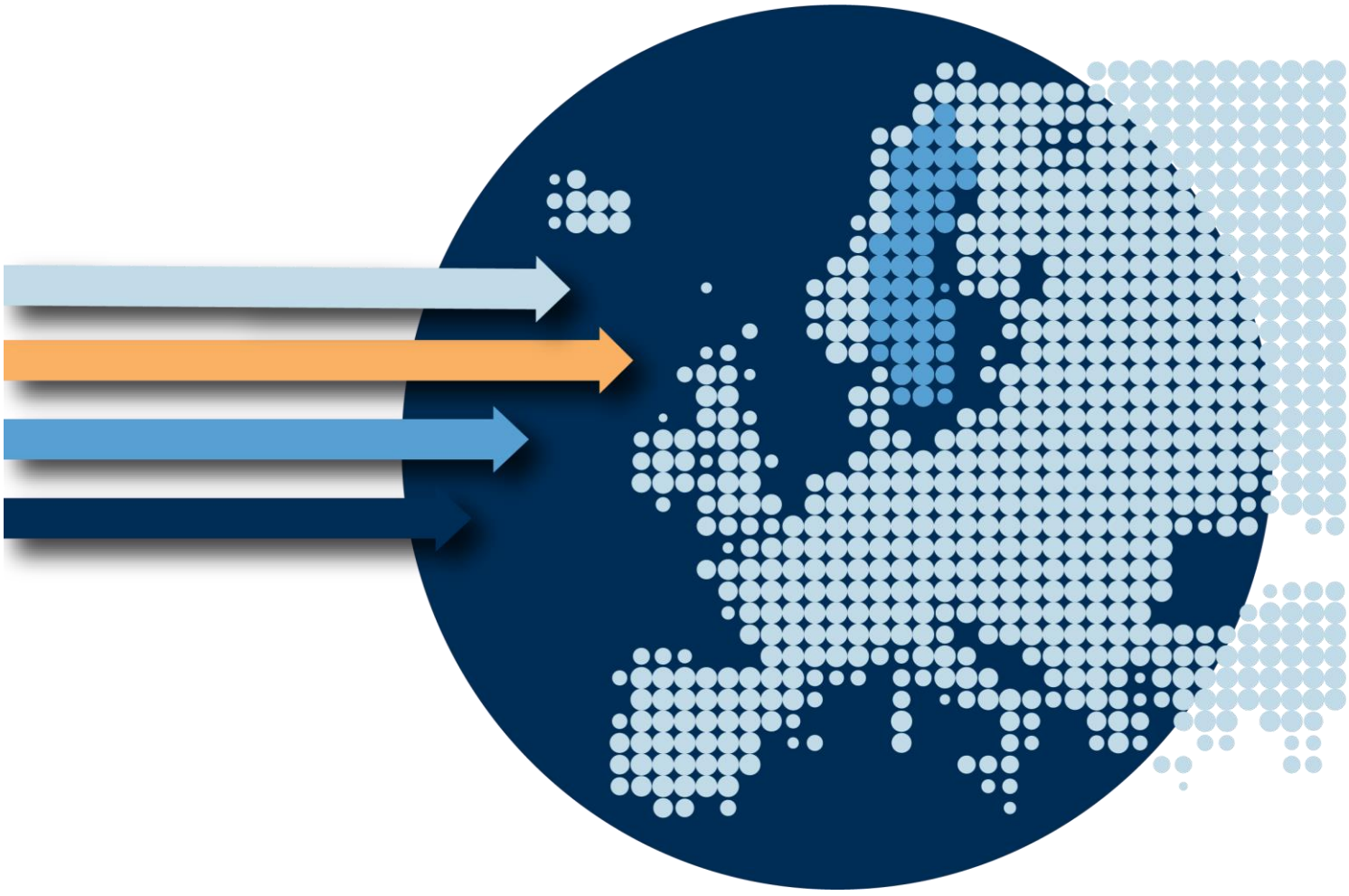
Opportunities and challenges of an innovative payment model for Advanced Therapy Medicinal Products in Sweden
– A hypothetical example in the treatment of β-thalassemia



Ulf Persson
Jenny Norlin

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OPPORTUNITIES AND CHALLENGES OF AN INNOVATIVE PAYMENT MODEL FOR ADVANCED THERAPY MEDICINAL PRODUCTS IN SWEDEN
– A HYPOTHETICAL EXAMPLE IN THE TREATMENT OF β-THALASSEMIA

Ulf Persson
Jenny Norlin

IHE - The Swedish Institute for Health Economics

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Preface

In this report the Swedish Institute for Health Economics (IHE) provides reflections about challenges and opportunities of a proposed innovative payment model for Advanced Therapy Medicinal Products in Sweden. A hypothetical one-time treatment of β-thalassemia, that can provide a substantial life-time benefit, is used as an example. The hypothetical example fulfil the two typical challenges for ATMPs; the ”affordability barrier” and “uncertainty of the full value”.

This report was prepared with the financial support of bluebird bio.

Lund, May 2020

Peter Lindgren
Managing Director, IHE

Sammanfattning

Avancerade läkemedelsterapier (ATMP) kommer att innebära ett paradigmskifte inom hälso- och sjukvården, då dessa läkemedel har stor potential för att förebygga och behandla ofta livshotande sjukdomar. Det finns två egenskaper hos ATMP som innebär potentiella utmaningar för det nuvarande systemet för finansiering, prissättning och återbetalning av läkemedel. För det första, eftersom ATMP ofta är engångsbehandlingar med livslånga fördelar, så innebär detta att värden som realiseras över en lång tid ska betalas på relativ kort sikt. Detta medför att inte ens väldigt kostnadseffektiva läkemedel kan finansieras med en traditionell betalningsmodell, på grund av en så kallad budgetbarriär. För det andra godkänns ofta ATMP med accelererade regulatoriska bedömningar, vilket är möjligt för sällsynta sjukdomar för vilka ingen behandling finns tillgänglig. Följaktligen finns det vid tidpunkten för godkännandet fortfarande osäkerheter om värdet av behandlingen, då det fulla värdet i klinisk praxis endast kan mätas flera år efter godkännandet.

Transfusionsberoende β-talassemi, är en ärftlig blodsjukdom. Nuvarande behandling innebär livslånga blodtransfusioner och järnkeleringsbehandling, som kan uppgå till 300 000 kronor årligen och innebära betydande nedsättning i den hälsorelaterade livskvaliteten.

I den här rapporten diskuterar vi ett hypotetiskt exempel på en engångsbehandling som förväntas ge betydande livslånga vinster, och som uppfyller de två typiska egenskaperna för ATMP; ”budgetbarriären” och osäkerhet kring det fulla värdet av behandlingen. Syftet är att diskutera möjligheter och utmaningar med en innovativ betalningsmodell för en ATMP i Sverige genom att använda behandling av ß-talassemi som ett exempel.

Den föreslagna utfallsbaserade betalningsmodellen inkluderar en initial betalning på en femtedel av priset och ytterligare fyra årliga delbetalningar, vilka betalas beroende på patienternas behandlingssvar mätt genom transfusionsoberoende.

Den föreslagna betalningsmodellen för har flera attraktiva funktioner som bidrar till att lösa de utmaningar som ATMP ofta står inför. Modellen gör det möjligt för betalaren och tillverkaren att dela risken och osäkerheten kring behandlingssvaret, både i andelen som svarar och hur länge de svarar. Det föreslagna utfallsmåttet, transfusionsoberoende, speglar sannolikt väl värdet på behandlingen, är enkelt att mäta och är förknippat med en låg administrativ kostnad. Den föreslagna betalningsmodellen minskar dessutom budgetbarriären genom att fördela betalningarna över fem år.

ATMP utvecklas oftast för små patientpopulationer, men den potentiella budgetpåverkan av de aggregerade patientpopulationerna är omfattande. I Sverige skulle mer flexibla budgetar och ytterligare finansiering från staten för nya innovativa behandlingar kunna bidra till att minska budgetbarriären som regionerna står inför vid införandet av ATMP.

Executive summary

Advanced Therapy Medicinal Products (ATMPs) represent a paradigm shift in health care as they have great potential for preventing and treating often life-threatening diseases. Two characteristics of ATMPs impose potential challenges to the current system of financing, pricing and reimbursement of drugs. Firstly, ATMPs are often one-time treatments where the value of life-long benefits is realized in relatively short time. The health care system may not be able to finance highly cost-effective treatments as the traditional up-front payment model can result in a so called "affordability barrier". Secondly, ATMPs are often developed with accelerated regulatory assessments in rare diseases for which no treatment is available. Consequently, at the time of approval there is still uncertainties of the full value of the treatment, which can only be measured after several years post-approval.

Transfusion-dependent β-thalassemia is an inherited blood disorder. Current standard of care includes life-long blood transfusions and iron chelation treatment, which can amount to SEK 300 000 annually and substantial Health Related Quality of Life impairment.

In this report we discuss a hypothetical example of a one-time treatment which is expected to provide a substantial life-time benefit and can be considered to fulfil the two typical challenges for ATMPs; the "affordability barrier" and "uncertainty of the full value". The objective of this report is to discuss the opportunities and challenges of a proposed innovative payment model for an ATMP in Sweden, by using treatment of β-thalassemia as an example.

The proposed performance-based payment model includes an initial payment of one fifth of the price upfront at drug product delivery, and another four installments to be paid annually, depending on the treatment success of transfusion independence.

The proposed payment model has several attractive features that contributes to solve the challenges often facing ATMPs. It allows for the payer and manufacturer to share the risk and the uncertainty of the response rate and the sustainability of the response. The suggested outcome measure, transfusion independence, is likely to well reflect the value of the treatment and meanwhile it is straightforward to measure and is associated with a low administrative cost. Furthermore, the proposed payment model reduces the affordability barrier by distributing payments over five years.

ATMPs generally target small patient populations, but the potential budget impact of the aggregated patient populations is extensive. In the Swedish system, more flexible budgets and additional funding by the state for new innovative treatments could help reduce the affordability barrier faced by the regions in the introduction of ATMPs.

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1. Introduction

Advanced Therapy Medicinal Products (ATMPs) is a new class of drugs in the EU that includes medical products for gene therapy, cell therapy or tissue engineering. They can be expected to lead to elimination of symptoms or disease activity in severely ill patients and thus create long-lasting positive effects on both health and healthcare costs.

The European ATMP field is still in its early stages. The first ATMP received market authorization in November 2012. By June 2019, 14 ATMPs have been granted marketing authorization in Europe. Of those, seven were gene therapies, three cell therapies and four tissue engineered products. Market authorizations for four approved ATMPs (Glybera, Provenge, Chondrocelect and MACI) were withdrawn by their sponsors for commercial reasons. However, in January 2019, there were more than 1,000 clinical trials of ATMPs ongoing worldwide and over two-thirds were in Phase II and III. (1)

Traditionally, the payment of drugs has occurred at the same time as the actual treatment and the treatment is typically taken for a period of time or, for chronic diseases, during an entire lifetime. Two characteristics of ATMPs have a potentially significant impact on the financing, pricing and reimbursement of ATMPs.

Firstly, ATMPs are often one-time treatments, that are long-lasting or even with curative potential, which implies that considerable values are realized over a long period of time. The traditional payment model can thus lead to affordability issues as large values, over a long period of time, is to be paid upfront. Even though the drug is cost-effective, it may not be possible to be pay for with the current payment model.

Secondly, as ATMPs are often developed in rare, severe indications where there is no standard treatment, or no treatment at all, the clinical trials tend to be small and sometimes without a control group. ATMPs are often developed with accelerated regulatory assessments in order to accelerate patients' access to innovative drugs that target a disease for which no treatment is available, or that provide patients with a major therapeutic advantage over existing treatments. As the approval often takes place at an early stage, and the full effectiveness can only be measured after several years post-approval, there may be considerable uncertainties regarding the full value of the ATMP.

In this report we discuss a hypothetical example of an ATMP in the treatment of transfusion-dependent β-thalassemia, which is an inherited blood disorder. The treatment is characterized by a one-time treatment expected to provide a sustainable benefit over a life-time and is thus expected to be priced according to a perceived value including a potential to cure. Even if the drug can be considered to be cost-effective, it can still face the so-called “affordability barrier”. Our hypothetical

example fulfil the two typical characteristics of ATMPs ”affordability barrier” and “uncertainty of the full value”.

The objective of this report is to discuss the opportunities and challenges of a proposed innovative payment model for an ATMP in Sweden, by using a hypothetical example in the treatment of β-thalassemia.

2. Payment models

A risk sharing agreement (RSA) payment model or managed entry agreement (MEA) is an agreement between the payer and the company to make the treatment available under certain conditions. These agreements typically use innovative payment models as tools to overcome hurdles and barriers that appear for pricing, reimbursement decisions and for uptake of new innovative medicines. The challenges that appears for ATMPs are generally related to the fact that ATMPs are often administrated just once, or perhaps a handful of times within a short time period. This short treatment period in combination with a curative potential and long-lasting positive impact on health can provide justification for a relatively high value for the treatment. Under a value-based pricing (VBP) concept, used by many European countries, this can result in a high upfront price for the treatment, which could be a challenge for a fixed budget system. The long-lasting health benefits are creating several types of uncertainties, particularly around response and of the sustainability of effectiveness but also around alternative treatments in the future. There are a variety of different payment models and the design differs depending on the type of product, type of uncertainties as well as the type of health care system in which they are being implemented.

A variety of definitions and terminology of payment models are used in the literature. Payment models that are generally discussed for ATMPs are population (indication) – specific arrangements, agreements based on financial risk, and outcomes-based agreements.

2.1 Population (indication) specific agreements

Population (indication) – specific arrangements restrict the reimbursement to a subpopulation of patients, e.g. per indication, treatment line, incidence only or by a defined severity level. The purpose could be to secure cost-effective usage of treatment by restricting the access to a subpopulation that receives the highest value of the drug. It is also a way to enable cost containment.

2.2 Agreements based on financial risk

Agreements based on financial risk are intended to make the cost to the payer predictable and manageable within the budgetary framework. For example, the price can be reduced through confidential discounts or volume-based spending caps i.e. that the total cost is reduced by reducing the price after a certain volume has been exceeded. Agreements based on financial risk can include patient spending caps, subscription “per member, per month” arrangements, stopping rules etc. These payment models only see to cost containment and are not linked to health outcomes.

2.3 Outcomes-based agreements

According to the taxonomy developed by Carlson and colleagues (2), performance-based health outcomes reimbursement schemes can be divided into two categories: conditional coverage/reimbursement and performance-linked reimbursement schemes.

Conditional coverage can be defined as schemes where coverage is granted conditional on the generation of real-world evidence from clinical practice is developed. Drug prices are agreed, and payments are made temporarily for a certain period of time (e.g. 3-5 years) whilst the manufacturer gathers real world evidence of the value of the drug. When new evidence is in place, prices and reimbursement are re-negotiated. Conditional coverage can be further broken down into two types: 1) Coverage with Evidence Development in which the coverage decision is conditioned upon the collection of evidence to support continued, expanded, or withdrawal of coverage at the population level, and 2) Conditional Treatment Continuation, in which the coverage for an individual patient is conditioned upon meeting short-term treatment goals. (2)

Performance-linked payment or reimbursement is defined as schemes where the reimbursement for covered products is linked to a measure of clinical outcomes. Performance-linked reimbursement can also be broken into two parts: 1) in a performance-linked reimbursement with "outcomes guarantees", the manufacturer provides rebates, refunds, or price adjustments if their product fails to meet the agreed upon outcome targets, which is typically the case for pharmaceuticals 2) in a performance-linked reimbursement scheme for pattern or process of care, the reimbursement is tied to the impact on clinical decision making, for example in different types of tests (2). Performance-linked reimbursement schemes are likely to arise when a manufacturer has sufficient confidence in their product that they are willing to accept a lower reimbursement level if it underperforms.

The performance-linked reimbursement schemes can be paid either as "payment-by-results", where drug costs are paid upfront and the manufacturer agrees to refunds depending on treatment outcomes, or as "payment-at-result", where the payment is made in the form of instalments staggered over a fixed period of time, e.g. annuity-based, and where no payment will be made upon treatment failure.

In 2017, Carlson and colleagues performed a review of 437 performance-based health outcomes reimbursement schemes from 1993 to 2016 (3). Coverage with evidence development made up of 34 percent of the cases, performance-linked reimbursement of 24 percent, conditional treatment continuation of 18 percent, financial or utilization of 16 percent, and hybrid schemes with multiple components of 8 percent. The pace of adoption varied across countries, but in general there was a renewed upward trend after a break in 2012/2013.

2.4 Why do ATMPs require innovative payment models?

A payment model should balance several different objectives, including incentives for development of new and innovative therapies, timely access for patients to new and cost-effective therapies and a financially sustainable health care system. There are two main arguments why the traditional payment model is challenging for ATMPs. One is the uncertainty of the full value of the ATMP and the second is the so-called affordability barrier and upfront payment of a one-time treatment.

2.4.1 Uncertainty of the full value

Since ATMPs have the potential to cure or provide substantial health benefits to patients with seriously debilitating or life-threatening diseases, it is considered unethical to withhold patients from a potential cure, while running extensive development programs. ATMPs are therefore often approved by regulatory authorities at an early development stage by accelerated assessment and conditional marketing authorisation. Randomised controlled trials, which is standard procedure in drug development, are often not an option in ATMP development as it may be difficult to recruit enough patients to randomize and, furthermore, it may be considered unethical to use a control group. The early approval is thus based in less complete clinical data than normally required. While less complete, the available data must still demonstrate that the benefits outweigh the risks. Comprehensive real-world data must be provided within an agreed timeframe after the market authorisation (4).

The effect of ATMPs is expected to last for a long time, possibly lifetime, and an evaluation of the full value would therefore require a very long follow-up time and an extensive set of outcome variables. The traditional drug development process and payment model could consequently result in delayed access for patients and a potential loss of health. The need for fast access of ATMPs leads to an uncertainty that creates challenges with the traditional payment model, as the payer does not know the full value of what they are paying for. Consequently, there is a need for innovative payment models for ATMPs as the traditional payment model does not meet the challenges of the main characteristics of ATMPs.

2.4.2 The affordability barrier

ATMPs address the underlying genetic cause or mechanism of the disease and therefore they have the potential to bring life-long values to patients. Most ATMPs are expected to target diseases with a high degree of severity, and for which there is no effective treatment options. The expected value of a curative treatment for these diseases can be very high due to large QALY gain and/or large cost offsets. (5, 6). The traditional payment model for health care is based on the payment being made at

the time of the treatment. The traditional payment model is thus not suitable for ATMPs as they are often given as a one-time treatment, and the payment would be paid during a short period of time whereas the value of health benefits and cost offsets are realized over several years in the future (5).

With value-based pricing, a conflict can therefore arise between what is cost-effective and what the payers can afford (7). This is usually called the "affordability barrier" and it occurs both in politically controlled tax-financed health care systems and insurance-based health care systems. With the traditional payment model, there is thus a risk that the goal of financial stability will be reached at the expense of patient access and incentives for innovation.

One example of this in a Swedish setting is when the new curative hepatitis-C drugs were introduced in 2014. The new drugs were found to be cost-effective, but due to the high budget impact the health care did not have the capacity to treat all patients in the short term. TLV decided that priority should be given to those with the greatest need and the drugs were only reimbursed for severely ill patients in fibrosis stages F3 and F4. For patients with less severe disease, the drugs were initially not reimbursed (8). Since 2018, as more drugs entered the market and pressured the price, the new drugs have been reimbursed for hepatitis C patients in all severity levels.

3. The Swedish context

In Sweden, health care is predominately publicly financed. Private insurance covers less than 1 percent and 15 percent are out-of-pocket costs for patients. Health care in Sweden is also predominately publicly produced by 21 regions. The regions are responsible for the drug budget, but they receive government contributions.

In Sweden, health care is provided based on the ethical platform, which relies on the three principles that are sometimes conflicting: the human-dignity principle, the needs-solidarity principle and the cost-effectiveness principle (9).

The Dental and Pharmaceuticals Benefits Agency (TLV) decides upon pricing and reimbursement for outpatient products included in the benefits scheme. Value Based Pricing applies for outpatient pharmaceuticals, which means that a drug is priced on the basis of the expected value in the form of health benefits and cost offsets. This creates incentives to develop drugs that lead to the greatest possible value for the patient.

The state and its authorities, TLV and the National Board of Health and Welfare, which issues national guidelines, applies a societal perspective in their cost-effectiveness analyses and decision-making. The state does not have any budget responsibility for health care. The regions on the other hand, have the budget responsibility and are responsible for cost containment.

The regions are responsible for the drug budget and pharmaceuticals administered in hospitals are completely financed by the regions. The regions receive contributions from the state which is directly linked to forecasted costs for outpatient products included in the benefits scheme and for some infectious drugs. When the hepatitis C drugs were approved in 2014, the state decided to finance the additional costs of the treatments in order to ensure equal access to treatments across the country (10). Since 2015, the regions receive a specific contribution from the state to cover 70 percent of the costs for the new hepatitis C drugs. The contribution from the state to the regions for 2020 is SEK 31,705 million in total, of which outpatient products in the benefits scheme amount to SEK 29,290 million and drugs for hepatitis C is SEK 795 million.(11)

Since the introduction of the hepatitis C drugs in 2014, the regions now collaborate on the managed entry agreements for new drugs administered in hospital care, through the New Therapies Council (NT-council). The NT-council is commissioned to make recommendations to the regions on the use of new drug therapies included in the managed introduction process or on the request on one of the regions. TLV provides the health economic assessments to support the NT-council.

According to the current legislation for municipalities and regions in Sweden (12, 13), the budget needs to be balanced and if there is a budget deficit, it needs to be adjusted for within three years.

However, exemptions can be made under special circumstances if the region has a plan for how to handle the deficit. A government commission of inquiry (SOU) was appointed by the Swedish Government in 2016 with the purpose to investigate the current system of funding, subsidising and pricing of pharmaceuticals. The commission of inquiry suggested that new innovative treatments that can generate cost savings over time, are likely to fulfil the requirements for such exemption (10).

A decade ago, coverage with evidence payment models were used for reimbursement decisions in Sweden by TLV (2). Currently, alternative payment models are increasingly being used to further share risk between the payers and the manufacturers. A recently published review of existing managed entry agreements in Sweden (14), showed that the uncertainties addressed included size of treated population, treatment duration, and effectiveness. The mechanism for risk-sharing was limited to refunds based on patient numbers, duration or just flat-rate refunds. The authors of review conclude that the main driver behind risk sharing in Sweden is affordability rather than managing uncertainty (14).

Even though agreements based on financial risks and straight discounts are most common, there are recent examples of innovative payment models. Often, these are payment models based on "Conditional treatment continuation" that requires analyses of follow-up data on treated patients to ensure that the right patients are treated and that they respond to treatment. One example in Sweden is Spinraza for the treatment of spinal muscular atrophy (SMA). Unlike gene therapies, Spinraza therapy is required over the long-term. The NT-council recommends the regions to use Spinraza if certain pre-defined conditions are fulfilled and if the treatment effect is followed-up continuously and the decision to continue or discontinue treatment is made according to specific criteria. The effect of treatment should be evaluated before dose number 7 and then every 12 months if treatment continues. If treatment is continued, the patient must not have worsened in pre-defined parameters including motor function and respiratory function.(15)

The Swedish government has appointed TLV to investigate the possibilities for innovative payment models for ATMPs during 2020. TLV will investigate how payment models for ATMPs can be developed to manage the large initial costs and the uncertainties associated with, among other things, the long-term effects of ATMPs. The assignment must be reported no later than May 1, 2021.(16)

In their last congress in November 2019, the Swedish Association of Local Authorities and Regions (SALAR) agreed on a similar initiative. The initiative seeks to, in cooperation with the state, regions and pharmaceutical companies, find innovative financing- and payment models for ATMPs that are sustainable in the long run in the Swedish setting. SALAR states that there are challenges with complex outcomes-based payment models, including administrative challenges that are difficult for the regions to handle. Nonetheless, that new innovative payment models are needed to make potentially curative treatments available. (17)

4. β-thalassaemia

β-thalassemia is part of the disease group hemoglobinopathies, a group of inherited blood disorders which are characterized by the formation of an incorrect haemoglobin protein. In β-thalassemia, a genetic mutation of the *HBB* gene on chromosome 11 causes reduced or absent synthesis of the β-globin chains of haemoglobin. This causes an imbalance in the production of α-globin and β-globin chains, resulting in an excess of the α-globin chains. As a result, patients lack sufficient red blood cells and haemoglobin (Hb) to effectively transport oxygen throughout the body, which results in severe anaemia. Severe forms of β-thalassaemia, with no or heavily reduced functioning Hb, causes life-threatening anaemia requires frequent and lifelong transfusions of packed red blood cells for survival. The transfusions result in unavoidable iron overload which can cause serious complications within the liver, heart and endocrine glands. Severe symptoms include liver cirrhosis and liver fibrosis. Heart failure, growth impairment, diabetes and osteoporosis are conditions which can be caused by β-thalassaemia. (18)

The incidence and prevalence of β-thalassaemia varies over the globe. The disease is most prevalent among populations in South Asia, the Middle East, North Africa, and Southern Europe (18). β-thalassaemia is still a rare disease in most of Europe, even if migration is changing the geographical spread. Globally, the total annual incidence of symptomatic individuals is estimated to 1 in 100,000 people and in the European Union, 1 in 10,000 people (19).

The severity of the disease depends on the nature of the mutation. Nearly 300 mutations have been identified that could result in clinical presentation of β-thalassaemia (20). Null mutations that eliminate the production of functional β-globin are referred to as β0/β0 mutations and all mutations that are not null mutations are classified as non- β0/β0 mutations.

According to Thalassaemia International Federation (TIF) Guidelines, the severity of disease for symptomatic patients can be evaluated based on transfusion requirements; Patients with β-thalassaemia are classified either as transfusion-dependent (TDT) or as non-transfusion dependent (18). There is a lack of data of the incidence and prevalence of TDT in Europe, partly due to the use of different terminologies to describe transfusion dependence. The prevalence of TDT in Sweden is estimated to about 100 individuals (21).

4.1.1 Standard of care

According to the National Board of Health and Welfare, regular blood transfusions are needed if the haemoglobin level drops below 70 grams per litre or if there are obvious signs of poor growth (21). According to guidelines from the Swedish Association for Haematology, transfusion at Hb is given below 95–105 grams per litre (22). Most adult patients with severe forms of β-thalassaemia need

transfusion every two to three weeks with 2-3 units to keep the haemoglobin level in accordance with treatment goals on levels over 105 grams per litre (22).

As a result of regular blood transfusions, which effectively manage the symptoms of TDT, patients need iron chelation treatment to manage the iron-associated morbidity and mortality. Iron accumulates in the liver, heart, and endocrine organs, which results in a wide array of complications. Several of chelation therapies are available and the treatment is optimized in accordance with the patients' needs. Moreover, patients sometimes need anticoagulation treatment to avoid thrombotic complications.

The only available curative therapy for β-thalassaemia is allogeneic hematopoietic stem cell transplantation. However, stem cell transplantation is not an option for most patients due to lack of matched sibling donors or due to the risk of life-threatening complications. It has been estimated that 25-30 percent of patients have matched sibling donors (23). Stem cell transplantation is mainly an option for children and adolescents. Most adult patients have too severe comorbidities to be able to go through a stem cell transplantation. Transplantation-related mortality is estimated to between 2-10 percent (23).

4.1.2 Health care resource use

Disease management for patients with TDT includes regular follow-up visits, blood transfusions, iron chelation therapy, laboratory tests, and treatment of side effects. A number of studies have investigating the economic burden of β-thalassemia with a large variation in total management costs. Differences are due to the settings, health care systems, and treatment patterns, (e.g. United Kingdom (24), Italy (25), Thailand (26), United States (27, 28), and Israel (29)), the study designs (e.g. model studies (24, 29, 30) observational studies (25), register-based studies (24, 27)), the year of the study, and the severity of included patients.

A multicentre, retrospective, observational study in Italy investigated costs of adult and paediatric patients with β-thalassemia major (25). The patients (n=137) had received transfusions and iron chelation therapy for at least 3 years. The study does not report the number of transfusions per year. The average cost was EUR 1,242 per patient per month in 2006 (≈162 000 per year SEK 2019), out of which 56 percent was iron chelation therapy, 33 percent was infusions and the remaining 11 percent was hospitalizations, laboratory, concomitant medications and travel costs.

A retrospective analysis in the United States, using the claims databases of inpatient and outpatient visits and outpatient drugs, analysed the total direct costs of patients with β-thalassemia in 2019 (28). The included cases had an average of 16.8 transfusions annually. The costs for transfusion and iron chelation therapy were $39,723 (≈376 000 SEK 2019) and $61,974 (≈586 000 SEK 2019).

There is limited available data from current Swedish clinical practice on the cost of blood transfusions. Glenngård and colleagues estimated the cost for a blood transfusions with filtered allogeneic red blood cells from a societal perspective in Sweden in 2003 (31). The cost included administrative costs to the hospital, travel costs, productivity loss and a minor reaction cost from medical reactions to the transfusion. The average cost for a two-unit transfusion was estimated to SEK 5,467 per blood transfusion in 2003 price level, which would be about SEK 6,572 in 2019 price level. Assuming 20 transfusions per year, the cost would be about SEK 130 000 annually. This is likely to be a conservative estimate given that the cost of transfusions for patients with β-thalassemia was SEK 7,891 in 2018, including the direct costs alone, according to the cost per patient (KPP) database (32).

We found no Swedish study on the cost of and iron chelation therapy. The extent of different iron chelation therapies used, as well as the characteristics of the patient population also influences the cost as the dosing of iron chelation therapies varies depending on the weight of the patient. In a British cost-effectiveness analyses from 2013 (30), the annual cost for iron chelation therapies in 2019 price level was estimated to about SEK 62 000 to about 259 000 SEK depending on treatment regimen (£5,519 for Ferriprox and £5,584 for desferrioxamine and £23,179 for Exjade in 2011 price level). The variation in cost was due to differences in administration and monitoring costs, but mainly in the acquisition costs of the different treatment options.

4.1.3 Health Related Quality of Life

A recent multicentre observational study in the UK investigated the Health Related Quality of Life (HRQoL) using the EQ-5D-3L in patients with TDT (n=134) and their caregivers (33). At enrolment the mean (SD) utility score was 0.69 (0.33) among patients above 16 years old (n=94), 0.73 (0.27) among patients 4-7 years old as completed by caregivers (n=9) and 0.88 (0.15) among caregivers (n=34) (33).

These utility values are in line with those found in a recent vignette study estimating the utilities associated with treatment approaches for TDT (34). The descriptions of the health states were developed with clinician, patient, and caregivers. Respondents from the general population in England (n=207) was asked to value eight different health state vignettes in time trade-off interviews. Mean (SD) utilities for the health state with oral chelation was 0.73 (0.25) and with subcutaneous chelation 0.63 (0.32). A post-transplant utility was estimate to 0.93 (0.15) for the transfusion independent health state (34).

Several studies have shown that patients with β-thalassaemia rate their HRQoL lower than the general population norms. For example, a cohort of 264 patients over 14 years old from north America and the UK, (35) reported significantly lower in the 36-item Short form (SF-36) survey

than did the general US population on the physical functioning, role-physical, general health, social functioning, and role-emotional domains, and on both summary scores. In a French study of a cohort of 24 patients with β-thalassaemia, patients reported lower SF-36 than those of the general French population (36).

An Italian study from 2013 analysed the HRQoL, using the SF-36, in patients who had received hematopoietic stem cell transplantation about 20 years ago. The authors found that the HRQoL was similar in the transplanted cohort as the general population. Furthermore, the study found that a cohort of patients receiving conventional treatment of β-thalassemia had poorer outcomes compared with the cohort of transplanted patients (37).

4.2 A proposed payment model for an ATMP in β-thalassaemia

The proposed payment model for an ATMP in β-thalassaemia could be defined as a performance-linked reimbursement schemes with outcomes guarantees (2). The payment model have a total of five suggested annual payments at months and the payment would be capped after five years. After an initial payment of 20 percent at drug product delivery, annual milestone payments would only be made upon treatment success and no payments are done upon treatment failure. Treatment failure could be defined by assessing episodes of transfusions of packed red blood cells. Treatment failure could be defined as more than one transfusion episode in the assessment period, with the transfusions separated by at least 2 weeks. One transfusion could be allowed as transfusions may be needed for other reasons, e.g. car accidents etc. A transfusion episode could be defined as a calendar day on which one or more transfusions has occurred. If the data on transfusions is not provided, treatment success could be assumed.

5. Challenges and possible solutions

5.1 Uncertainty of the full value

We identify two main reasons why there are uncertainties of the full potential value of an ATMP. Firstly, there is uncertainty of the real-world effectiveness and the features of the payment model. Secondly, there is a structural uncertainty and the uncertainty of future competition.

5.1.1 Uncertainty of the real-world effectiveness and the features of the payment model

Clinical trials that are the basis for the regulatory approval of ATMPs, often show promising results with potential to provide lifelong benefit. Nonetheless, the number of included patients in the trials are often limited and there often is no comparator, which differs considerably to the regulatory procedure in drug approval under normal circumstances. Consequently, the uncertainty of whether the treatment response will be similar under real-world conditions is considerable. When more patients are treated with the ATMP, they may have somewhat different patient characteristics than those selected for the clinical trials, e.g. older and milder disease. Consequently, there is an uncertainty whether they will respond in the same way as patients included in the clinical trials.

One uncertainty of the response regards the proportion of patients that achieve transfusion independence, which may be higher or lower than the success rate showed in the clinical trials. Another uncertainty of the response is whether the response is sustained over time. There could be a so called “waning effect” which indicates that the effect is not stable, and that the effectiveness diminishes after a couple of years.

The uncertainty of the real-world effectiveness is handled in the proposed payment model to a certain extent. As the payment model suggests that the payer only pays the first 20 percent of the price, and the remaining 80 percent is only paid upon treatment success, the manufacturer takes a great proportion of the risk. Nonetheless, the agreement is proposed to run for five years. After five years, the full payment is made, whereas the full value is realised over a lifetime.

Uncertainty of the features of the payment model is related to acceptability and applicability of the proposed payment model in a certain jurisdiction. There is always an uncertainty whether the outcome measure selected for a payment model is a good surrogate measure for the full value of a new technology, once implemented in clinical practice. Simplicity of collecting outcome information is crucial for limiting the administrative costs for data collection. At the same time, there is a demand for the measurement to reflect the value of the treatment. There is thus a trade-off between reducing

the administrative costs for collecting follow-up data and collecting information that can capture the value of future outcomes in clinical practice.

The value of the drug in clinical practice should be measured and followed-up, but all measurable variables should not be linked to the payment. The surrogate measure should correlate with the value drivers in the ex-ante cost-effectiveness analysis. In the case of our hypothetical example, the measure of treatment success used in the proposed payment model, transfusions independence (TI), measures a value associated with reduced health care resource use of blood transfusions. But this definition of treatment success is only one of several value drivers. Additional values, that are correlated to the effect on blood transfusion, include the cost of comorbidities of iron overload, the cost of doctor visits and possible admissions, improved quality of life and improved overall survival. Furthermore, when more evidence is in place, there may be additional values in clinical practice that were unforeseen. It is important for payers to understand how "well" transfusion independence correlates to all the values that arises in clinical practice as a consequence of the new treatment.

Previous experience from outcomes-based payment models internationally, shows that the outcome measures tied to the payment need to be easy to measure and collect in order not to impose an administrative burden for health care providers. For example, the administrative burden in outcome-based payment models for oncology drugs in the UK was shown to be a major challenge. Hospitals had problems to track patients and ensuring claims are made to refund for non-responders. Variation between the administrative requirements of different schemes for different drugs added to the problem (38). Outcome-based payment models should therefore be clinically robust, clinically plausible, appropriate, and monitorable and there must be a straightforward way to measure a patient’s clinical response (38).

In the case of our hypothetical example, the achievement of transfusion independence is clinically meaningful, and it is associated with eliminating the need for regular blood transfusions as well as the health care resource use of handling the comorbidities due to iron overload. Meanwhile, transfusion independence is straightforward to measure and is likely to have a relatively low administrative burden to register. The number of patients is limited and consequently the treatment centres could be able to keep track of their treated patients and their blood transfusions, for example bi-annually. Alternatively, transfusions can be tracked on an annual basis from the regions administrative registers based on ICD-codes. This is in line with the NT-council’s follow-up requirements for cell therapy Yescarta, in which patients are tracked in the patients register held by the National Board of Health and Welfare by registering the administration code (KVÅ-kod) and ATC codes for Yescarta.

5.1.2 Structural uncertainty and uncertainty of future competition

Structural uncertainty is uncertainty related to future comparators and future standard of care, cost of standard of care, potential cost offsets and future life expectancy. The introduction of new technologies will increase the competition and that will increase the payers' willingness to pressure the prices.

In the case of β-thalassemia, several ATMPs are currently being developed (39). Furthermore, a number of other drugs for β-thalassemia is currently under development (40, 41), which may change the standard of care and alter the cost-effectiveness of the ATMPs over time.

The dynamics of a competitive market is not reflected in the proposed payment model. Payers are therefore likely to require an opportunity to re-negotiate the agreement after a couple of years. Another reason for re-negotiations in a shorter time-period than the suggested five years, is if the regions can only commit to three years due to the current budget legislation. Another reason for a shorter time period may be that the politicians are in office for four years and may be reluctant to commit to longer time periods.

5.2 The affordability barrier

In a traditional payment model, the payment of a drug occurs at the same time as the actual treatment and the treatment is typically taken for a period of time or, for chronic diseases, during the entire lifetime. ATMPs are often one-time treatment, with potential lifelong effect. Even though the drug is cost-effective from a value-based pricing perspective, it may not be possible to pay for with a traditional payment model due to the so- called affordability barrier. As large values, over a long period of time, is to be paid during a short period of time, an alternative payment model is needed. In the proposed payment model the payments are distributed over five years to handle the affordability issue for payers. The affordability barrier may however still be an issue, especially for small regions, due to the budget impact. One solution to the affordability barrier is to limit the treatment to a subpopulation most in need of therapy.

5.2.1 Estimated budget impact

Given that there are about 100 patients with TDT in Sweden, the number of patients within the indication for treatment with an ATMPs can be assumed to be 25-30 patients in Sweden. Assuming a the price of our hypothetical example is 16.8 million SEK per patient, the total budget impact nationally would be up to SEK 504 million without a payment model with risk-sharing nor annuity-based payments (table 1). If the proposed payment model is used, the first-year budget impact will

be about SEK 100.8 million and the expected budget impact, assuming the same success rate as in clinical trials, the following 4 years would be SEK 90.7 million per year.

As the budget impact is substantial it is likely that the NT-council will suggest that a subgroup of patients should be treated initially. The selected subgroup may for example be younger patients, as adults often already have organ failure due to iron overload. Assuming that a third of the eligible patients are selected initially (subgroup A), the budget impact the first year would be SEK 33.6 million.

Table 1. *Example of an estimated budget impact of an ATMP in transfusion dependent thalassemia in the total population and in subgroup of the population*

	Number of patients Nationally	Total Budget Impact Nationally	First-year Budget Impact	Expected* Budget Impact the following 4 years, per year
Total population in indication	30	SEK 504 million	SEK 100.8 million	SEK 90.7 million
Subgroup of patients (A)	10	SEK 168 million	SEK 33.6 million	SEK 30.2 million
Subgroup of patients (B)	5	SEK 84 million	SEK 16.8 million	SEK 15.1 million

*Assuming a success rate of 90 percent.

By initiating treatment in subgroups of patients, the affordability barrier may be less of a problem to payers. In β-thalassemia it would be possible for patients to wait for their treatment as it is not a fatal disease in the short run, such as cancer. If the initial subgroup would include 5 patients (subgroup B), and 5 patients per year would start treatment subsequently, and so on until the total prevalent population would be treated, the total budget impact for the second year would be SEK 32 million, SEK 47 million the third year, SEK 62.2 million the 4th year and SEK 77.3 million year 5, and so on. The prevalent population would be treated within 6 years and the payments would be made within 10 years in our example above. After that time period, only new cases would remain for treatment with the ATMP.

Based on the information in the scarce published literature (referenced in 4.1.2) the current management costs of blood transfusions and iron chelation therapies in patients with TDT adds up to between SEK 200 000 and SEK 400 000 annually, depending on the iron chelation treatment used.

Furthermore, there are additional costs due to productivity loss and the costs of future complications of iron overload. Assuming a conservative total cost of standard of care of SEK 300 000, the cost-offset per patient using the ATMP would be approximately SEK 1 500 000 over merely a 5-year period. This cost-offset also needs to be considered in the budget impact analyses of decision-makers.

5.2.2 ATMPs require societal perspective and a change in the financial model

The affordability barrier in ATMP is due to that potentially curative treatments provides large values over a short period of time. Moreover, the values are realised in many parts of society, not only in the health care sector. Potentially curative treatment in severe diseases is likely to improve the productivity in patients and result in savings in home care for municipalities. Nonetheless, it is the regions, responsible for the drug budget, that are to finance the ATMPs.

Currently, drugs with high initial budget impact are a challenge for regions due to the requirement of a balanced budget over three years. It is unclear to what extent ATMPs will fulfil that requirement for exemption under the current legislation on a balanced budget. Firstly, whereas the exemption refers to cost-savings, ATMPs are mainly associated with health gains and values outside the health care sector, such as productivity loss. Secondly, even if each therapy itself targets small patient populations, the potentially aggregated patient population, and its potential budget impact, is extensive. Given the large number of ATMPs under development, it is thus unlikely that all future ATMP:s can be considered exemptions. The affordability barrier with ATMPs has even been referred to as “the next frontier”(42) and a “global crisis” (43). If the regions are to finance ATMPs, it is thus likely to require a change in the legislation to allow for more flexible budgets for regions.

Another solution, which has previously been proposed by Persson and colleagues (44), would be that the state would finance new innovative treatments such as ATMPs, whereas the regions continue to be responsible for the remaining drug budget. This is in line with the situation when the curative drugs for hepatitis C were approved in 2014 and the state initiated a specific contribution to the regions to cover some of the costs of the treatments in order to ensure equal access to treatments across the country (10).

This is also in line with suggestions proposed by the government commission of inquiry on funding, subsidising and pricing of pharmaceuticals (10). The commission of inquiry proposed that the state allocates a part in the state budget to handle high costs for a limited group of drugs. The criteria suggested for a drug to be subject for state funding is that 1) the product is a drug (both prescription and requisition drugs), 2) The drug is considered cost- effective, 3) The drug is particularly costly and the disease is unevenly distributed geographically.

6. Conclusion

There are two main challenges for payment models for ATMPs; the uncertainty of the full value of the ATMP and the so-called affordability barrier. The proposed payment model in this report has several attractive features that contributes to solve these challenges: First, it reduces the affordability barrier by using annual payments over five years. Second, it reduces the uncertainty of the real-world effectiveness during the first five years, particularly uncertainty in the response rate of transfusion independence and in the sustainability of effectiveness among those who respond. Third, the proposed payment model is an acceptable and applicable payment model with a well-balanced trade-off between low administrative cost and using an outcome measure, transfusion independence, that reasonably well reflect the value of the treatment.

Based on these features, we believe that the proposed payment model could be implemented in the Swedish context. However, the proposed payment model does not handle the structural uncertainty of changes in future treatment patterns. By allowing for the opportunity to re-negotiate the agreement after two or three years if new comparative treatments opportunities appear, the structural uncertainty can be handled.

Despite the proposed payment model over five years, the affordability barrier for regions is likely to remain. This issue cannot be resolved by the manufacturers themselves. This challenge calls for changes in the current Swedish system, by allowing for more flexible budgets or for financing of new innovative treatments by the state. It remains to be seen if the new initiatives by TLV and SALARs will lead to progress in this matter.

In this report we show how an outcome-based payment model in the treatment of β-thalassemia can solve some of the problems facing ATMPs. In the coming years, several new ATMPs will continue to face challenges due to the affordability barrier and the uncertainty of data, which will require, tailored, case-by-case solutions in terms of innovative payment models.

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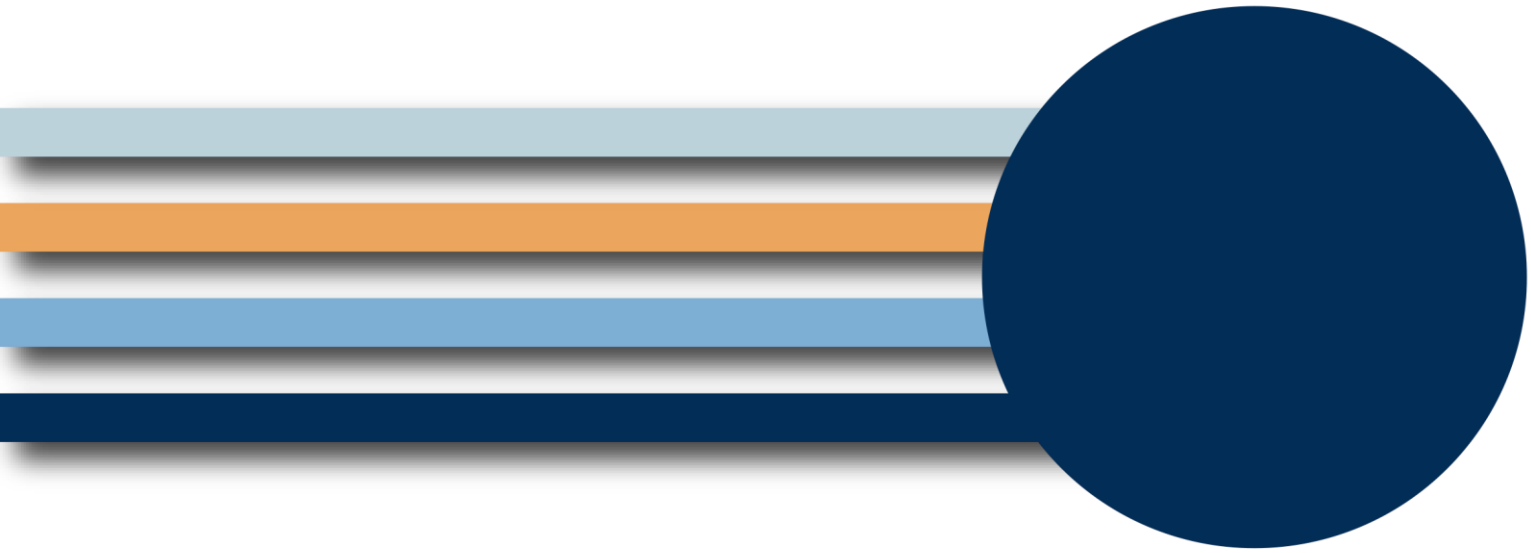

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