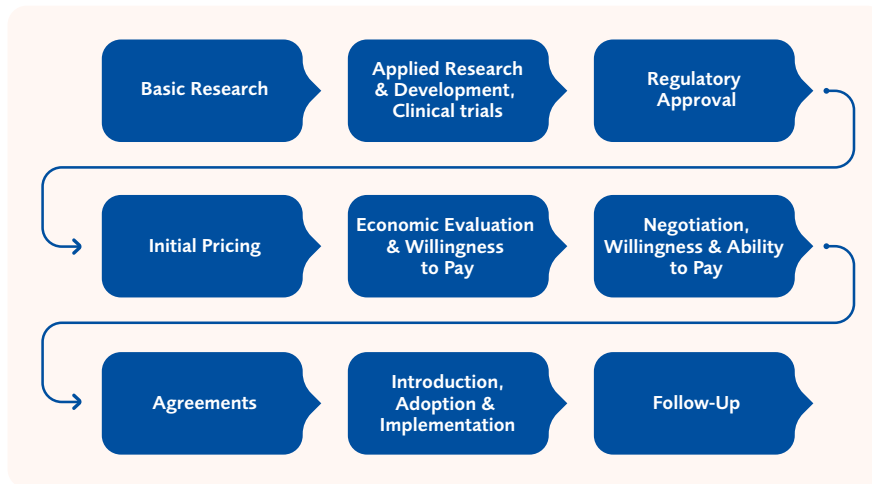


Illustration of process flow for introduction of new therapies in Sweden (Region Västerbotten, 2020)

The current system for introduction of new therapies in Sweden and patients' access to treatments consist of several components – defined by reciprocal interdependence. The image above illustrates a simplified version of the complete process flow – from research to patient access and monitoring and evaluation of treatment.

The process starts with basic research, which is translated into applied research and development. For medicinal products, this includes clinical trials. The result of the clinical trials is the basis for evaluation of the safety and efficacy of the treatments prior to commercialization. A formal market authorization for the European market is approved by EMA. The prerequisite for the approval is that benefits (positive effects) of treatment outweigh the risks (potential harm), i.e. that the benefit/risk balance is assumed to be positive. The market authorization process neither considers the benefits in relation to other therapies available to the patient population, nor the benefits in relation to the costs. This is included in the scope of the health economic evaluation, performed at national level.

A European market authorization of a new therapy triggers the national process for introduction. The pharmaceutical company announce the initial, officially listed, price. The Dental and Pharmaceutical Benefits Agency (TLV) performs the health economic evaluation. The evaluation analyses consequences of using alternative treatments in terms of costs and health gains, applying a societal perspective when determining cost-effectiveness. The health economic evaluation helps inform the subsequent negotiation process between the regions – in Sweden responsible for health care – and the pharmaceutical companies. The aim of the negotiation is to secure equitable patient access of cost-effective treatments, while ensuring a sustainable agreement about price, payment and conditions. The underlying principles of the negotiation are based on applicable willing-

ness to pay – in combination with the ethical platform for priority setting in Swedish health care, and criteria of degrees of rarity and severity, assumed efficacy, and reliability of sourced decision-making material. Provided successful negotiations and a positive recommendation of introduction, the agreement is legally formalized, and the 21 regions are offered to sign the agreement with the companies individually.

Introduction, adoption, and actual patient access to treatment is, in Swedish health care, needs-based and evaluated by the medical profession. Treatment can be undertaken in or outside the region where the patient resides. The regional ability to pay is of essence to the adoption as the financial responsibility of hospital administered medicines falls on the regions. Monitoring and evaluation of treatment is undertaken from a medical perspective as well as a legal perspective. Safety and efficacy are monitored in various ways, in different information systems and registries. Real world data can create real world evidence. The quality, relevance, and reliability of available data, as well as the complexity and administrative burden of the follow-up determine how comprehensive the follow-up will be. The level of interoperability between information systems is also of essence.

The opportunities and challenges presented through new advanced therapies and innovative medicines demonstrate the importance of a well-functioning system. For the whole system to work towards the same goal – access to safe, effective, and cost-effective treatment options for patients in Sweden – a systemic approach is needed throughout the whole process. This will grant that the right treatment is given to the right patient, at the right time, to the right cost, and according to needs. It will also mitigate potential displacement effects and ensure that other patient groups will be granted the same right to treatment.



Conclusions: Opportunities and Challenges within the Current System

This section summarizes the main features of the opportunities and challenges that has been identified within the current system for introduction of new therapies.

About new therapies

There is a need to extend the focus on new therapies, to include both advanced therapies as well as other innovative medicines for patients with unmet medical needs (including orphan drugs for rare and severe diseases).

Applied Research & Development, Clinical trials

There is a need for incentives to strengthen evidence generation and knowledge development based on implementation in clinical practice (real world evidence) – in addition to the clinical trials that precede market authorization of commercial medicinal products.

There is a need to bridge the gap between patients' access to treatment within the scope of clinical trials and patient access through early adoption and implementation in clinical practice.

Regulatory Approval

There is a need for increased participation from health care providers and payers in regulatory affairs, for an integrated implementation and payer perspective in policy making in the field of pharmaceutical medicines – at European as well as national level.

There is a need for greater consensus and a more pragmatic application of key regulatory terminology, such as "unmet medical needs", "special needs" and "non-routine".

There is a need to shift from a regulatory system that primarily promotes commercial and marketed medicinal products, to a regulatory system that promotes availability of all types of safe, effective and cost-effective treatment options for patients.

Financing

There is a need for governmental funding mechanisms to stimulate early adoption, implementation and evidence generation for new therapies targeting patients with unmet medical needs, including a shared financial responsibility between national and region level.

There is a need to clarify the central role and responsibility of the government and government authorities when it comes to the system-wide changes required in the paradigm shift in the field of pharmaceuticals. This role needs to extend beyond financing of medicinal products.



Initial Pricing

There is a need for fair and reasonable pricing from pharmaceutical companies and a flexibility to apply greatly reduced net prices in cases of early adoption and implementation of new therapies with limited evidence. This should be coupled with conditions on complementary evidence generation and experience from clinical practice over time. Models for adaptive pricing and price adjustment linked to evidence should be considered.

Economic Evaluation & Willingness to Pay

There is a need for health economic evaluations that better manage the uncertainties of safety, efficacy, and cost-effectiveness of new therapies. This should be coupled with conditions on complementary evidence generation based on implementation in clinical practice, and models for adaptive and iterative processes of evaluation of benefits and costs.

There is a need for dialogue, common understanding and greater consensus about thresholds values of willingness to pay for different types of patient needs as well as different levels of uncertainty. This should consider realistic resource constraints and be politically mandated.

Negotiation, Willingness & Ability to Pay

There is a need for a shift from assumed willingness to pay to actual ability to pay based on the payer perspective. Aspects of affordability need to consider where the financial responsibility of various therapies lies, as well as long-term sustainability for the health care system.

There is a need for payment models that better absorb the uncertainties with regard to total cost, budgetary impact and cost-effectiveness. This should be coupled with conditions on complementary evidence generation from implementation in clinical practice. Models for adaptive reimbursement should be considered, premiering safe, effective, and cost-effective treatments in the long-term.

Agreements

There is a need for legal agreements that can manage uncertainties in the short and long term, and greater flexibility to apply conditions for evidence generation in agreements for introduction of new therapies with limited evidence.

There is a need to reduce administrative burden and introduce higher degree of automation in management and follow-up on agreements for the introduction of new therapies.

Introduction, Adoption & Implementation

There is a need for commitments from the regions towards early adoption and implementation for patient groups with real unmet medical needs, prioritized by decision makers and practitioners within Swedish health care.

There is a need for commitment from health care providers towards evidence generation, knowledge development and follow-up on safety, efficacy, and de facto cost-effectiveness when it comes to early adoption and implementation of new therapies.

Follow-Up

There is a need for improved quality, relevance and reliability of available health, care, and cost data. This is essential for research, development, and innovation as well as the continued sustainable development of health care services.

There is a need to clarify the legal aspects with regard to data collection, storage, management, use, as well as sharing of data between government authorities, regions, municipalities, academia, pharmaceutical companies, and patients.

Prioritization

There is a need for continued vertical priority setting as well as increased horizontal prioritization at regional level. Priorities need to better reflect real patient needs, goals and benefits that can contribute to long-term sustainability in the health care sector.

There is a need for a joint national priority setting – horizontally across the whole health care system – based on patient needs, goals, and benefits. In the light of limited resources and budget constraints it should be clear what the priorities are in publicly funded health care in Sweden.

The System

There is a need for strengthened collaboration and partnerships to solve the complex challenges embedded within the system. This applies to all key actors and stakeholders. System-wide change also requires national leadership.

There is a need for a shift from sub-optimization within the system, to a greater focus on the system as a whole and its overall goals.





Region Västerbotten's Recommendations for Enhanced Patient Access to Advanced Therapies and Innovative Medicines

Region Västerbotten's proposal includes five areas of recommendation, formulated under one mission statement for Sweden:

Enhanced access to advanced therapies and innovative treatments for patients with rare and severe diseases, in a way that contributes to evidence generation and ensures long-term sustainability for the health care system.

The mission statement calls on a shift from the current sub-optimization to a more holistic approach that encompasses the system as a whole.

In addition to the five areas of recommendation, Västerbotten also proposes an initial draft con-

cept for Sweden as a REAL WORLD LAB for early adoption and implementation of new therapies in clinical practice. This can position Sweden as an early adopter of new therapies and at the same time contribute to evidence generation in an emerging field of life science.

The key messages of the five areas of recommendation are presented below.





Recommendation Area 1:

A regulatory system that secures availability of both well established and new safe, effective, and cost-effective treatment options to patients.

Recommendation area 1 addresses the regulatory system and calls for a shift in focus from primarily commercial and marketed medicinal products, to a regulatory system that promotes a greater diversity of treatment options for health care to implement – including all types of safe, effective, and cost-effective treatments for patients. This also includes older drugs that do not necessarily hold market authorization for Europe, as well as medicinal products that have not been developed for commercial purposes, but where treatment of patients have proven safe and effective in a real-world setting, through implementation in clinical practice, over time. The right treatment needs to be available to the right patient, at the right time, to the right cost, and according to needs. The regulatory system is key for this to be possible as it regulates what, when and how therapies are authorized for use.

Specific proposals presented in the White Paper are:

Short-term proposals:

- To work for greater consensus and a more **pragmatic interpretation of key regulatory concepts** - such as "unmet medical needs", "special reasons", "non-routine" - that can help healthcare with long-term sustainable drug use.
- To **extend practice** of the Medical Products Agency's in terms of **approval for medicinal products with special permission (license)**, to also include considerations of economic character as a basis for special needs when e.g. the risk of displacement of funds may otherwise jeopardize health of other patients. This would also counteract locking effects in full favor of marketed commercial products when other relevant treatment alternatives are available.
- To **facilitate the availability of advanced therapies within the hospital exemption**, and thereby also expand the Medical Products Agency's responsibility and role to promote innovation capacity stemming from the medical profession and from within the health care system – particularly when it comes to methodologies developed out of clinical practice in a real-world setting.
- To review the flexibility of the **regulatory processes for off-label use** in a way that supports safe, efficient, and cost-effective drug use outside approved indications, based on implementation in clinical practice and proven experience from a real-world setting.

Proposals in the short and / or medium term:

- To strengthen the implementation and payer perspective as well as increased participation from the health care system in the regulatory system at both European and national level. This is a way of safe-guarding that incentives and regulatory processes contribute to the main objective of actual patient access to new therapies.

Recommendation Area 2:

An adaptive pricing and reimbursement system for new therapies for rare and severe diseases that reduces barriers to early adoption and implementation in clinical practice and thereby facilitating patient access.

Recommendation area 2 includes a shift in focus from assumed willingness to pay to actual ability to pay. It addresses price, valuation, payment, and contractual agreement models that adjust for uncertainties associated with limited evidence and lack of experience from drug use in real-world settings. It includes a more iterative perspective on price and reimbursement and should be applied to facilitate early adoption and implementation and stimulate evidence generation through financial incentives for safe, effective, and cost-effective treatments over time. New therapies should be introduced in a way that ensures long-term sustainability in terms of total costs, budgetary impact, and cost-effective use of public resources. This also ensures sustainability for patients as well as for the pharmaceutical industry. The pricing and reimbursement system is key in making this possible.

Specific proposals presented in the White Paper are:

Short-term proposals:

- To introduce an **adaptive pricing and reimbursement** system which can absorb the uncertainties of early market approvals of novel treatment options and new therapies with little evidence, to promote evidence generation and knowledge development from clinical practice.
 - This entails an acceptance from pharmaceutical companies for more adaptive pricing where early market approvals and limited evidence also lead to acceptance of **lower initial net pricing**.
 - This also entails health economic evaluations and **cost-effectiveness assessments that absorb uncertainties** and adjust for limited data of short-term clinical trials in relation to expected outcomes over time for the real world patient population.
 - This requires more adaptive reimbursement and payment models that can **manage uncertainties through price negotiations payments schedules and risk sharing** with regards to delivered outcomes. An iterative process for reimbursement can also open up for revaluation based on complementary and more comprehensive longer-term evidence.
 - Joint **commitments to evidence generation, knowledge development** and follow-up of patients treated with new therapies should be integrated into an adaptive price and reimbursement system, to minimize uncertainties over time.





Short and/or medium-term proposals:

- To introduce the proposals for adaptive pricing and reimbursement as a whole – in **an iterative process for introduction, early adoption, and implementation of new therapies** – following a similar logic as the regulatory system's "adaptive pathways" and aiming to strengthen evidence levels and maintaining a positive balance between benefits and costs over time.

Recommendation Area 3:

A governmental funding mechanism for new medicinal therapies targeting unmet medical needs of patients with rare and severe diseases, stimulating early adoption, implementation in clinical practice and evidence generation from real-world settings.

Recommendation area 3 entails a shift of focus from research, development and innovation that generates products and services to the utilization of research, development, and innovation in clinical practice – in a way that benefits patients over time. It also stresses the government's role and responsibility as a facilitator of change and value creation, and a facilitator for patient access in Sweden. The recommendation includes proposals for increased cost-sharing responsibilities for medicinal products, as well as proposals concerning the government's responsibility to national leadership when it comes to system-wide changes.

Specific proposals presented in the White Paper are:

Short term proposals:

- To address identified gaps in the system for funding new therapies and a **shared cost responsibility** between government and regions. This, in order to avoid potentially negative consequences of the affordability problem and the challenges of implementation and patient access of new therapies expected to be marketed in the coming years. This includes the challenges of:
 - **Skew distribution of the cost burden for endemic diseases** when drug use is concentrated to one or a few individual regions.
 - **Loss of cost control and ownership of priority-setting** for the regions in terms of the financial responsibility of prescription (special) medicines for unmet medical needs that are not approved for government subsidy, but which are introduced according to the free pricing policies via pharmacies and prescribed to patients outside the paying region as part of out-of-county care.
 - The **mismatch between the society's willingness to pay** and the regional ability to pay for advanced therapies and innovative medicines that are administered in hospitals and where the regions today are sole payers.

Short and/or medium-term proposals:

- To **establish a governmental funding mechanism for early adoption, implementation and evidence generation**, for access to advanced therapies and innovative medicines for patients with rare and severe diseases. This type of mechanisms should include shared cost responsibility between the government and regions as well as companies, through lower initial net prices.
- To strengthen the **government's role and responsibility in the system-wide changes** that are required within the current system of introduction of new therapies to be well-functioning. This address both the government and relevant government agencies.

Recommendation Area 4:

A national commitment to strengthen the possibilities of data collection, storage, management and use as well as sharing of reliable and relevant health, care, and cost data from clinical use of new medicinal therapies.

Recommendation area 4 entails a shift in focus from data collection for the sake of data collection to data that can be used for research, development, innovation as well as continued development of health care services. It addresses the need for improved quality, relevance, and reliability of available data as well as a common understanding on when, where, and how different types of data can be used and by whom - in a legally sustainable way. The latter requires clarifications of legal aspects, at the national level.

Specific proposals presented in the White Paper are:

Short term proposals:

- To develop **national guidelines on the legal aspects of data use** in order to ensure that applicable follow-up of medicinal therapies is possible. As a basis for this guidance, a common understanding need to be outlined of what kind of follow-up is necessary.

Short and/or medium-term proposals:

- To review the **quality, relevance, and reliability of available data** that can contribute to the intended follow-up of medicinal therapies as well as evidence generation from real-world settings and thus knowledge development over time.
- To strengthen the legal prerequisites for governmental authorities, regions, municipalities, academia, companies, and patients to be able to collect, store, manage, use, and share data across organizational boundaries.



Recommendation Area 5:

A joint commitment between national and regional stakeholders to horizontal priorities in Swedish health care, including the role of early adoption and implementation of new medicinal therapies targeting unmet medical needs.

Recommendation area 5 includes a shift in focus from primarily vertical priorities here and now, to strengthen the level of horizontal priorities based on real patient needs, goals, and benefits that can contribute to long-term sustainability in the health care sector, today and in the future. It highlights the importance of common understanding and transparency about what types of needs that should be given priority in publicly funded health care, particularly when resources are limited, and the displacement of funds may risk loss of health in other patient groups.

Short-term proposals:

- To **systematize the regional priority-setting based on needs, goals and benefits**. This needs to address medicinal therapies and treatments, but also reflect how resources are used in other areas within the regions, e.g. health care interventions and initiatives, properties and facilities, medical equipment, and digitalization.

Short and/or medium-term proposals:

- To initiate **joint national priority-setting** that includes the role of government and governmental authorities, regions, and municipalities, as well as patients. This is based on **horizontal priorities** and includes consensus on how public resources should be used to meet the needs of the population, as well as clear roles and responsibilities of key actors and stakeholders, across organization boundaries.



The proposed recommendations are essential from a patient perspective as they are prerequisites for enhanced patient access to new therapies, and a life in good health, when other satisfactory treatment options are missing.

Proposed concept for REAL WORLD LAB

For Sweden to succeed with the mission of enhanced patient access, Västerbotten also proposes a comprehensive concept for

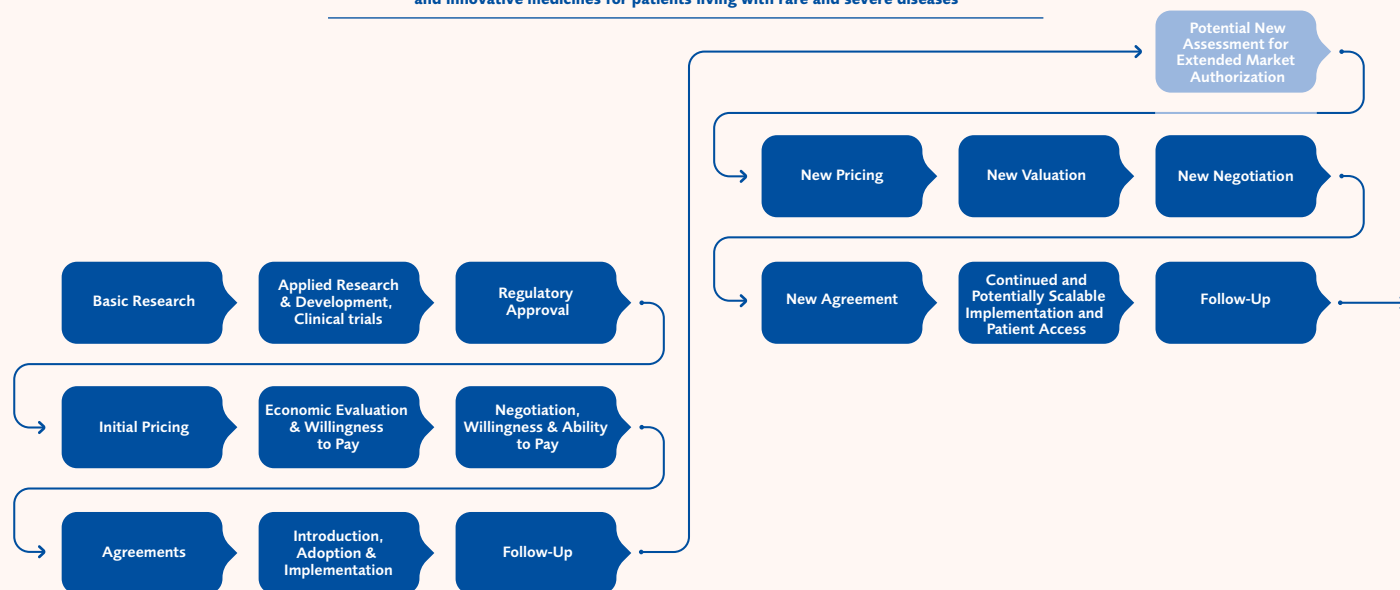
Sweden as a REAL WORLD LAB for early adoption and implementation of new therapies in clinical practice

The concept of REAL WORLD LAB is drafted based on the assumption that the government and government authorities, the regions, pharmaceutical companies, academia, and patients can eliminate obstacles and reduce barriers to patient access of new therapies. This while also jointly contributing to evidence generation and knowledge development in a novel field, enabling scalable implementation of new safe, effective, and cost-effective treatment options over time. As an early adopter of new therapies for patients living with rare and serious diseases, Sweden can become a forerunner and actively contribute to the paradigm shift towards more precise and potentially curative treatment options. Region Västerbotten believes that Sweden is well positioned to harness these opportunities, if embarking on this national initiative with joint forces and full commitment. Sweden has proven strengths when it comes to innovation, collaboration, and partnerships, which are important for Sweden's ambitions as a leading life science nation. This would also attract investment in research and development, stimulate growth and development, and contribute to a long-term sustainable welfare.

In the REAL WORLD LAB, new treatment options are used and evaluated for prioritization needs and patient populations with unmet medical needs – directly in a real-world setting. The introduction of these therapies is undertaken according to the established processes for introduction, with some added flexibility, and based on an iterative, step-by-step, implementation process. A more adaptive procedure for pricing, valuation, and reimbursement also includes conditions on evidence generation, to reduce uncertainties and at the same time ensure that the balance between benefits and costs remains positive over time. This is similar to the underlying principles of the regulatory processes for "adaptive pathways", the scientific concept for medicines development and data generation that allows for early and progressive patient access in Europe, from a regulatory perspective. Equally, adaptive pricing, valuation, and reimbursement can allow for early adoption and progressive an implementation and payer perspective. Considerations to willingness to pay as well as actual ability to pay are necessary in light of uncertainties of new therapies.

A system-wide approach is needed in implementing the concept as well as adoption of new working methods, processes and procedures within the system – from all involved actors and key stakeholders who directly or indirectly affects the introduction of new therapies. This would include risk sharing and joint responsibilities.

**Draft iterative process for introduction of new therapies
Sweden as a "REAL WORLD LAB" early adoption, implementation and access to advanced therapies
and innovative medicines for patients living with rare and severe diseases**



The concept for REAL WORLD LAB can integrate the proposed iterative process for introduction as well as adaptive pricing, valuation and reimbursement of new therapies.

The iterative approach to introduction is based on five underlying principles:

- Limited evidence and early market approvals result in higher uncertainty and thus lower valuation. **Co-sharing responsibilities** for financing by the pharmaceutical companies **through reduced initial net prices** and acceptance of reduced reimbursement for early adoption and implementation.
- Utilization of research, development, and innovation is subject to practical application. **Governmental co-sharing of financing responsibilities** to incentivize, stimulate, and facilitate early adoption, implementation in clinical practice, and evidence generation from a real-world setting. The governmental funding for introduction of new therapies is conditioned to the acceptance of co-sharing arrangements by the pharmaceutical companies.
- New treatment options are used and evaluated in health care as a kind of "proof of concept" in a real-world setting. **Regional co-sharing of financing responsibilities** and a commitment to early adoption of new therapies according to prioritized patient needs, goals, and benefits. The regional funding and commitment are conditioned to the acceptance of co-sharing arrangements by the pharmaceutical companies as well as governmental funding.
- **Joint commitment** to contribute to **evidence generation and knowledge development** from implementation of new therapies in clinical practice. Comprehensive follow-up is undertaken to evaluation safety, efficacy as well as cost-effectiveness. This can help in future priority-setting for introduction of new therapies.

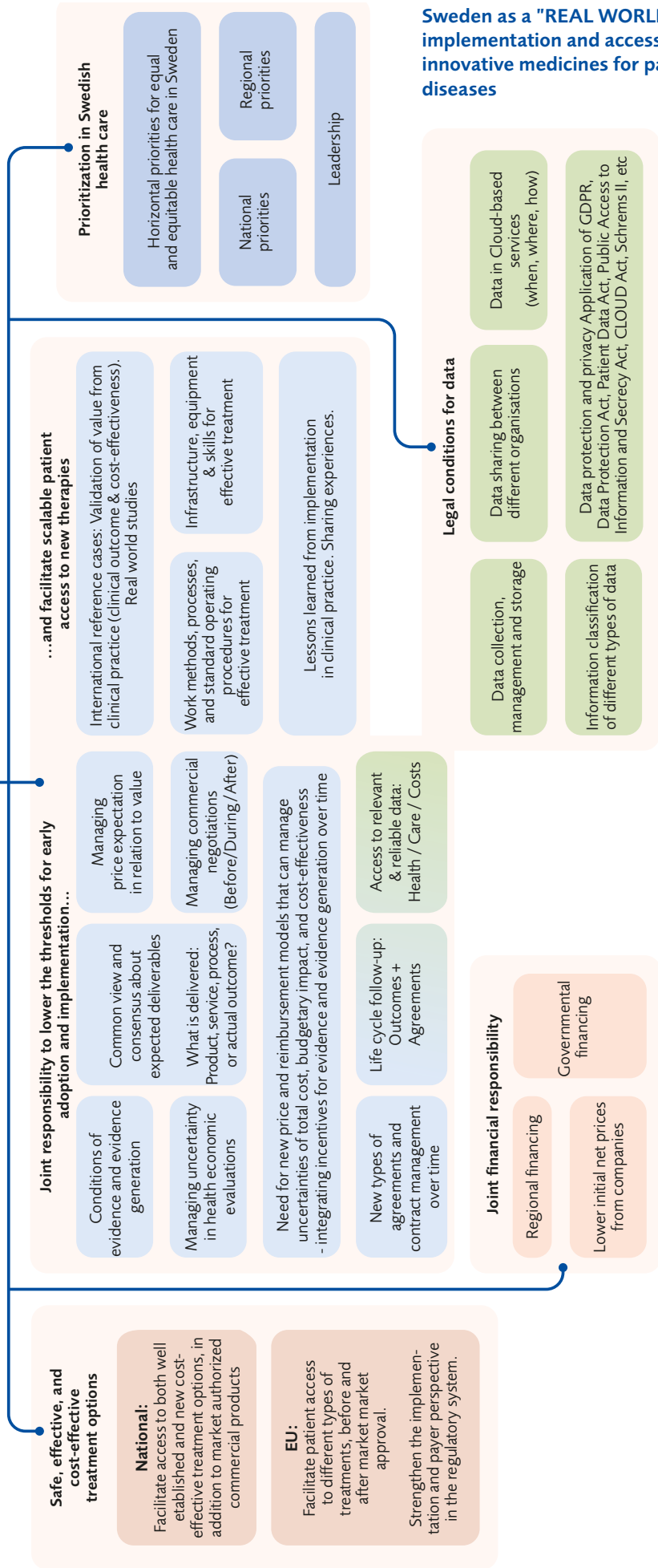
- **The treatment options of the future** are established based on the actual value they create and according to long-term sustainability for the health care system. This needs to be based on evidence, knowledge and experience over time – in terms of safety, efficacy and cost-effective treatment options.

The concept for REAL WORLD LAB aligns with the mission statement for **Enhanced access to advanced therapies and innovative treatments for patients with rare and severe diseases, in a way that contributes to evidence generation and ensures long-term sustainability for the health care system**. A joint mission with common goals in terms of new therapies benefits the government and governmental authorities, the regions, and pharmaceutical companies. The greatest benefit will without a doubt be granted patients with unmet medical needs. A joint mission is of essence for Sweden to strengthen its position as a life science nation of future relevance.

An illustration of REAL WORLD LAB and what components it entails is presented on the next page.



Enhanced access to advanced therapies and innovative treatments for patients with rare and severe diseases, in a way that contributes to evidence generation and ensures long-term sustainability for the health care system



Sweden as a "REAL WORLD LAB" for early adoption, implementation and access to advanced therapies and innovative medicines for patients living with rare and severe diseases

Concluding Remarks

This white paper has presented the challenges and opportunities for patient access of new advanced therapies and innovative medicines within the Swedish health care system – presenting an implementation and payer perspective, yet formulating a system-wide approach for the future. As many more new treatment options for patients with unmet medical needs are to be expected, it is necessary to facilitate actual adoption and implementation in clinical practice, throughout the whole system. Solving complex societal challenges is possible but require full commitment and contributions from all actors and key stakeholders. Harnessing the opportunities presented in the pharmaceutical field – ensuring patient access to safe, effective, and cost-effective treatment options – is a joint responsibility.

The perspectives presented in this white paper further strengthened with complementary perspectives and trade-offs may be necessary. Matters relating to medicine, economics, politics, ethics as well as philosophical reasoning need to coexist. The recommendations proposed herein are therefore to be considered as a first step on the road ahead. The journey will require national leadership and the courage to think and act differently throughout the system. Sweden now has the chance to channel the power of innovation and partnerships in a way that can strengthen Sweden's position as a life science nation and a country where possibilities turn into realities.

Together.