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Final report for Swelife-ATMP system development project 3 (SDP3)

Business models and health economics

December 2020

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Abbreviations

ATMP	Advanced Therapy Medicinal Product
BeNeLuxAIr	Belgium, Netherlands, Luxembourg, Austria, and Ireland
BSC	Best Supportive Care
CAMP	Center for Advanced Medical Products
CAR	Chimeric antigen receptor
CAR-T cells	Genetically modified T cells with CAR
CED	Coverage with Evidence Development
EMA	European Medicines Agency
FAP	Familial Amylodiosis with Polyneuropathy, also known as "Skelleftesjukan"
FINOSE	Finland, Norway, Sweden
FoU	Research & development
FVIII	Factor-8
GMP	Good Manufacturing Practice
HTA	Health Technology Assessment (synonymous with "health economic evaluations" in this report)
ICER	Incremental Cost-Effectiveness Ratio
La Valetta Group	Italy, Spain, Greece, Portugal, Slovenia, Cyprus, Malta, Croatia
LFN	Predecessor of TLV
Swedish MPA	Swedish Medical Products Agency
LY	Life Years
MSC	Mesenchymal Stem Cells
NK cells	Natural Killer cells
The NT council	The New Therapies Council

OS	Overall survival
QALY	Quality-Adjusted Life Years
QoL	Quality of life
SBU	State Preparation for Medical and Social Evaluation
SKR	Sweden's municipalities and regions, formerly Swedish Municipalities and County Councils (SKL)
SMA	Spinal muscular atrophy
SME	Small and medium enterprise
TEP	Tissue-engineered product
TLV	The Swedish Dental and Pharmaceutical Benefits Agency
TPP	Target Product Profile
TTR	Time to Relapse
TUFT	Tufts Center for the Study of Drug Development
Visegrad	Czech Republic, Hungary, Poland, Slovakia, Croatia

Summary

Background and purpose

The aim of the project has been to map the ATMP area, gather relevant information and create different data in the form of surveys, checklists, selected cases, and references, which is presented in this report with appendices. The long-term goal of the project is to contribute to the success and patient accessibility (nationally and internationally) of ATMP drugs developed or marketed in Sweden (or by Swedish actors).

The main focus of the report is the challenges of valuation and payment of ATMP drugs. Demonstrating value requires not only evidence that the treatment is working, but also health economic evidence showing that the cost is acceptable in relation to the health benefits of other, relevant treatment options.

The report is intended to support those who want to familiarise themselves with the conditions for developing and commercialising ATMP drugs. These may be academic groups considering converting a project into product development or SMEs getting ready for the development of their activities, but also other stakeholders in the field.

The project's main objectives

During the project, the following main objectives have been developed

- During the development of ATMP drugs, it is crucial to have good insights into the conditions the whole way through to market approval and health economic assessment as a basis for health care priorities.
- Well-founded planning for the formal milestones of the development process reduces the financial and developmental strategic risks associated with product development, which indirectly increases the value of the project.
- ATMP drugs may provide the opportunity to treat certain diseases in a completely new way. Therefore, the system susceptibility to health care also needs to be developed in parallel.
- The health economic evaluation of ATMP drugs is fundamentally no different than the health economic evaluation of other new technologies intended to be introduced into health care. However, ATMP drugs may require an address regarding the increased uncertainty in relation to comparable options and long-term effects.

Collated basis for the four objectives above

As a developer of an ATMP drug, it is important to understand that one is in the field of drug development, an area that is regulated by specific sections of

law and which is often based on a structured process. This applies both to the production of the product and to the collection of information proving the benefits in relation to the risks of both efficacy and health economic evaluation. Market approval is a milestone on the journey towards creating value for the patient. There must also be a health economy basis, a willing payer, and health care must have the conditions to be able to offer treatment with the product in question. ATMP drugs are often associated with complex manufacturing processes where the responsibilities of health care and companies overlap in a new way. ATMP drugs are often targeted at small defined patient groups where it can be ethically challenging to conduct randomised studies. Studies with a larger patient pool are not possible. Clinical development can often take place in parallel with the build-up of production capacity, which in turn can further limit the clinical patient pool. These factors may increase uncertainty in the interpretation of available efficacy and safety data.

In order to succeed in your business in the end, a fundamental aspect is to understand the conditions for passing the important milestones in the development journey and reach high to create sufficient and relevant knowledge along the way and thus reduce the uncertainty in the assessment.

We are faced with the fact that treatment options with a new type of complexity are on their way into health care. It is therefore important that society and health care develop system susceptibility to ensure that Swedish patients are effectively and safely granted access to treatment. Part of the complexity is that the responsibilities of health care and companies overlap in a new way. The management of tissues in care becomes part of the manufacturing process in which the company is responsible for the quality of the product, which is also taken into account in pricing. Sweden needs to both demonstrate the ability to ensure patients' access to effective treatment, as well as competitiveness in research and product development in the field. Both these aspects are expressed by politics and through the national strategy for Life Science, which highlights that Sweden should be a leading nation in life science. For this to become a reality, an effective process for the implementation of new therapies is required.

Some of the hopes behind the new treatment options that ATMP drugs have the potential to offer are significantly increased survival and/or quality of life compared to today' s treatment; for some ATMP drugs, lifelong efficacy after a one-off treatment compared to lifelong treatment is expected. When these opportunities are met, a treatment can be estimated to be cost-effective and well within the established willingness to pay even at what are perceived as high costs for each individual patient. For other ATMP drugs, neither the price nor the frequency of treatment may differ from traditional drugs, but new

treatment options are being created where there are currently no alternatives. When we finally see ATMP drugs being introduced to a wide range of disease, and to larger patient groups, the overall cost can be challenging from a budgetary perspective and lead to questions about displacement effects, ability to pay, and the need for priorities. Against this background, uncertainties in health economics need to be addressed, as well as funding and payment models developed to ensure that patients have access to treatment.

Background and methods

This report was produced within the SDP3 (System Development Project-3, referred to henceforth as the "project") sub-project, which is part of the strategic Swelife project Swelife-ATMP[1]. Swelife-ATMP started in June 2017 and ends in June 2021. It is important to point out that the report has been produced based on Swelife's goal of enabling and accelerating innovation and collaboration in life science – from ideas to societal benefits. The report should not be understood as a national investigation.

The initial project proposal was built around two work packages, WP1 and WP2, consisting of several different activities. The application for WP3 was added in autumn 2019, and is thus an extension of the project until June 2021. This work package is led by Region Västerbotten and will be presented separately.

WP1 focused on defining and planning the project, mapping the area, identifying existing information, stakeholders and issues to work on. This work package has also addressed the hospital exemption, various legal aspects around ATMP drugs, and how the HTA (Health Technology Assessment) process looks like in countries outside Sweden. During this process, a number of educational activities have also taken place within the project, through seminars and discussions led by different project participants, in order to raise the common level of knowledge and understanding of different areas of expertise related to the project's issues, which has been a prerequisite for starting WP2.

WP2 focused on HTA and business models for ATMP drug in Sweden, from the perspective of different target groups. An important part of this work package has been to take into account different stakeholders and to engage in dialogue with them, as has happened in small meetings, seminars and open project meetings. WP2 has been led by a core team of health economists,

[1] https://swelife.se/projekt/atmp/

operating in several different sectors (companies, healthcare regions, and consulting) with broad experience in HTA and pricing negotiations.

WP3 is an independent continuation of the project, which focuses on the introduction of new treatments for familial amyloidosis with polyneuropathy (FAP), also known as "Skelleftesjukan" which, although not formally an ATMP drug, shares several of the challenges facing ATMP. The aim is to engage in dialogue with policy makers and other stakeholders on the basis of this concrete example, thereby drawing knowledge and proposing solutions that are generic and applicable to different ATMP drugs at a national level. The project has also worked with stakeholder analyses for the ATMP pharmaceuticals area in Sweden from a broader perspective. A summary of this work will be included in the WP3 report, to be delivered in spring 2021.

Teams and project partners

The embryo of project proposals was developed by Anna Ridderstad Wollberg (RISE), Agneta Edberg (Idogen) and Örjan Norberg (Region Västerbotten) and was submitted as an application to the agency of CAMP/Swelife-ATMP in August 2018 and invited project partners to participate in the project. In Table 1 you can see all project partners (organisations) and names of project members, who have been involved in a significant part of the project work. Some participants have been with a shorter period and then been replaced by another participant from the same organisation, these are not listed below.

Table 1. Project partners (organisations) and names of project members.

Project partner	*Project member*
Academic Hospital	Alexandra Karlström, Anna Björkland
CellProtect Nordic Pharmaceuticals	Karin Mellström
Idogen	Agneta Edberg
Institute of Health Economics (IHE)	Ulf Persson, Peter Lindgren
The Karolinska Cell Therapy Center (KKC)	Kristina Kannisto (Project owner), Pontus Blomberg
LIF (the research pharmaceutical companies)	Dag Larsson, Johan Brun (Steering Group)
NextCellPharma	Mathias Svahn, Leo Groenewegen
Novartis	Johanna Jacob, Katia Eriksson Bragazzi
BMS	Åse Rosenqvist
Pfizer	Ann-Charlotte Dorange, Kim Persson
Pre-GMP KI	Matti Sällberg, Anna Pasetto
Region Örebro County	Petros Nousios
Region Skåne	Ulf Malmqvist
Region Västerbotten	Örjan Norberg, Elham Pourazar
RISE (Research institutes of Sweden)	Anna Ridderstad Wollberg (project manager), Ronja Widenbring, Charlotte Nilsson
Swelife	Ebba Carbonnier (Steering Group)

The project is a collaborative project within the framework of Swelife-ATMP, a strategic project funded by Swelife (strategic innovation programme for life science funded by Vinnova). Cooperation takes place between the parties who have wished to participate, where the parties contribute co-financing linked to their own activities and their area of competence. RISE, a nationally available infrastructure (a state-owned company) has taken the project manager role for this project. According to Swelife's guidelines, the project's deliveries are publicly available and there is no confidentiality agreement between the parties within the framework of the project. The aim is for the project to facilitate for all actors in the field, even if it has not been part of the project.

Introduction

ATMP (Advanced Therapy Medicinal Products), i.e. cell and gene therapies and modified tissue technology products[2] create, in a brand-new way, the possibility of relief and cure for patients in need. Research in this area has gone on for several decades, but now new knowledge about the immune system and pathological processes as well as other advances in biology have led the area to move to clinical phase and is in the process of taking the world market. The ATMP area is prioritised in the national strategy for life science from the government[3] that came in December 2019 and an important part of the working group "precision medicine(PM) and ATMP" in the government's strategic collaboration program within Health and Life Science. The ambition for the national collaboration programmes CAMP (Center for Advanced Medical Products), Swelife-ATMP, and Innovation Environment - Vision-driven Health[4] is also to contribute to Sweden's international attractiveness in the ATMP area.

Sweden has a deep-rooted tradition and expertise in the field of drug development, which is based on previous, and existing pharmaceutical companies with R&D (Research & Development) located in Sweden, such as Kabi, Pharmacia, AstraZeneca, SOBI, and Medivir. For historical reasons, much of this knowledge lies in the fields of chemical and protein drugs. The development of ATMP drug is now taking place at a global level and new knowledge of the whole chain must be created. Here there is a great need to help SMEs in particular to understand what the process looks like, what is important to include in the development chain, what the regulations look like, and which actors one is required to interact with over the entire development and commercialisation pathway in order to be well-placed to reach patients with their product.

One challenge that ATMP drug developers/marketers have is to obtain decisions on reimbursement or national recommendation on post-marketing authorisation. A specific challenge for ATMP developers is to find a model that finances treatment in a long-term and economically sustainable way together with paying parties. These are the challenges we address in this project and in order to do so, we need to look at the whole development chain. For example, several different perspectives need to be taken into account along the way in order to predict the value of treatment, so that a sustainable business plan can

[2] www.lakemedelsverket.se
[3] https://www.regeringen.se/4a48d8/contentassets/cdda3e9fc7be4ea5b55afc99c5221fab/2019_ls_webb_tlg.pdf
[4] https://atmpsweden.se/

be developed. Of course, ATMP drugs, like other drugs, have many other challenges that are not addressed in this report.

Project scope

The priority areas of the project relate to health economic evaluations, namely Health Technology Assessment (HTA) and payment and business models for ATMP drugs. In order to be able to link the reasoning to different stages in the development journey of an ATMP drug, we have developed a generic roadmap, from idea to patient. We have also developed generic target profiles, based on target product profile (TPP) for different types of ATMP drugs, with various supplements that link to the HTA process. The project will not deal in detail with issues related to development processes such as research, Good Manufacturing practice (GMP), toxicology, clinical trials, or regulatory work and documentation for market approval, as it is largely covered by another project within Swelife-ATMP[5]. The focus will be on products classified as ATMP drugs and therapies with similar challenges, although comparisons will be made against cell transplants and to some extent even treatment under the hospital exemption.

Since no ATMP medicinal product is currently included in national highly specialised care in accordance with the National Board of Health and Welfare's mandate (The Health and Medical Services Ordinance (2017:80) Chapter 2), this form of care will not be addressed in detail within the project. The project will also not address disease prevention as a separate purpose, as ATMP drugs are widely used today to compensate for significant pathophysiological conditions. The focus of the project is therefore on identifying barriers and proposing solutions for ATMP drugs to reach all the way to the patient. However, it is noted that some ATMP treatments, such as gene therapies, are developed to help slow down/prevent disease progression and its complications by correcting defective genes.

Project target groups

The project's work is expected to affect several different spheres of influence and we have identified a number of target groups (listed below) that we believe have an interest in the project's results.

- Patients
- Patient organisations

[5] https://atmpsweden.se/swelife-atmp-2/projects/regulatory-support-functions-and-educational-activities/

- Academic groups and researchers and start-ups in the ATMP field
- Innovation support system
- SMEs in the ATMP field
- Major pharmaceutical companies
- Health care personnel
- Payers (venture capital and research payers)
- Politicians
- SKR (Sweden's municipalities and regions), TLV (The Swedish Dental and Pharmaceutical Benefits Agency)
- Authorities

The project assesses that these target groups are reached in different ways. The report is written mainly from the perspective of the unfamiliar developer (such as start-ups, SMEs), as we have put a lot of focus on roadmaps, checklists, generic target profiles (TPP) for ATMP drugs for Swedish conditions and an insight into the HTA process in countries outside Sweden. The same perspective is relevant for actors in the innovation support system. Larger pharmaceutical companies and financiers also have an interest in SMEs having knowledge of the process and doing the right thing from the start, as they become more attractive for financing and possibly takeovers later on.

The project also aims to create a knowledge base that can contribute to constructive solutions and necessary changes that allow more patients to be treated with and possibly cured by ATMP drugs. We therefore see SKR, TLV[6], and the Agency for Health and Care Services Analysis[7] as important recipients of the report in their respective policy assignments for ATMP drugs.

In addition to the report, the project has conducted two open project meetings[8] with discussions on, among other things, the patient perspective and the policy perspective, two target groups that the report does not focus on. The project report with appendices will be delivered in autumn 2020, it is also hoped that the material created during the project period will be discussed in open forums with the project's stakeholders and will be discussed further in ongoing national collaboration programs within the ATMP area.

[6] https://www.tlv.se/om-oss/om-tlv/regeringsuppdrag.html
[7] https://www.vardanalys.se/pagaende-projekt/uppdrag-att-analysera-precisionsmedicinens-paverkan-pa-halso-och-sjukvarden/
[8] https://www.lif.se/kalendarium/2019/191115-oppet-projektmote-atmp-affarsmodeller-och-halsoekonomi/

Impact targets

The project is expected to create a basis and initiate and to some extent also carry out interventions that increase the likelihood that ATMP drugs developed or marketed in Sweden (or by Swedish actors) will succeed and reach out to patients.

The project meets **Swelife's impact power logic** by:

1. Promote the interaction and coordination of actors in the field.
2. Strengthen the competence of stakeholders in the field (first step within the working group, second step in the project's target groups).
3. Promote nationally scalable solutions for better health by creating generic cases, checklists, roadmaps and solution proposals that can be scaled up to national level and to different products.

Results from the project work

The following pieces have been produced during project work, by project participants and in dialogue with experts in relevant areas. These can be used as a knowledge base describing important aspects of the development of an ATMP drug, with a specific focus on health economics and business models. The results can also be used as a basis for finding solutions for several parties, including the developer, society and healthcare, around the new problems that ATMP drugs encounter in their journey from idea to patient.

Problem area description

One problem for many start-ups is a lack of knowledge of what it takes to develop a research idea all the way to a commercially viable product that reaches the market and the patient.

In order for the final product to be covered by a national compensation scheme or accepted by a healthcare responsibility organisation, there must be a health economic evaluation. Health economic evaluations are a tool for demonstrating the value of treatment and for putting a price on treatment, so-called value-based pricing. Many countries apply value-based price setting (see further Appendix D: Value-based price setting). A high price may be justified for a treatment with a large health benefit. A large health benefit can at best contribute to significant cost-savings in health care or society as a whole, although the budgetary impact from a short-term perspective can be significant. There may therefore be a budgetary barrier that prevents the payer from paying for the new treatment, i.e. a lack of ability to pay. It has been

described as having a cost-effective treatment within the framework of a general willingness to pay but at the same time a problem of financial affordability (i.e. the ability to pay is lacking). One way to solve these budgetary problems may be to identify and select payment models in order to pay for the treatment.

Those involved in the development of new treatments and especially ATMP drugs must take into account both these aspects, i.e. both cost-effectiveness and payer budget constraints, early in the development process.

Value of the treatment

For ATMP drugs, it is perhaps even more important than for traditional drugs to generate evidence throughout the development journey that proves the value of the final product and justifies its price. At the same time, this is a major challenge for many ATMP drugs as they are naturally tailored to a patient, control groups are lacking, and clinical studies are small, which can create great uncertainty and high risk. The degree of uncertainty in the data affects the willingness to pay for the product.

Demonstrating value requires not only evidence that the treatment is working but also economic evidence showing that the cost is acceptable in relation to health benefits and relevant treatment options. This needs to be taken into account in the clinical drug trial and its data collection.

The value of a drug depends on the effectiveness and safety. The value can also be different from different perspectives, for example from the point of view of society or health care. In addition to this, the value also depends on:

1. Which patient group is intended to be given treatment and what characterises that group.
2. Which treatment option to compare the new treatment with. It is necessary to demonstrate the net effect of the new treatment in the selected patient population and that it is worth the cost of the new treatment.

The cost-effectiveness of the new treatment can be difficult to assess in the early stages of the development of a new treatment. However, this issue does not prevent this issue from being taken into account in the early stages and it is important to recognise that the development programme to demonstrate clinical efficacy will not give the whole picture. To demonstrate this value, clinical data often need to be supplemented with additional data that can be used to produce health economic efficacy.

Roadmap

Both academia and SMEs need to have an overall knowledge of the entire development chain for advanced therapies: from idea development, preclinical and clinical testing for market approval to inclusion in the national benefits package or recommendation and finally access to patients. It is essential to be able to plan the time, costs and critical deliveries in the projects. The project has developed a "roadmap" (Figure 1) describing the steps from research to patient on an overall level and from this one can deduce in which parts one needs to keep the health economic aspect in mind. This roadmap also provides a sense and general knowledge of the many elements that may be required to achieve success in the development of ATMP drugs. It is important to ensure that the treatment under consideration is effective enough to be health-economically justifiable. The challenge remains great for healthcare providers to be able to offer patients treatment with ATMP within their budgetary framework.

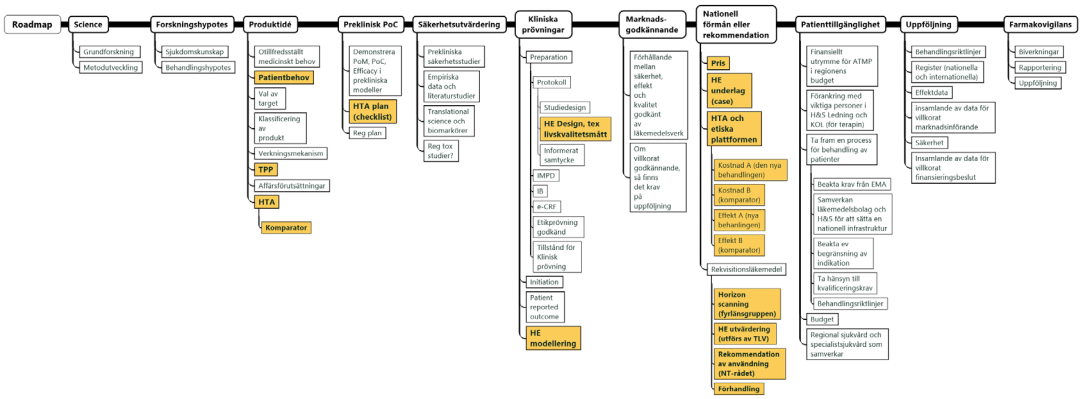

Figure 1 Overview of the project's "roadmap" for ATMP from idea to patient. Yellow boxes are addressed in this report.

Legal aspects

It is important to understand that current legislation usually lags behind technical and scientific developments and that the legal spaces covering ATMP medicinal products are not always designed with ATMP development in mind. Legislation on medicinal products shall ensure that patients have access to safe and effective drugs through the market. Other legislation covering ATMP medicinal products may aim, for example, to protect the privacy of the individual. It is not uncommon to have conflicting objectives between different legislative areas and the developer of ATMP drugs needs to relate to all relevant legislation in order to succeed. In the long run, it is also important that the development of the application of existing legislation be speeded up and,

where appropriate, development of the legislation in order to realise the full potential of ATMPs. It is also important to understand that each ATMP developer is responsible for, and must understand, what regulations apply to their own development and research activities.

To highlight some regulatory issues, a number of questions are presented in Appendix E. The table is set up to clarify the difference between traditional drug development, ATMP drugs (which do not contain versus contain human cells or tissues) and cell/tissue transplants.

The table is based on the project participants' questions, is not all-embracing and is only an example of when better knowledge of regulations could have improved and simplified the development process. The starting point for the table is the legislation that applies in Sweden. Product developers and authorities can use the table as a basis for discussing regulatory interpretations and to enable an understanding of why those who come from the left-hand side (traditional drugs) versus the right-hand side (cell/tissue transplants) in the table experience difficulties when the legislation covering the "other side" come into force. For further guidance on manufacturing, pre-clinical testing and clinical trials, please refer to the regulatory guide developed in another Swelife ATMP sub-project[9].

Hospital exemption

The legislation regulating ATMPs was established as a complement to European legislation regulating drugs[10]. The purpose of the legislation is to ensure product quality and clinical benefit/risk balance with regulatory approval, as well as the conditions applicable to traditional drugs. At the same time, attention was drawn to the fact that there were already established activities and ongoing development projects with well-founded underlying arguments that new legislation should not be disruptive. This procedure had to be supplemented by a regulation to allow medically justified exemptions, which came to be termed as the hospital exemption[11], a Lex specialis of the ATMP Regulation.

Manufacturing permits for hospital exemption allow a hospital, under the responsibility of a treating physician and with the permission of a competent regulatory authority (the Swedish MPA), to manufacture ATMP drugs and treat patients. Note that this is precisely an exception that is not intended to

[9] https://atmpsweden.se/atmp-regulatory-guide/
[10] Directive 2001/83/EC of the European Parliament and of the Council and Regulation (EC) No 1394/2007 of the European Parliament and of the Council
[11] https://www.lakemedelsverket.se/sv/lagar-och-regler/foreskrifter/2011-3-konsoliderad

serve as a scalable and persistent solution. The permit is limited to five years with annual reporting requirements demonstrating that traceability, safety findings (pharmacovigilance) and specific quality standards have been met.

Treatment with ATMP medicinal products before the product has been approved for marketing may be carried out under the hospital exemption or in the context of a clinical drug trial. The hospital exemption provides for the possibility to treat individual patients and the clinical study aims to develop knowledge about the treatment. The conditions for these different options are summarised in Table2.

An example of an ATMP, which in Sweden today is manufactured and given under the hospital exemption, is autologous keratinocytes given in cases of severe burns at Uppsala University Hospital.

Table2. Comparison of requirements between hospital exemption and clinical drug trial for an ATMP. (LV: Swedish Medical Products Agency, EMA: European Medicines Agency)

	Hospital exemption	Clinical trial	Approved product
Manufacturing permit	Yes	Yes	Yes
Risk/benefit assessment	Treating physician/head of operations	LV and Ethics Review Authority	The company applies EMA/LV approves
Protocols that define usage	No	Yes	No
Informed consent	Yes	Yes	No
Adverse reaction reporting	Yes	Yes	Yes
Systematic risk/benefit evaluation	No	Yes	Yes
Systematic risk/benefit reassessment	No	No*	Yes
Time limit	Yes, five years	Aims to lead to an approved product	No

(*) A clinical trial protocol may contain "interim reconciliation" where an external expert group assesses whether it is ethically justifiable to continue, so-called futility analysis.

In the 1970s, a method of in-vitro cultivation and expansion of autologous keratinocytes was developed to treat patients with large skin losses, predominantly caused by burns. Cultured keratinocytes are a strategy that can be taken when the standard treatment with autologous subcutaneous grafts is not enough to cover the wound surfaces. The treatment strategy has gone from growing up shoals of cells (poly-layer) to today preferably applying the cells in a single cell suspension, which means that a larger proportion of undifferentiated keratinocytes can be added to the wound surface. This promotes the ability of cells to proliferate and grow into the skin A skin biopsy is taken, this is treated mechanically and enzymatically to isolate keratinocytes which are then grown in-vitro to the quantity needed for the patient's wound surfaces. The cells are added to the wound surfaces by mixing them in tissue strips and spraying on the wound surfaces. The wound surfaces should be well

prepared both surgically (purified from microbiological contamination) and biologically (well-vascularised with a good wound base). The newly transplanted keratinocytes and the newly formed epidermis they create are fragile and initially need to be well protected from stress. In the small run, however, an adequate (outer) skin coverage is obtained for the patient.

The purpose of the hospital exemption is not to replace a clinical drug trial but to be used as a complement to enable treatment of a few patients where few/no alternative treatment strategies are available.

By the time EU directives and subsequent national legislation were established, the treatment of severely burn-damaged patients had already been in clinical use for several decades, which meant that there was no ethical or moral basis for the usual development of medicinal products with clinical studies. Treatment is done with autologous cells and the patient group is characterised by decision incompetence, which makes consent impossible both for the procurement of starting material and participation in a clinical trial.

Despite the trials made, there is currently no commercial product based on the cultivation of patient-based keratinocytes. This could be explained by the fact that the production is manual and individualised for each patient and thus so far not suitable for automation. A costly manufacturing process and an unpredictable patient group can be the reasons why it is difficult to develop a business model that is economically sustainable.

All in all, the hospital exemption plays a central role in this cell therapy.

Generic target product profiles (TPP) for type cases of ATMP drugs

A TPP is precisely a target profile, i.e. a summary of the attributes (properties) needed for the product to pass both market approval and become commercially viable.

The development work of a drug candidate (including ATMP drugs) and the clinical trials aims to reach market approval. However, approval is not the same as a commercially viable product. There are already a number of examples of ATMP drugs where product quality and benefit/risk balance are established but the willingness to pay is lower than the price that is business-economically justifiable. This means that the aim should also be to develop, while at the same time, a basis justifying a health-economically justifiable price, a price that also provides a business-credible investment calculation.

Crucially, the extent to which convincing evidence is provided for persuading the payer, i.e. the person responsible for financing purchases and patients' access to treatment. Here, the "signal-to-noise ratio" shown in relation to current or future standard treatment is absolutely crucial, i.e. the net effect in relation to the treatment option that the treatment is intended to replace. If we can credibly demonstrate that a large number of quality-adjusted life years (QALYs) gained with the new treatment can be credibly achieved in comparison with a comparable treatment acceptable to the payers in a well-defined patient population, it is likely to have a justifiable financial case. Moreover, this evidence may serve as an argument for persuading investors. Everything must be based on the willingness of the intended market to pay for the additional benefit offered by the product. And this additional benefit can only be established in relation to a relevant comparison called the comparator.

Five different generic target profiles with different designs depending on the type of ATMP drug have been designed (Figure 2). The purpose of the generic cases is to illustrate what a TPP can look like and how it can be used in these types of processes to illustrate that there are different types of ATMP drugs with different challenges in terms of regulatory requirements and health economics conditions. A TPP helps to define which development steps and studies need to be carried out in order to reach the desired target image when launching a product on the market.

A target profile should be based on a well-founded view of the regulatory and competitive landscape likely to apply at the time of market introduction of the product. It is therefore a good investment to provide a basis for a well-founded likely scenario describing the situation at the time the product was introduced. As with any other objective, the target profile should only be changed on the basis of clear changes in the conditions dictated by the rest of the world. A well-founded target profile should not be changed solely on the basis of own progress or setbacks. It is recommended to keep the current target profile separate from other documentation that summarises the current progress documented. The motive for this is that an application in the form of "moving goalposts" is not a good basis for an objective analysis that aims to answer whether one is in a position to create a competitive product.

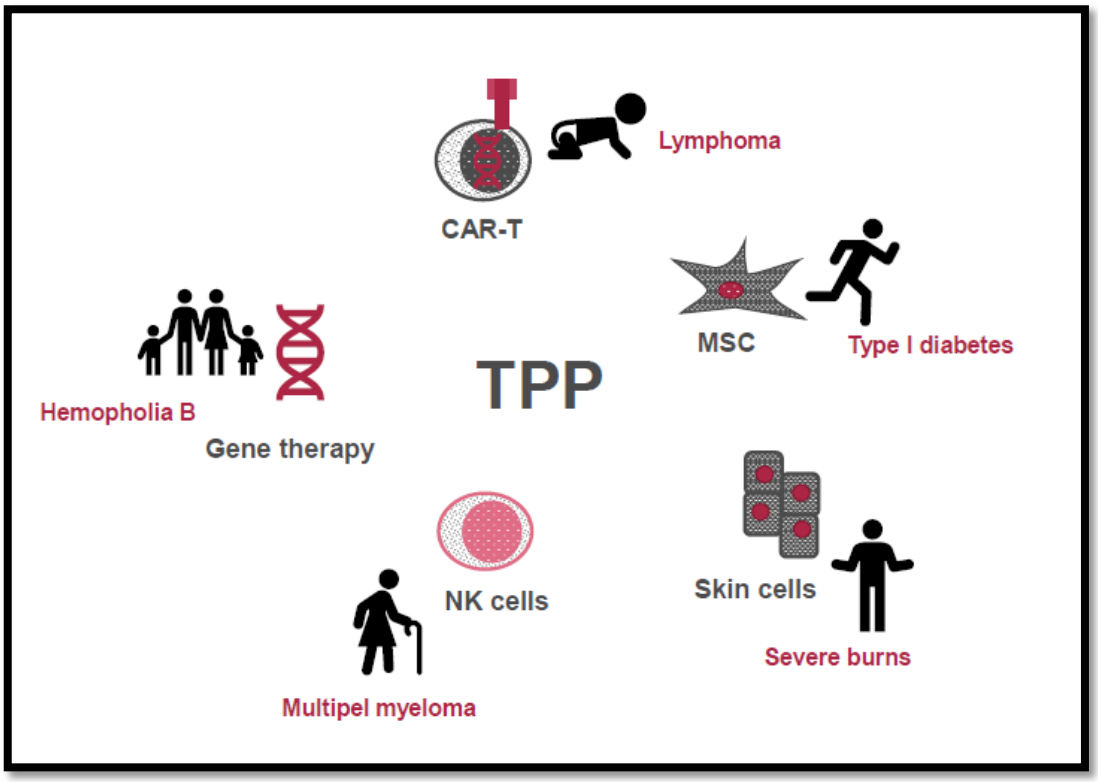

Figure 2. Sketch illustrating the five different generic cases for ATMP (patient and type of product)

In the project, we have chosen to generally highlight the different generic target profiles from the perspective of different stakeholders. Our assessment is that it may be of value to express a form of "customer offering" at different stages of the development of a product. The starting point is a set of basic attributes that are then translated to meet the needs of different stakeholder spheres, in order to evaluate what the product offers. It is primarily a question of addressing the needs of the payer, the patient/investor/product developer, while at the same time meeting the regulatory requirements. A well-researched TPP that is exposed to the payer perspective provides valuable information about the project's potential to be commercially successful. The same TPP, in dialogue with patients or patient representatives, can provide valuable insights into the extent to which the product's attributes meet patients' needs. In addition, a complementary perspective involving remaining development activities and expected costs can provide a general access to financing in dialogue with investors.

Table 3. Five generic target profiles (TPP) for ATMP. (TTR: Time to Relapse, QALY: Quality-Adjusted Life Years, TEP: Tissue engineered product)

	#1	#2	#3	#4	#5
Type of ATMP	Cell Therapy Patient's own cells	Gene therapy	Gene therapy Patient's own cells, genetically modified	TEP (tissue engineering product) Patient's own cells	Cell Therapy Cells from another donor
Type of case	Autologous NK cells, multiple myeloma	Gene therapy, haemophilia B	CAR-T, lymphoma or leukaemia	Allogeneic keratinocytes, severe burns	Allogeneic MSC, type 1 diabetes
Descriptive case-definition	Allogeneic ex-vivo expanded polyclonal NK cells, preserved cytotoxic activity	Adeno-associated viral vector (DNA) gene replaces F8 or F9 mutation of coagulation factor VIII or IX	Genetically modified autologous CAR-T cells, expressing CD19 specific Ig receptor	Allogeneic ex-vivo expanded keratinocytes from skin biopsies	Allogeneic cord-derived, pooled MSC for the treatment of major patient groups
Dosage	Multiple infusions	Single-use treatment	Single intervention	Intensive care	Single or multiple times
HE uncertainties	Expected TTR variation in comparative group	Sustainability for long-term effects	No follow-up after 24 months	Limited patient base, efficacy measurement	Mainly a matter of determining the right cost per QALY

HTA and health economic evaluations in Sweden

HTA description

Health Technology Assessement (HTA), also called a health economic assessment, is a method for prioritising and pricing (so-called value-based pricing) in the health sector. Not all countries use value-based pricing where HTA is an important part, but many countries instead use so-called reference pricing where other countries' prices are an important component. HTA is dominant mainly in the UK, the Nordic region, and Canada, but many more countries use HTA but not fully for pricing decisions but as a priority guide. Appendices F, G, H, and I provide a brief description of several countries' systems and the management of drugs and interventions in health care. Health

economic evaluations play a central role in Sweden for both subsidy and recommendation of drugs, but also in health economic assessments of medical devices.

HTA can be defined as a multidisciplinary systematic way of evaluating the consequences of a treatment or method. HTA means that methods in health care are evaluated from a single medical, economic, ethical and societal perspective (Zethraeus, 2009) In general, it can be said that HTA is a broader approach than both the health economic evaluation and the systematic overview. The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) believes that the systematic HTA overview of effects, risks and costs is complemented by also covering ethical and social aspects which are not included in the health economic evaluation (SBU, Handbook 2010). In the future, however, these two concepts are used synonymously in the report.

Health economic evaluations are based on comparing the costs and benefits of an alternative use of resources. The purpose of the evaluation is to assess the "value for money" of different programmes and interventions in health care and is an incremental analysis, i.e. the cost of intervention or treatment is compared against an alternative use cost where impact differences are also highlighted. It has been described as "The comparative analysis of alternative courses of action in terms of both their costs and consequences in order to assist policy decisions" (Drummond et al. 1997, 2005).

In short, it can be summarised as the best available data summarised and structured in a mathematical model, a so-called health economics model in which the disease and its treatment dictate the structure of the model. The health economic models therefore differ from one therapeutic area to another.

Comparator

It is essential not only to take into account the costs, revenues and health effects of a treatment, but also the comparison option. The comparator can be clinical practice today, no treatment, drug treatment, surgical procedures, cognitive behavioral therapy, etc.

The choice of appropriate comparator is fundamental to HTA, as well as choice of perspective (health perspective, socio-economic perspective). The practice in Sweden is that the comparator should correspond to what is most cost-effective today based on available evidence. In addition, the choice of the relevant health economic model (e.g. decision tree, Markov model, etc.) and time horizon is important.

Cost-effectiveness always applies in comparison to something in a defined patient population, with a certain perspective and may differ depending on the patient population/group receiving treatment.

Ethical platform

Decisions taken in health care are made after a weighting of the matter on the basis of an ethical platform decided by the Swedish Parliament, which applies three main principles:

1. The principle of human dignity: All people have equal value and the same right regardless of personal characteristics and functions of society.
2. The principle of need and solidarity: Resources should be allocated primarily to those areas where needs are greatest.
3. Cost-effectiveness principle: A reasonable relationship between costs and impact, measured in terms of improved health and quality of life, should be sought when choosing between different areas of activity or measures.

Depending on how the drug/technology is used, there are a variety of authorities and actors all in common that the entire ethical platform is applied where cost-effectiveness is of great importance:

TLV

In order for prescription-only drugs to be included in the national benefits package and be reimbursed, the company that has the marketing authorisation must submit a subsidy application to the Dental and Pharmaceutical Benefits Agency (TLV), which, after an investigation, decides on the treatment's reimbursement status. TLV is also responsible for the health economic evaluation of so-called clinic drugs/hospital drugs.[12] How this is done is described below under "More about HTA and the introduction of drugs in Sweden".

The Public Health Agency

The Public Health Agency is a national agency working for better public health. It does this by developing and supporting society's efforts to promote health, prevent ill-health, and protect against health threats. An important task is to develop and disseminate scientifically based knowledge that promotes health and prevents diseases and injuries. In cooperation with other actors, the

[12] TLV has developed both general advice and a handbook aimed at applicant operators;
https://www.tlv.se/download/18.467926b615d084471ac3396a/1510316400272/LAG-lfnar-2003-2.pdf
https://www.tlv.se/system/poc/publikationer/publikationer/2019-12-18-handbok-for-foretag-vid-ansokan-om-subvention-och-pris.html ;

agency develops knowledge and methodological support as well as monitors and evaluates different methods and actions for good and equal health throughout the population.

SBU

The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) is responsible for conducting independent evaluations of methods and interventions in health care, dental care, and methods and interventions in social services and the field of functional conditions/barriers. SBU also developed a method book for health economic evaluations.[13]

The Swedish National Board of Health and Welfare

The Swedish National Board of Health and Welfare works, among other things, to develop national guidelines to support priorities and to provide guidance on which treatments and methods different activities in health care should invest resources in.[14] The National Board of Health and Welfare is also responsible for prioritising which measures in health care should be included in highly specialised care. At present, ATMP drugs are not included in the priorities for such decisions.

The region's collaborative model

Swedish regions have agreed to a model for the national structured introduction of priority drugs. This means selecting, on the basis of horizon scanning, those drugs that are perceived as particularly urgent or challenging in terms of introduction, patients' and society's expectations of equal access to treatment. Cases are handled on the basis of a health economic evaluation carried out by TLV before treatments are considered for recommendation of inclusion by the NT Council (Council for New Therapies) decisions. The collaboration model also includes the Lifecycle- and Market function units , which are staffed by the four largest regions and the NT Council.

Regions are expected to implement the recommendations issued by the NT Council. The NT Council's recommendations may be made conditional by agreements between the pharmaceutical company and the regions aimed at achieving a cost-effectiveness ratio within the framework of established willingness to pay, see further under the section "More about HTA and the introduction of drugs in Sweden".

[13] https://www.sbu.se/sv/publikationer/vetenskap-och-praxis/sbu-beskriver-hur-utvardering-gar-till/
[14] https://www.socialstyrelsen.se/regler-och-riktlinjer/nationella-riktlinjer/

More about HTA and the introduction of drugs in Sweden

Medicines in Sweden can generally be divided into three categories: 1) prescription medicine within the national pharmaceutical benefits package (so-called outpatient drugs), 2) requisition medicines (so-called hospital or inpatient drugs) and 3) over-the-counter medicines that can be purchased in pharmacies or shops.

Outpatient drugs are prescribed to a patient who then buys them at an outpatient pharmacy through the so-called high-cost protection. The regions are responsible for the costs but also receive a special grant (commonly known as pharmaceutical subsidies) from the state via an agreement based on the National Board of Health and Welfare's annual medicine forecast as the basis for reimbursement, both for the benefit costs and for medicines in the treatment of hepatitis C.[15] The medicine contribution is paid monthly with a two-month delay (SOU 2018:89).

Requisition medicines are administered in health care and are directly funded by the regions.

The respective processes for the introduction of requisition and preferential medicinal products are set out below. Although the introduction of requisition and outpatient drugs reflects different decision-making processes and regulations, the boundary between the different categories of medicines has become fluid. What is common is the significant role of health economic evaluations carried out by TLV irrespective of the categories above. Given the characteristics of ATMP medicine use, our assessment at present is that the vast majority of treatment options will fall outside the benefit system and mainly concern requisition medicines.

HTA and the introduction of requisition drugs

The process of introducing requisition drugs consists of the following steps: horizon scanning, national cooperation decision, health economic evaluation, negotiation, recommendation, and follow-up (Figure 3).

In the case of horizon scanning, new medicines, or new indications are identified for existing medicines that may be considered for healthcare. Horizon scanning is carried out within the regions' medicine collaboration model and means that medicines that are judged to have a major impact on healthcare are identified according to certain criteria, after which the scientific

[15] https://skr.se/halsasjukvard/lakemedel/kostnaderlakemedel/overenskommelselakemedelskostnader.26347.html

state of knowledge of these medicines/indications is described in an assessment report.

The NT Council assesses whether the medicinal product/indication should be (or not) of national coordination based on the horizon scanning assessment report or information from the regions nominating a medicinal product for recommendation by the NT Council[16]. For drugs that are requisitioned and used in inpatient care, a health economic analysis needs to be carried out by TLV before issuing a recommendation from the NT Council. TLV's assessment is sent to the NT Council and the companies and consists of an examination of the existing evidence base as well as the results of TLV's and usually the companies' own analyses. In the case of requisition medicinal products subject to nationally orderly introduction, TLV is given the task of delivering a health economic analysis which then serves as a basis for the evaluation leading up to the recommendation of the NT Council. The recommendation shall be based on the ethical platform that the Swedish Parliament has decided for priorities in health care and where cost-effectiveness is an aspect together with the human dignity principle and the principle of need and solidarity. After that, negotiations between the pharmaceutical company and the regions/delegation can be conducted with the aim of creating an agreement, so-called bipartisan agreement. Based on the outcome of the negotiations and the TLV report, the NT Council sends its recommendation to the regions published on the nationally coordinated implementation website[17]. The recommendation may be positive, negative or cautious. The NT Council makes recommendations for implementation which are then implemented on the basis of the economic conditions of the regions.

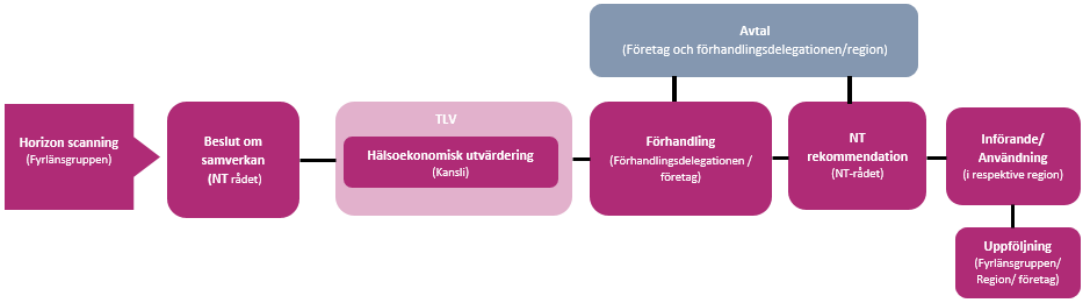

Figure 3. Introduction of requisition drugs.

[16] The NT council. 2020. Decision on cooperation taken 02/03/2020 from https://janusinfo.se/nationelltordnatinforande/saarbetarvi/arkiv/beslutomsamverkan.5.4771ab7716298ed82ba97add.html

[17] https://www.janusinfo.se/nationelltordnatinforande/rekommendationer.4.728c0e316219da813569b2c.html

Reimbursement application

The process of including a medicinal product in the pharmaceutical benefits package begins with the pharmaceutical company's subsidy application to TLV (Figure 4). The application is structured in accordance with the guidance and guidelines published on the Authority's website. TLV conducts a health economic assessment based on the dossier submitted to determine the price and decide on reimbursement status. Medicinal products may be granted a general coverage, limited coverage or rejected. It is worth mentioning that TLV's decision on price and reimbursement is open to appeal. Here, too, great emphasis is placed on cost-effectiveness. There may also be negotiations for preferential decisions, known as tripartite consultations. Both regions and companies have the right to request consultation with the TLV Board for decisions.

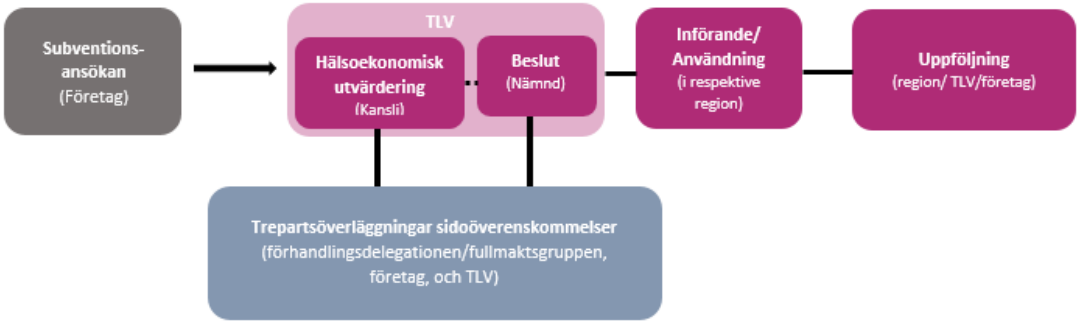

Figure 4. Introduction of preferential medicinal products.

Tripartite deliberations

Decisions on the following paragraphs may often be the subject of tripartite consultations between companies, regions and TLV[18]. These are consultations in which TLV contributes to the interpretation of the health economic base and in which the regions and companies are the negotiating partners in what aims to lead to an agreement on acceptable price as a basis for a recommendation that the drug can be introduced into Swedish healthcare:

- Drugs with significant uncertainty as to the underlying efficacy (e.g. duration of treatment, selection and size of relevant patient group, duration of treatment effect, etc.)
- drug targeted at diseases of high severity or rare diseases

[18] https://www.tlv.se/lakemedel/utveckling-vardebaserad-prissattning/fordjupad-samverkan.html [retrieved 12/02/2020]

- drug with a high budgetary impact

The purpose of the deliberations is to address uncertainties in the evidence base, to share risk between the company and the region, and may result in a side agreement and a preferential decision with or without restrictions or follow-up conditions. The restrictions may apply to specific duration of treatment, patient group, etc. Although tripartite consultations have not always succeeded, they have played an important role in decisions around drugs for hepatitis C, cancer and various inflammatory diseases[19]. Such agreements play an important role in keeping down the increase in public pharmaceutical costs, not least because they define conditions and the number of pay back[20].

Follow-up

The follow-up is based on conditions established during the tripartite negotiations by TLV or the regions and may involve further data collection or the conduct of a study. Reimbursement decisions from TLV may also be conditional on follow-up.

HTA practices

There are a number of manuals and general advice on how to properly assess health economic evaluation in order to be transparent and answer the question of whether intervention is cost-effective.

The Swedish subsidy authority TLV has developed general advice TLVAR 2017:1, here is what should be included in a health economic analysis[21]. In short, this means that TLV believes that the following should be taken into account:

- What costs and revenues should be included (i.e. choice of perspective for the analysis)?
- Choice of comparison option, comparator
- Choice of patient group
- Analytical method: i.e. both the choice of the type of model to be used and the most appropriate analytical method e.g. cost-effectiveness analysis, cost minimisation analysis.

[19] https://www.tlv.se/om-oss/press/nyheter/arkiv/2016-12-15-uppdaterade-subsidysbegransningar-for-hepatit-c-lakemedel-efter-trepartsoverlaggningar.html [retrieved 12/02/2020]

[20] https://www.tlv.se/download/18.780dcd01163ea3f00899a2aa/1529050689398/180615_uppfoljning_lakemedelskostnader.pdf [retrieved 12/02/2020]

[21] https://www.tlv.se/om-oss/om-tlv/regelverk/allmanna-rad.html

- All relevant costs (including the societal perspective), both direct and indirect costs should be described. This also includes cost reduction if this is the case, as well as the price of drug treatment and costs for various care interventions that are carried out.
- Health outcomes have two dimensions, quality of life and length of life. This is usually summarised in the measure of quality-adjusted life years called QALYs. There are a number of different methods for measuring and evaluating quality of life and it is of great importance that this is captured and measured in order for an evaluation to be possible.
- The time horizon should cover the period during which the main health effects and costs arise.
- Both costs and health effects should be discounted.
- Sensitivity analyses are carried out to address uncertainties in assumptions and parameters.
- Transparency in the model is of great importance. Methods and assumptions made should be clearly and easily followed.

The SBU has developed a method book for health economic evaluations that can also serve as advice in the development of a health economic analysis.[22]

ISPOR (International Society for Pharmacoeconomics and Outcomes – an organisation for health economists and others active in this industry) has also made Modelling Good Research Practices public in a handful of reports (Caro et al. 2012).

The project has developed a checklist (Appendix A: HTA Checklista) and guidance on how to use it (Appendix B: Vägledning HTA Checklista) to support ATMP drug developers (SMEs) to assess value and build a business model for communication with financiers. We also see that this checklist is valuable for the innovation support system in dialogue with start-ups and SMEs.

Generic target product profiles and consequences for HTA

We have created five different types of generic target profiles to use as a basis for how a product should be documented and characterised in order to get through different decisions on the way to a commercially viable product. The five types of cases are chosen to illustrate different types of ATMP drugs, which in turn have significantly different characteristics.

[22] https://www.sbu.se/sv/publikationer/vetenskap-och-praxis/sbu-beskriver-hur-utvardering-gar-till/

A brief summary of the five generic cases for ATMP drugs produced by the working group is set out in Table 3 and a detailed summary can be found in appendix C.

ATMP and value-based price setting

ATMP treatments have the potential to lead to a "cure" or absence of symptoms or disease activity. Treatment programmes can be associated with treatment for a short period of time, but at the same time have very long-lasting lasting positive effects on both health and the costs of the health system and other society. This leads to challenges in determining clinical efficacy and cost-effectiveness and how the expected high values generated can be paid for over a short period. This leads to two major challenges with ATMP drugs: (1) How can we demonstrate the value of ATMP treatment at an early stage in the development of the new treatment? (2) How can a payment model be designed for a processing that can be given on a single occasion or for a short period of time and at the same time generates a very large value accumulated over the long future?

Experience so far has shown that pricing for ATMP drugs may be of a different magnitude than we are used to concerning pharmaceuticals. Table 4 shows a summary of several current ATMP medicines (January 2020) and the list price in the USA.

Table 4. Several current ATMP, January 2020.

Type of ATMP	Disease/indication	Cost per treatment
Gene therapy	Haemophilia	1,5-3 million USD
Gene therapy	Spinal muscular atrophy	2,1 million USD
Gene therapy	Beta-thalassemia	1,8 million USD
Genterapi (CAR-T)	Acute lymphoblastic leukemia / lymphoma	0,373 – 0,475 million USD
Gene therapy	Hereditary retinal disease (mutation in the RPE65 gene)	0,425 million USD

Abbreviations: CAR-T: Chimeric antigen receptor T cells

Cohen et al. (2019) and Chambers et al. (2019) have compiled published cost-effectiveness analyses for ATMP medicines. The compilation is based on seven ATMP medicines in nine different analyses. The health benefits have also been calculated for 46 biological and 127 conventional medicines approved by the

FDA between 1999 and 2015, which were found in TUFT Institute's database (Tufts Center for the Study of Drug Development). The results show that health benefits per average patient for cell and gene therapy far exceed the corresponding health benefits per patient for biological and conventional medicines. For the nine ATMP analyses, the health benefits have been calculated at an average of 5.78 QALY per patient. For biological medicines, 0.43 QALY and for conventional medicines, 0.49 QALY per patient.

According to calculations by Cohen et al. the consequences that generate value for ATMP can vary from a large increase in survival-rate and quality of life 11.77 QALY per patient from Zolgensma for the treatment of spinal muscular atrophy (SMA) and 5.17 - 8.18 QALY per patient from Kymriah for acute lymphoblastic leukaemia, to a low increase in survival-rate and quality of life (e.g. 1.3 QALY per patient from gene and cell therapy for haemophilia). However, gene and cell therapy for haemophilia can generate cost savings for reduced or non-existent use of FVIII preparations (Factor eight preparations), which at present can amount to more than one million SEK per patient and year for boys for a lifetime.

This shows that the prices set for several of the ATMP medicines are not unreasonable from a value-based pricing perspective, see Appendix D. Since the health benefits can be much greater for ATMP medicines and the cost savings can also be significant, it can in many cases justify a much higher price than can be justified for conventional and other biological medicines. The other characteristic that can also justify a high price for ATMP medicines is that often only a single treatment is required to provide the health effect. For biological and conventional treatments there are often continuous treatments or treatments over a long period time and the price per treatment can be relatively low even if the cost for a longer period of treatment is high.

HTA for ATMPs

Prior to the health economic analysis and the analysis of the issue of affordability, we have constructed three hypothetical examples: one conventional medicine and two ATMP medicines, based on the five generic target profiles for ATMP medicines developed by the working group. For each of the three hypothetical examples, we have expressed health benefits in QALYs (quality-adjusted life years), cost savings in SEK, and patient populations, in incidence and prevalence, respectively.

Table 5. Three hypothetical medicines, one conventional and two ATMPs with substantial health benefits and cost savings per patient.

	Conventional medicine	ATMP associated with a large increase in OS	ATMP associated with substantial cost savings
Current treatment:			
Overall Survival (OS)	70 years	30 years	70 years
Quality of life (QoL)	0.8	0.8	0.8
QALYs (OS x QoL)	56	24	56
Current treatment, Cost / patient	0 SEK/year	200,000 SEK/year.	1 million SEK/year
Total cost	0 SEK	6 million SEK	70 million SEK
New treatment cost (supplement)	800,000 (for 10 years 60-70)	16 million SEK (at year 0)	20 million SEK (at year 0)
OS	72.	60 years (+30)	72.
New QALYs	57.6 (+1.6)	+24.	57.6 (+1.6)
Cost savings	0 SEK	6 million SEK	70 million SEK
ICER in million SEK per gained QALY	(0,8-0,0)/(57,6-56)=0,5	(16-6)/(48-24)=0,42	(20-70) / (57,6-56)=dominant (cost savings with maintained or improved health)

Abbreviations: ICER: Incremental cost-effectiveness ratio; OS: Overall survival; QALY: Quality-Adjusted Life-Years; QoL: Quality of Life

Conventional treatment

The first hypothetical medicine in Table 5 (the conventional one) is to be compared to an existing situation: the patient's average lifespan is 70 years with a quality of life corresponding to 80 percent of a fully healthy individual. The expected number of QALYs for the individual will then be 70 years x 0.8 = 56 QALYs.

The new treatment is estimated to provide 2 additional life years at a cost of 800,000 SEK per patient. The quality of life is unchanged so the increase will be 2 years x 0.8 = 1.6 QALYs. Therefore, we will have an Incremental Cost-Effectiveness Ratio (ICER) of 0.5 million SEK per gained QALY (800,000 SEK / 1.6). This is a level which, in most cases, should be acceptable for TLV, for example.

Substantial increase in survival

The second hypothetical example represents a new ATMP medicine that provides substantial health benefits in a patient that has a life expectancy of only 30 years with a quality of life of 0.8. Therefore, the expected number of QALYs will be 30 x 0.8 = 24. The patient is estimated to cost 200,000 SEK per year during their 30 years of life and the total cost per patient will therefore be 6 million SEK for their entire lifetime.

The new ATMP medicine increases life expectancy to 60 years, i.e., an increase of 30 additional years of life. The quality of life remains the same therefore we will have improved health corresponding to 24 QALY. In this case we now avoid the current annual treatment cost of SEK 200,000 per patient and achieve a cost savings of 6 million SEK per patient. The net cost for the new treatment will be 16-6 = 10 million SEK. Thus, we have an ICER of 10 million SEK / 24 QALY = 0.42 million SEK per gained QALY.

Large cost offset

The third hypothetical example represents patients who currently have a life expectancy of 70 years with a quality of life of 0.8, have an expected QALY of 56, and a cost of 1 million SEK per year for treatment during all 70 years. The current total treatment cost for the entire lifetime is 70 million SEK. The new treatment does not affect the quality of life, but gives 2 additional life years. The largest benefit of the new treatment is that the entire current long-term treatment cost can be saved. The new treatment is estimated to cost 20 million per patient for a single occasion. Therefore, we have both a saved total cost per patient 20 - 70 million SEK = 50 million SEK in savings and an increase of 1.6 QALY. ICER then dominates because we gain in both cost savings and health.

The result is that we have the most advantageous ICER in the third case because it is dominant. The second best ICER we have is in the second case where we have a substantial health gain. We have our worst ICER, even if it could be considered acceptable, with the new conventional medicine.

Consideration of incidence and prevalence

In the following table, we will analyse what occurs to our hypothetical medicines when we assume that there are a number of patients to treat, i.e. when we also consider incidence and prevalence.

Table 6. Conventional medicine - Prevalence and budgetary impact

	New treatment supplement	**Best Supportive Care (BSC)**
Cost million SEK	800 000 (10 years)	350 000 (10 years)
QALY	57.6	56
LY	72	70
ICER (SEK)	500,000	
# patients in Sweden	1000	
Total budgetary impact of the new pharmaceutical product over 10 years (national)	800 million SEK	
The first year's budget impact (national)	80 million SEK	
First years' treatment costs, spread out annually over 5 years (national)	N.A.	

Abbreviations: BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; LY: Life-years; QALY: Quality-Adjusted Life - Years: Quality of life

An incremental cost-effectiveness ratio, i.e., a cost per gained QALY of 500,000 SEK is usually accepted by prize and subsidy authorities in Sweden and several other countries.

A total annual budget increase of 80 million SEK per year for the entire country is fairly evenly distributed across different regions is often possible to manage. Considering that we have a prevalence of 1000 patients, which will therefore have an increased burden on the budget, the introduction of a new conventional treatment will not be unaffordable. The reason is that the cost of the new conventional treatment is spread out evenly over a ten-year period.

Before we analyse the budgetary implications of the new hypothetical ATMP medicines, we will discuss what value-based pricing of ATMP medicines may imply. In short, value-based pricing means that the price for a new technology must be set in relation to the value that the technology adds in addition to the current treatment. For a more detailed discussion of value-based pricing, see Appendix D.

In this hypothetical case with a new ATMP medicine, the value lies mainly in the very large health benefits. The health benefits consist of an increase of 30 years in life expectancy with a quality of life per year of 0.8 (i.e., 80% of full health), which gives a supplement of 24 QALY.

There are divided opinions about how much health benefits should be worth. Several values of a QALY appear in Swedish and international literature. A common value applied by the TLV and the NT Council in Sweden is that a QALY should be valued at less than 1 million SEK, but that 1 million SEK is acceptable if the health condition being treated is very severe. It may also be possible to accept a valuation of up to 2 million SEK per QALY if it is also a very rare condition that is being treated.

In Table 7, we have illustrated the price of the treatment that could be accepted if the health benefit were valued at 1 million SEK and 3 million SEK per QALY, respectively. If the company has set a price of 16 million SEK on its ATMP medicine, it appears that an even higher price could be accepted by the payer or the price and subsidy authority, provided that the health benefits are valued at 1 and 3 million SEK, respectively.

Table 7. ATMP medicine with large health benefits and a value-based pricing system.

	New ATMP large increase in OS	BSC	Gradual
Cost (million SEK)	16	6	+10
QALY	48	24	+24
LY	60	30	+30
ICER (SEK)	417000		
Value-based price for 1 million SEK per QALY	30 million		
Value-based price for 3 million SEK per QALY	72 million SEK		

Abbreviations: BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; LY: Life-years; QALY: Quality-adjusted Life-Year; QoL: Quality of Life

In the following table, we analyse the budgetary implications of the hypothetical ATMP medicines. The first example is expected to provide very large health benefits in terms of large increases in QALY. This means that the health benefit is a combination of an increase in survival and in quality of life. The comparator, BSC has a lower increase in survival and a lower quality of life where the associated costs are more evenly distributed over patients' lifespan.

Table 8. New ATMP - Large increase in longevity - prevalence and budgetary impact.

	New ATMP large increase in OS		BSC	Gradual
Cost (million SEK)	16		6 (0.2/year)	+10
QALY	48		24	+24
LY	60		30	+30
ICER (SEK)	417000			
# patients in Sweden	10	100		
Total budgetary impact of the new pharmaceutical product over 10 years (national)	100 million SEK	1 000 million SEK		
The first year's budget impact (national)	158 million SEK	1 580 million SEK		
The first years' treatment costs, spread out annually over 5 years (national)	32 million SEK/year	320 million SEK/year		

Abbreviations: BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; LY: Life-years; QALY: Quality-adjusted Life-Year; QoL: Quality of Life

The new ATMP treatment in the example above gives an incremental cost-effectiveness ratio of 417,000 SEK, which is usually acceptable. If we assume that only 10 patients are treated in a total population of 100 patients, the budget effect will be 158 million SEK, which can be affordable if the patients are evenly distributed across the country. If, on the other hand, we plan to treat the entire population, we will have a budget impact corresponding to 1,580 million SEK, which is probably difficult to finance.

If we spread out the payment over five years, it will be 32 million SEK per year in the first case and 320 million SEK per year in the second case if we assume that everyone is treated. However, spreading the payment out over 5 years is not compatible with the Local Government Act, which allows a maximum of 3 years of annual instalment unless special reasons can be invoked (SFS 2017: 725, Chapter 11).

Table 9. Large cost savings - prevalence and budget implications.

	New ATMP large increase in OS		BSC	Gradual
Cost (million SEK)	20		70	Save 50
QALY	57.6		56	+1.6
LY	72		70	+2
ICER (SEK)	Dominant			
# patients in Sweden	40	400		
Total budgetary impact of the new pharmaceutical product over 10 years (national)	Save 2 000 million SEK	Save 20 000 million SEK		
The first year's budget impact (national)	760 million SEK	7 600 million SEK		
The first years' treatment costs, spread out annually over 5 years (national)	152 million SEK/year	1 520 million SEK/year		

Abbreviations: BSC: Best supportive care; ICER: Incremental cost-effectiveness ratio; LY: Life-years; QALY: Quality-adjusted Life-Year; QoL: Quality of Life

A new dominant ATMP treatment means that we can expect both cost savings and health benefits. The first year's budgetary impact corresponding to 760 million SEK for a treatment of 40 patients is perhaps acceptable. However, a strategy in which all 400 cases are processed in one year has a budgetary impact corresponding to 7,600 million SEK, which is hardly possible without major redistributions of resources in the healthcare sector.

An annuity of 152 million SEK per year in a risk-sharing program is probably preferable. However, whether an annuity of 1,520 million SEK per year is possible is not at all certain. Annuity over 3 years would have a budgetary impact corresponding to 253 million SEK in the first case with treatment of 40 patients and in the second case where 400 patients are treated, we would have a budget effect corresponding to 2,533 million SEK per year. This would probably be associated with major adjustment problems or would involve significant borrowing.

First of all, we see that we will have a budget problem in both cases with the introduction of new ATMP medicines as soon as we consider treating an entire

population; the larger the population, the larger the budget problem. We also see that we have a budget problem for the ATMP medicines even though they are expected to provide large cost savings. This is because the initial cost of treatment with ATMP medicines occurs immediately, while the cost savings, although many times greater than the cost of the ATMP treatments, do not occur until the future.

It is also obvious that with the assumed long-term perspectives, we will have great uncertainties in the outcome regarding both the QALY increase and the cost savings. There are two uncertainties about the clinical outcome that are important. In part, the degree of probability in which the patient responds to the treatment and partly that the effect of the treatment lasts over time for those who did respond to it. In addition to this clinical uncertainty, there is also a structural uncertainty that is not related to the new ATMP treatment, but that has to do with what the alternative treatment will look like in the future. In our examples, we have assumed that the current treatment practice and associated costs will last over the entire period considered. In reality, this would be a very unlikely assumption because we can often expect treatment routines to evolve, relative prices to change, and new competing therapies to be introduced.

It is from this perspective that we will see new innovative payment models that can serve as tools for dealing with both the budget problem and the uncertainty problems. There are several types of innovative payment models, all of which can be linked to an agreement between producers and healthcare payers. The payers may of course have other interests than the producer, but it is likely that both want to be able to reduce the budget problem and the uncertainties in the valuation. Performance-based payment models can help address both of these difficulties. However, there are several performance-based payment models. A few of these are described below.

Payment models

A payment model is an agreement between marketing authorisation holders and payers for the purpose of making a treatment available under specific, agreed upon terms. The terms take into account the uncertainties in the evidence base and the health economic analysis, as well as the payer's need to manage budgetary impact when introducing the new treatment. Payment models can be structured in different ways and categorised into non-performance-based and performance-based variants (Grimm et al. 2016, Carlson et al. 2010, Gerkens et al. 2017, Ferrario and Kanavos 2013).

Non-performance-based payment models

The non-performance-based payment models can have different purposes, including managing the uncertainty concerning budgetary effects for the payer and making costs manageable and predictable within the budget framework. Such models usually require no further data collection / analysis and can be implemented at both patient and population / cohort level as reported in Table 10 below.

Table 10. Non-performance-based payment models.

Implementeringsnivå					
Patient		**Population/Cohort**			
1	**2**	**3**	**4**	**5**	**6**
Discounted treatment initiation	Utilisation cap	Fixed cost per patient	Discounts	Expenditure ceiling or cap	Price-volume agreement
The company finances the cost of the first treatment, i.e., the initial treatment period is reimbursed at less than the stated price for each patient	The company and the payer implement a price reduction after an agreed treatment period for each patient	Reimbursement is based on a fixed payment regardless of the number of treatments per patient	The negotiated price differs from the list price	Limits on total expenditure without restrictions on quantity received	Unit costs are reduced after an agreed number of doses / volumes has been reached

Sources: Grimm et al. (2016), Wenzl et al. (2019)

The agreements may consist of the price being reduced through discounts or the total cost being limited by the price being reduced after a certain volume has been exceeded. Examples of these include price-volume agreements and expenditure ceilings.

These agreements are normally kept confidential in order to enable the price reduction without affecting the list price used in reference pricing (Persson et al., 2016). However, this has been criticised for presenting the risk of undermining international reference pricing in Europe. Another problem with these agreements is that they send signals to the industry about the value of innovation and there is a risk that the focus shifts from new and innovative therapies to therapies that lead to incremental improvements. An additional problem with many of these models is that their design has been based on the adoption of repeated treatments, unlike ATMP treatments which often involve one-time or only a few treatment sessions. The latter characteristics create a non-negligible irreversibility problem for payers in the event that new evidence

becomes available that would require treatment interruption (Towse et al., 2019). Similarly, these models can potentially increase the risk of bias towards single-use treatments, by setting prices that may prove inappropriate in cases where the treatments are found to have a better or (more) lasting effect in the longer term.

Volume-based agreements aim to reduce the total cost for the payer by limiting access to a subpopulation that receive the highest value from the medicine. For example, price and payment decisions can be conditional on compensation being paid to the companies only for patients of a predetermined group. This can be defined on the basis of patient characteristics, which indicate that the patients' issues exceed a certain degree of severity or with the condition that the patients have first tried one or more treatments. These payment models are called populations (indications) –based and specifically aim to ensure cost-effective use.

One problem with limiting the availability of new therapies is that there is a loss of health. The therapies have the potential to improve the health of more patients than those who receive them. For ATMP medicines, such as gene therapy, it can be difficult to identify a subpopulation because they already refer to a small patient population. In addition, it can be controversial to deny patients access to curative treatments. Finally, there is a risk that the incentives for innovation of new and innovative medicines will be negatively affected as the application of the therapies will be limited and unpredictable.

The above non-performance-based models suggest different solutions to the ATMP problem of affordability and predictability for payers and treatment uptake for companies. The complexity of ATMP products and the uncertainties in the evidence base of the treatments mean that individual non-performance-based solutions may not be completely optimal. Agreements that take into account whether patients receive sufficient and long-term clinical benefit / effect could be more appropriate (Towse et al. 2019). Such solutions would enable a much better assessment and distribution of risks and ensure that payments are made for agreed results in a more accurate and transparent manner.

It should be noted that an evaluation of the effects of performance-based payment models has not been possible due to the confidentiality in the negotiations between the company and the payer (Antonanzas et al. 2019; Wenzl et al. 2019). In addition, the collection of outcome data required for a more systematic evaluation of ATMP products in clinical practice may be burdensome for the healthcare system and some countries have changed their

regulations to limit reimbursement to certain indications or patient groups until further evidence becomes available (Makady et al. 2018; Gerkens et al. 2017; Powells et al. 2019; Wenzl et al. 2019). The report takes into account these factors and the experience of other countries and proposes a payment model based on outcome measures that are clear, unambiguous, clinically relevant, and that can be mutually agreed upon between interested parties (Annemans et al. 2020; Drummond, 2015). The recommendation also reflects the agreements chosen for the introduction of Yescarta and Kymriah in five major European countries, which are discussed further below. In addition, Sweden has good access to various registers and great opportunities for follow-up. TLV (2020) has recently presented a report that shows the potential for such arrangements. The report (Pilot 1) shows that it is possible to collect information concerning pharmaceutical use and to automate the reporting of data on prescription medication from the regional data warehouses to the national patient register without burdening healthcare staff. In addition, the report shows that an evaluation of a treatment's long-term effects in everyday clinical practice can be carried out using various existing registers, as well as methods that can check for confounders and selection bias in case patient groups have not been randomised.

Performance-based payment models

Performance-based payment models primarily aim to deal with uncertainty when introducing a new therapy by making the payment conditional on showing effect in clinical practice. This can be done by paying back the payment received if it is not possible to prove effect or that further processing takes place on the condition of proving effect. The effect can be measured at group or individual level and involves systematic collection of data reported in Table 11 below.

Performance-based payment may mean that the company agrees to bear the costs of treatment for those patients who do not reach the agreed treatment goals or that the company pays for an alternative treatment that has previously been shown to work satisfactorily for those who do not achieve the agreed upon treatment goals with the company's product. Similar arrangements were made during the introduction of Velcade for multiple myeloma treatment in the UK in 2009.

With conditional treatment and payment, the treatment continues as long as the treatment goal is achieved. If this is not achieved, the treatment is interrupted, and payment is not made to the producer. An example may be the conditional treatment with Etanercept only for patients who respond to

treatment, Australia 2005. Another example is treatment of SMA 2 patients with Spinraza in Sweden 2019.

Table 11. Performance-based payment models.

Implementation level				
Patient			**Population**	
1	**2**	**3**	**4**	**5**
Coverage with evidence development (CED)	Payment-by-result (PbR)	Conditional treatment continuation (CTC)	Coverage with evidence development (CED)	Payment-by-result (PbR)
Treatment costs are only covered for patients who join a study Remuneration / subsidy is extended or withdrawn or prices are adjusted based on the study results	Payment is made only if the patient reaches a predetermined and agreed upon goal Payers can withhold payment (in whole or in part) or receive a refund for patients who do not respond nor receive free additional products to treat subsequent patients	Treatment is continued only for patients who achieve a predetermined response to treatment The company provides products free of charge or at a discount for patients who do not achieve the agreed upon outcome	Treatment costs are only covered for patients who join a study Remuneration / subsidy is extended or withdrawn or prices are adjusted based on the study results	Payment due to achieving an agreed upon result in the treated cohort Payers can withhold payment in full or in part until the result is achieved, receive a full or partial refund if the result is not achieved, or receive free additional products

Source: Wenzl and Chapman (2019)

Compensation linked to evidence documentation, Coverage with Evidence Development (CED), involves data collection related to long-term effectiveness. There are many examples from Sweden before 2010 and agreements between LFN (TLV's predecessor) and companies regarding CED. Some examples are treatment of type-2 diabetes with insulin glargine (LFN 2003), treatment of schizophrenia with Risperdal Consta, and advanced Parkinson's treatment with Duodopa (Asseburg et al. 2012; LFN 2003; LFN, 2004; LFN, 2007; Willis et al. 2010; Willis et al. 2010).

The CED study on insulin glargine was initiated because the randomised study focused on reducing the risk of hypoglycaemia. LFN stated that patients could change their behaviour and take part in the benefit in the form of lower or higher HbA1C (a measure of the average blood sugar level that should be low to avoid disease complications). HbA1C is more important for determining the

value of glargine treatment than the change in hypoglycaemic risk and LFN therefore wanted to see RWE (Real World Evidence). The CED study that LFN requested and that the company conducted provided this information and LFN was able to make a decision on a better basis.

The example of Risperdal Consta also concerns patients' behaviour in the real world. In this case, it was LFN who wanted to see if better compliance with the long-acting Risperdal Consta really led to reduced re-onset and less care days. CED was implemented in several countries, including in Sweden, Finland, and Germany. In all cases, the authorities received more evidence that could improve external validity and not just rely on internal validity and protocol-driven results.

The example including Duodopa is another case where the randomised study provided protocol-driven costs and a far too short time interval that needed to be supplemented with data not available at the time of application, but which took several years to collect. CED enabled a faster introduction of a therapy (LFN 2004; Willis et al. 2010). Advanced Parkinson's treatment with Duodopa is a treatment method that was later not questioned, but was judged to be underused according to the Swedish National Board of Health and Welfare's latest guideline work for Parkinson's disease (Swedish National Board of Health and Welfare, 2016).

Outcome-based agreements presuppose that the parties agree upon an outcome-based measure and the time period in which it is to be measured. Another condition is that there are resources to follow up and document outcomes.

Performance-based agreements have been criticised for being too expensive and complicated to implement (Raftery, 2010). Other problems with outcome-based agreements are that they can create incentives for the care provider to treat more patients than necessary because no effect is required to be paid, or incentives for the company to set an extra high initial price to take into account expected reduced income in the case of no effect. Withdrawal of a therapy that does not work can also be perceived as controversial and give rise to protests among patients.

Innovative payment arrangements in connection with the properties of ATMPs

The properties of ATMP drugs are characterised by a short treatment period, often only a single treatment. At the same time, the effects of the treatment are expected to last for a very long time. The effects of ATMP treatments have also been shown to be much greater than those of treatment with conventional

medicines. Calculations show that health benefits for cell and gene therapies (5.78 QALYs) are significantly greater than conventional treatments (0.49 QALYs) (Cohen et al. 2019; Chambers et al., 2019). Such large health benefits in combination with single treatments provides conditions for much higher prices per treatment with ATMP medicine than for continuous treatment with conventional medicine. At the same time, there will be great uncertainty about how long the health effects will last and for how many patients they will provide lasting results for.

High prices for treatment in the short term pose a challenge for budget systems that are not designed for great flexibility. Payment of compensation for treatment that is associated with great uncertainty about the future is an additional challenge[23].

The development of innovative performance-based payment models for ATMPs

Two ATMPs, Yeskarta and Kymriah, both CAR-T medicines for the treatment of cancer, are reimbursed via performance-based payment models in five major European countries, i.e. France, Italy, Spain, the United Kingdom, and Germany (Jørgensen et al., 2020). In France and the United Kingdom, funding is linked to Coverage with Evidence Development (CED). In France, there is an annual assessment of the outcome and a possible adjustment of compensation if the goal is not met. Goal fulfilment is linked to factors such as patient survival, remission, progression, and side-effects. In the UK, future price adjustments are linked to long-term follow-up of patient survival and the possibility for patients to undergo stem cell transplantation.

In Italy and Spain, the payment for the treatment is divided into three and two occasions respectively (annuity payment with follow-up conditions). In Spain, follow-up is linked to survival and complete response. Italy's follow-up conditions have not been highlighted in public documentation.

In Germany, the agreement includes an outcome-based discount linked to patient survival.

One interpretation of the agreements reached in the five major European countries is that outcome-based payment models for ATMP medicines have

[23] It should be noted that in healthcare systems where patients can choose and change insurance companies, these characteristics mean that incentives to provide treatment are reduced. An insurance company naturally has limited incentives to take a significant cost if there is a risk that the patient will change insurance company within a short time. This problem is significant in countries where patients regularly change insurance companies, but occur, albeit to a lesser extent, also in systems where financing is linked to the region where the patients reside. These challenges pose risks that new effective ATMP medicines will not be utilised and will not be available to patients to the desired extent. Innovative payment arrangements can be a way to reduce this risk and enable a rapid uptake of cost-effective treatments, while at the same time sending signals to those who develop ATMP medicines that there are financing opportunities.

been chosen in an effort to deal with the uncertainty in the clinical outcome. For those countries that have chosen annuity payment with follow-up terms, the budget barrier has been important to overcome. For three of the countries, a simple follow-up measure has been important and they have therefore refrained from entering into agreements with CED that are associated with more advanced follow-up data.

The future will prove which payment models will include the new ATMP medicines that are now being assessed by HTA organisations in Europe. If performance-based payment models are chosen, there are several possible performance measures to base payments on. Payment can be linked to results and is paid at any time interval only if certain results are achieved. A current example of a payment model for new ATMP medicines is:

- Zynteglo in the treatment of beta-thalassemia - Payment is proposed as long as treated patients are not dependent on transfusions (Persson et al. 2020)

ATMP medicines do not involve discontinuation of treatment, as this is usually given only once. However, it may be a question of not reimbursing the producer if the treatment does not achieve its goal.

The uncertainty concerning how alternative standard treatments or any newly introduced competing treatment works and what they cost must be resolved in another way. This is a structural uncertainty that cannot be linked to outcome measures for patients treated with the new ATMP medicines. Rather, the structural uncertainty may be addressed with the possibility of renegotiation when and if new competing effective treatments come in to play or when the price for existing competing treatments changes, for example due to patent expiry.

Overview of the HTA process in other countries

Smaller companies in particular need an overview of other countries' HTA processes prior to the development and launch of ATMP medicines outside Sweden. The project has analysed markets in parts of Europe and Asia as well as North America.

For each country, the following parameters have been examined: pricing and available compensation models: which main stakeholders exist and how they work, as well as which HE-specific requirements exist in each country. The attached material (Appendices G, H, I) also present cases of specific ATMP medicines in each country examined.

Table 12. Countries examined.

Norway	France
Denmark	Spain
Finland	Italy
Germany	China
The Netherlands	Japan
The United Kingdom	South Korea
USA	Canada

Information collected comes from two reports commissioned by the project: one on selected Asian markets (Appendices G and H) and one on European countries (Appendix I). The information from North America was obtained during May 2020. A detailed summary of the two reports and other references are available in the form of a Power Point presentation (Appendix F).

Overall summary of health economic analysis of global markets

EMA currently approves all ATMP medicines and the individual countries within the EU therefore have no locally established authorities that assess ATMP medicines on the basis of market approval. On the other hand, health economics benefit in some member countries are assessed by one or more actors and are based on the companies' own reported calculations. Other countries set prices based on a basket model where the cost is approved as an average price for already registered products in a certain number of EU countries. The common goal for these authorities is to achieve the maximum benefit from new products at the lowest possible cost. However, different priorities can be made locally, as well as the use of different assessment methods, which can affect the outcome in the individual country. There are as yet no established frameworks for common, established health economic models with which to measure and demonstrate the effects of ATMP treatment. All in all, this can lead to a delay in an approval, or that the approval is not forthcoming, and that the different countries may vary in their assessments.

The number of approvals of ATMP medicines in Europe as well as globally is still too low to enable a well-founded analysis of which of these pricing solutions are the most common and well-functioning from a cost-effectiveness perspective. New payment models, e.g. conditional approval, outcome-based

pricing and split payment over time, have been tested in some countries (e.g. Italy and Germany).

Within Europe, there are several examples of how HTA authorities in different countries cooperate across national borders: BeNeLuxAIr (Belgium, the Netherlands, Luxembourg, Austria, and Ireland), La Valetta Group (Italy, Spain, Greece, Portugal, Slovenia, Cyprus, Malta, and Croatia), FINOSE (Finland, Norway, and Sweden) and Visegrad (Czech Republic, Hungary, Poland, Slovakia, and Croatia).

An example of joint HTA assessment / pricing is Belgium and the Netherlands, which jointly negotiated with the company Biogen on the price of Spinraza (nusinersen; indication spinal muscular atrophy). The negotiations resulted in Spinraza now, with similar economic conditions, being available in both countries.

Recently, all Nordic countries (Denmark, Finland, Norway, Iceland, and Sweden) have started joint negotiations on the gene therapy Zyntenglo[24].

Health economic analysis of a selection of European markets

With regard to health economic analysis in individual countries, it can be mentioned that in Norway, for example, indirect costs that arise outside hospitals are also taken into account in order to compare the effectiveness of treatment and illness.

In Germany and France, special rules apply for "orphan ATMP." In Italy, so-called "Managed Entry Agreements" are used, which enable faster assessment of ATMP medicines, as well as faster market availability.

For the United Kingdom, France, and Spain, for example, there are clear descriptions of how cell and gene therapy treatments are assessed and approved[25].

In several countries (Spain and Italy) decisions on reimbursement of ATMP medicines are made or implemented at regional level, which often means that budgetary implications outweigh other aspects.

A complicating factor for therapies that have a long or lifelong effect is that in several countries such as France and Spain, at least for the time being, it is not

[24] https://janusinfo.se/nationelltinforandeavlakemedel/nyheter/nyheter/genterapiforstutinordisktsamarbete.5.4a09469f17225dd434b377e.html
[25] https://ct.catapult.org.uk/how-we-work/health-economics-and-market-access

allowed to commit to reimbursement models which allow for payment to be spread out over several years.

Health economic analysis of the Asian markets

As far as China is concerned, it can be noted that the number of CAR-T projects is very large (currently over 900) and that it can therefore generally be challenging to compete in the CAR-T area in particular. In China, however, a large number of previously untreated patients are still available for clinical trials. The compensation for new / innovative treatments is often 50-90% lower than in the western world. However, there are financial resources available through the Chinese state for local actors / development, and it is possible to obtain conditional approval if the medical need is considered high, but is not met. The level of corruption is still relatively high and IP protection is considered questionable in some cases.

In Japan, a special fast track (SAKIGAKE) has been developed for products / projects that are at least partially developed within the country. Pricing is at European level, but prices are often reduced over time.

In South Korea, domestic companies are very active in the ATMP area. Price levels are lower than in Japan. The market for ATMP medicines in South Korea has been shaken in recent years by several corruption and quality scandals.

Health economic analysis of the North American market

In Canada, the decision-making process for market approval and compensation is centralised (with the exception of the Quebec region). A fast track for the process exists only in Ontario. The process of market approval and reimbursement is handled by Health Canada in collaboration with the Patented Medicine Prices Review and the Canadian Agency for Medicines and Technologies in Health. There is no specific process for ATMP medicines. Medicine administered in hospitals is reimbursed by the general public, while medicine used outside hospitals is reimbursed by private insurances held by the vast majority of Canadian residents.

In the United States, which is still the world's largest market for pharmaceuticals, the Food and Drug Administration (FDA) is responsible for both market approval and reimbursement, along with a number of both public and private decision-makers. Price levels (list prices) are often higher than corresponding prices in Europe. Manufacturers are free to set prices, but compensation levels are determined by payers. These are often private insurance companies, but both Medicaid and Medicare intend to support gene and cell therapy treatment for certain patient groups. The FDA currently has

an Accelerated Approval Program, which enables faster market approval for medicines which focus on specific indications and that meet a need. Although the programme is not specifically designed for ATMP medicines, both current and future ATMPs should be able to benefit from this programme.

Different countries' collection and assessment of utility data for HTA

In preparation for the HTA process, utility data is collected from various published sources on the subject, or generated in other ways. How this happens and which perspectives are taken into account, differs between different countries, which is summarised by Rowen et al. (2017), from which the following examples are taken. In some countries (e.g. France, the Netherlands, and Sweden), but far from all (e.g. Canada, Germany, and Spain), not only costs in the health sector (hospital care, medicines, etc.) or so-called direct costs are taken into account, but also societal costs related to working life and care outside the healthcare care system, so-called indirect costs. In terms of clinical data, France, for example, prefers to generate data in its own country. The benefit for the custodian QALY can also be weighted differently in different countries, where, for example, The Netherlands has different threshold levels depending on the need for treatment. In summary, the country-specific management of "utility data" is another area that ATMP-developing companies need to familiarise themselves with.

Conclusion

It is necessary to acquire solid knowledge about each country's approval processes and about how AMTP medicines are assessed and replaced. This is so that a company can design its risk assessment in good time, TPP (see Table 3 and Appendix C and the future business model (see Appendix F, PPT slide deck HTA Europe, Asia). In addition to knowledge of processes, cultural differences and language difficulties should not be underestimated as companies aim for development, assessment, and replacement of ATMP medicines in different markets.

The payment systems for ATMP medicines differ between countries, as described above. Ultimately, it is up to the payer / HTA authority to decide which payment model can be considered the most advantageous. However, it is important that companies are given the opportunity to understand which models may become relevant for the individual therapy, prior to the commercially crucial planning of the clinical trial programme. In many countries, the parties agree through negotiation within the framework stipulated by law and competition in each individual country.

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Appendices

The appendices are separate documents, below is a list of appendices

A. HTA Checklist
B. Guidance HTA Checklist
C. Generic Target Profiles (TPP) for ATMP
D. Value-Based Pricing
E. Regulations
F. PPT Slide Deck HTA Europe, Asia
G. Report ATMP Market Overview Asia (ABD)
H. Report ATMP Japan Sakigake (ABD)
I. Report ATMP_HTA Mapping Europe (monocl)