
**ΠΑΝΕΠΙΣΤΗΜΙΟ
ΠΕΙΡΑΙΩΣ**



**ΤΜΗΜΑ
ΟΙΚΟΝΟΜΙΚΗΣ
ΕΠΙΣΤΗΜΗΣ**

**ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
«ΟΙΚΟΝΟΜΙΚΑ και ΔΙΟΙΚΗΣΗ της ΥΓΕΙΑΣ»**

**ΜΟΝΤΕΛΑ ΑΠΟΖΗΜΙΩΣΗΣ ΚΥΤΤΑΡΙΚΩΝ ΚΑΙ ΓΟΝΙΔΙΑΚΩΝ
ΘΕΡΑΠΕΙΩΝ ΣΕ 6 ΕΥΡΩΠΑΪΚΕΣ ΧΩΡΕΣ: ΑΓΓΛΙΑ, ΓΕΡΜΑΝΙΑ, ΓΑΛΛΙΑ,
ΙΤΑΛΙΑ, ΙΣΠΑΝΙΑ, ΠΟΛΩΝΙΑ**

ΡΑΙΣΑΚΗ ΕΥΑΓΓΕΛΙΑ

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Μεταπτυχιακού Διπλώματος Ειδίκευσης στα Οικονομικά και Διοίκηση της Υγείας.

Πειραιάς, 2026



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**Μοντέλα Αποζημίωσης Κυτταρικών Και Γονιδιακών Θεραπειών Σε 6
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M.Sc. in Health Economics and Management

**Reimbursement Models for Cell and Gene Therapies in 6 European Countries:
United Kingdom, Germany, France, Italy, Spain, Poland**

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ΒΕΒΑΙΩΣΗ ΕΚΠΟΝΗΣΗΣ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ

«Δηλώνω υπεύθυνα ότι το έργο που εκπονήθηκε και παρουσιάζεται στην υποβαλλόμενη διπλωματική εργασία, έχει γραφτεί από εμένα αποκλειστικά στο σύνολό της. Δεν έχει υποβληθεί ούτε έχει εγκριθεί στο πλαίσιο κάποιου άλλου μεταπτυχιακού προγράμματος ή προπτυχιακού τίτλου σπουδών, ούτε είναι εργασία ή τμήμα εργασίας ακαδημαϊκού ή επαγγελματικού χαρακτήρα.

Δηλώνω επίσης ότι αναφέρονται καταλλήλως στο σύνολό τους οι πηγές στις οποίες ανέτρεξα για την εκπόνηση της συγκεκριμένης εργασίας. Παράβαση της ανωτέρω ακαδημαϊκής μου ευθύνης αποτελεί ουσιώδη λόγο για την ανάκληση του πτυχίου μου».

Ονοματεπώνυμο

Ευαγγελία Ραϊσάκη

Υπογραφή Μεταπτυχιακού Φοιτητή

A handwritten signature in black ink, appearing to be 'AR' with a large loop and a vertical line extending downwards.

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Η παρούσα διπλωματική εργασία βασίστηκε σε δική τους ιδέα και δεν θα είχε πραγματοποιηθεί χωρίς τη δική τους συμβολή, καθώς με καθοδήγησαν βήμα-βήμα σε κάθε στάδιο της υλοποίησής της.

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Glossary of Abbreviations

AEMPS	Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency of Medicines and Health Products)
AIFA	Agenzia Italiana del Farmaco (Italian Medicines Agency)
AMNOG	Arzneimittelmarktneuordnungsgesetz (Medicines Market Reorganization Act)
AOTMiT	Agency for Health Technology Assessment and Tariff System (Poland)
ASMR	Amélioration du Service Médical Rendu (Additional Clinical Value)
ATMPs	Advanced Therapy Medicinal Products
ATU	Temporary Authorization of Use
CBER	Center for Biologics Evaluation and Research
CDF	Cancer Drugs Fund
CED	Coverage with Evidence Development
CEPS	Economic Committee for Health Products
CIPM	Comisión Interministerial de Precios de Medicamentos y Productos Sanitarios (Interministerial Committee on Drug Prices)
CPR	Comitato Prezzi e Rimborso (Price and Reimbursement Committee)
CTS	Commissione Tecnico Scientifica (Scientific Technical Committee)
DGCBSF	Dirección General de Cartera Básica de Servicios del Sistema Nacional de Salud y Farmacia (General Directorate for Medicines of the Ministry of Health)
DRG	Diagnosis-Related Group
EMA	European Medicines Agency
FDA	Food and Drug Administration
GDP	Gross Domestic Product
G-BA	Federal Joint Committee
HAS	Haute Autorité de Santé
HSTP	Highly Specialized Technologies Program
HTA	Health Technology Assessment
HTACG	HTA Coordination Group
HTD	Health Technology Developer

ICER	Incremental Cost-Effectiveness Ratio
IMF	Innovative Medicines Fund
IQWiG	Institute for Quality and Efficiency in Health Care
JCA	Joint Clinical Assessment
JSCs	Joint Scientific Consultations
MA	Marketing Authorization
MAH	Marketing Authorization Holder
MEAs	Managed Entry Agreements
MFG	Medical Research Act (Germany)
NHS	National Health Service
NHF	National Health Fund
NICE	National Institute for Health and Care Excellence
NUB	Neue Untersuchungs- und Behandlungsmethoden (New Examination and Treatment Methods)
OECD	Organisation for Economic Co-operation and Development
P4P	Pay-for-Performance
PEI	Paul-Ehrlich Institute (Germany)
PRIME	Priority Medicines
QALY	Quality Adjusted Life Year
REvalMed	Red de Evaluación de Medicamentos (Spanish Network for Economic Evaluation of Medicines)
RMAT	Regenerative Medicine Advanced Therapy
RWE	Real-World Evidence
SMR	Service Médical Rendu (Absolute Clinical Value)
STA	Single Technology Appraisal

«ΜΟΝΤΕΛΑ ΑΠΟΖΗΜΙΩΣΗΣ ΚΥΤΤΑΡΙΚΩΝ ΚΑΙ ΓΟΝΙΔΙΑΚΩΝ ΘΕΡΑΠΕΙΩΝ ΣΕ 6 ΕΥΡΩΠΑΪΚΕΣ ΧΩΡΕΣ: ΑΓΓΛΙΑ, ΓΕΡΜΑΝΙΑ, ΓΑΛΛΙΑ, ΙΤΑΛΙΑ, ΙΣΠΑΝΙΑ, ΠΟΛΩΝΙΑ»

Σημαντικοί Όροι: ATMPs, Ορφανά φάρμακα Αποζημίωση, HTA, EMA, Συμφωνίες Ελεγχόμενης Εισόδου, MEAs, Πραγματικά Δεδομένα (RWE), Ηνωμένο Βασίλειο, Αγγλία, Γαλλία, Γερμανία, Ιταλία, Ισπανία, Πολωνία.

Περίληψη

Η παρούσα μεταπτυχιακή εργασία εξετάζει τα μοντέλα αποζημίωσης για τις κυτταρικές και γονιδιακές θεραπείες (ATMPs) σε έξι χώρες της Ευρώπης: το Ηνωμένο Βασίλειο, τη Γαλλία, τη Γερμανία, την Ιταλία, την Ισπανία και την Πολωνία. Τονίζει τις διάφορες στρατηγικές και τα ρυθμιστικά πλαίσια που χρησιμοποιούνται για τη διαχείριση της αποζημίωσης των θεραπειών αυτών και της προσβασιμότητας σε αυτές. Πιο συγκεκριμένα, εξετάζεται το κανονιστικό πλαίσιο που έχει θεσπιστεί από τον Ευρωπαϊκό Οργανισμό Φαρμάκων και οι διάφορες διαδικασίες Αξιολόγησης Τεχνολογιών Υγείας στις χώρες που μελετώνται. Η ανάλυση αποκαλύπτει πώς οι κανονισμοί, οι οικονομικές συμφωνίες και οι δαπάνες υγείας διαμορφώνουν τις αποφάσεις αποζημίωσης, με τη Γερμανία να αναδεικνύεται ως πρότυπο όχι μόνο λόγω της σημαντικής επένδυσης στον τομέα της υγείας αλλά και λόγω της εξισορρόπησης μεταξύ της ταχείας πρόσβασης σε θεραπείες και της διαχείρισης του οικονομικού κινδύνου. Η μελέτη υπογραμμίζει τη σημασία των Συμφωνιών Ελεγχόμενης Εισόδου (MEAs), ιδιαίτερα των βασισμένων στην απόδοση και των συνδυαστικών MEAs, για την ισορροπία μεταξύ οικονομικής βιωσιμότητας και πρόσβασης των ασθενών. Επιπλέον, η επικείμενη διαδικασία της Κοινής Κλινικής Αξιολόγησης (JCA), στο πλαίσιο του κεντρικού ευρωπαϊκού συστήματος Αξιολόγησης Τεχνολογιών Υγείας (HTA), αποτελεί μια ευκαιρία για την εναρμόνιση των κλινικών δεδομένων και τη βελτίωση της πρόσβασης στις Προηγμένες Θεραπείες (ATMPs) σε όλη την Ευρώπη. Ωστόσο, παραμένουν προκλήσεις, όπως το υψηλό κόστος, η αβεβαιότητα και η ανάγκη για ενσωμάτωση πραγματικών δεδομένων (RWE).

Αναγνωρίζονται περιορισμοί όπως η διαθεσιμότητα δεδομένων, τα ζητήματα εμπιστευτικότητας και η διακύμανση στον αριθμό των ασθενών ανά χώρα. Συμπεραίνεται ότι η συνεργασία μεταξύ των ενδιαφερομένων και τα καινοτόμα μοντέλα πληρωμής είναι κρίσιμα για τη διασφάλιση ευρύτερης πρόσβασης στα ATMPs στο μέλλον.

“Reimbursement Models for Cell and Gene Therapies in 6 European Countries: United Kingdom, Germany, France, Italy, Spain, Poland”

Keywords: ATMPs, Orphan drugs, Reimbursement, HTA, EMA, JCA, Managed Entry Agreement (MEAs), Performance-Based Agreements, Patient Access, RWE, UK, France, Germany, Italy, Spain, Poland.

Abstract

This dissertation examines the reimbursement models for Advanced Therapy Medicinal Products (ATMPs) in six European countries: the UK, France, Germany, Italy, Spain, and Poland. It highlights the diverse strategies and regulatory frameworks used to manage the reimbursement and accessibility of these therapies. Specifically, it examines the regulatory framework established by the European Medicines Agency (EMA) and the various Health Technology Assessment (HTA) processes in the studied countries. The analysis reveals how regulations, economic agreements, and healthcare expenditures shape reimbursement decisions, with Germany emerging as a model not only due to its substantial healthcare investment but also due to its balance between rapid access to therapies and management of financial risk.

The study underscores the importance of Managed Entry Agreements (MEAs), particularly performance-based and combination MEAs, in balancing financial sustainability and patient access. Additionally, the forthcoming Joint Clinical Assessment (JCA) as part of the centralized EU Health Technology Assessment (HTA) process presents an opportunity to harmonize clinical assessments and improve ATMP access across Europe. While clinical assessments (JCA) will be centralized, pricing and reimbursement decisions will remain at the national level. However, challenges remain, such as high costs, uncertainty, and the need to integrate real-world evidence (RWE).

The dissertation acknowledges limitations such as data availability, confidentiality issues, and variability in patient numbers across countries. It concludes that collaboration among stakeholders and innovative payment models are crucial for ensuring broader access to ATMPs in the future.

Introduction

Currently, a significant focus in biomedical research and clinical applications is on Advanced Therapy Medicinal Products (ATMPs). The main goal of ATMPs is incurable diseases, orphan diseases and chronic diseases that traditional drugs are unable to treat. In particular, genetic and metabolic diseases, degenerative neurological diseases, malignancies and hematological diseases, serious cardiological and orthopedic cases are the field of their application, whereas their action for the regeneration of damaged tissues is essentially responsible for the rapid development of the field of regenerative medicine. ATMPs are highly sophisticated medicines that enable targeted and personalized patient treatment as they use human cells and tissues which have undergone modifications in the laboratory. The donor and the recipient of the cells/tissues may be the same individual or different. ATMPs can be categorized into three primary types (EMA, 2020):

Gene Therapy Medicines: These contain recombinant nucleic acids that produce therapeutic, prophylactic, or diagnostic effects relevant to the recombinant nucleic acid sequence . They work by inserting the recombinant genes into the body to treat a variety of diseases, including genetic disorders, cancer, or chronic illnesses. A recombinant gene is a segment of DNA created in the laboratory by combining DNA from different sources. They can be used to treat inherited diseases, cancer, and for tissue regeneration (e.g., lost of sight)

Somatic-Cell Therapy Medicines: These contain or are comprised of cells or tissues that have been modified in vitro and as a result, manipulated to alter their biological characteristics or are used differently from their original function in the body. They can be used to cure, diagnose, or prevent diseases, as products against immune disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Alzheimer's disease, cartilage defect, products for cardiac repair, skin replacement, and cancer immunotherapy.

Tissue-Engineered Medicines: These contain cells or tissues that have been modified to repair, regenerate, or replace human tissue. Examples of their application are small diameter vascular grafts, trachea replacement, tissue-engineered esophagus, liver and kidney implantation, nerve conduits.

Some ATMPs may also include one or more medical devices as an integral component of the medicine, referred to as combined ATMPs, such as cells embedded in a biodegradable matrix or scaffold. (Woods & MacLoughlin, 2020; Goula, et al., 2020)

ATMPs hold the potential to save, extend, and enhance patients' lives by addressing the root causes of diseases. Their potential in future treatments is invaluable. Most of them are orphan medicines, and this drug status is a special designation given to medications that are developed to treat rare diseases or conditions, typically affecting fewer than 200,000 people in the EU.

However, these novel treatments are often extremely expensive, which challenges established reimbursement models. In France, for instance, a single treatment with ATMP Kymriah® – a CAR-T cell therapy – costs 320,000 €, and additionally the ATMP Upstaza® costs 3,500,000 € (Santé, 2024)

Due to high costs and the lack of appropriate reimbursement models, access to these potentially lifesaving therapies is not guaranteed for all patients. (Picecchi, et al., 2020)

Governments recognize the potential of ATMPs and are working diligently to create regulatory, HTA, and commercial environments that allow suitable patients to access these transformative therapies. A key challenge remains how to reimburse these often single-administration therapies, which can have high upfront costs and greater uncertainty regarding long-term outcomes. The primary payment model-related challenges for ATMPs are characterized by affordability and uncertainty (magnitude and durability of clinical benefits). While health systems could initially absorb the upfront costs of these treatments when only a few new ATMPs were launched per year for small patient populations, the affordability issue has become more pronounced with the increasing number of ATMPs entering the market. ATMPs present unique data and policy challenges, likely requiring changes in existing regulatory, HTA, and financial systems. However, these adjustments can build on the current foundation of regulatory and incentive systems for innovation, accelerating progress in ATMPs. To address these challenges, healthcare systems and companies must collaborate to ease patients' access to the right treatments while maintaining system sustainability. Introducing innovative payment models to accommodate revolutionary treatments like ATMPs requires overcoming several barriers. These include annual budgeting and associated accounting constraints, administrative burdens of data collection and patient monitoring over time, and engaging providers and commissioners with the challenges of ATMPs. Focusing

on acceptability, feasibility, flexibility, and predictability offers a helpful framework for managing uncertainties. (Picecchi, et al., 2020)

1. CHAPTER 1

1.1 The Creation of the Regulatory Framework

Without a clear legal framework, initial efforts to utilize ATMPs were undertaken by the research laboratories which were the same bodies that developed them. At the physician's request, laboratories providing an applied service, processed cells or tissues from the patient or a related donor and sent them back for patient treatment. These were personalized therapies prepared for a particular patient. Then an attempt was made to systematize ATMP production from academic research centers through spin-off companies and biotech small and medium-sized enterprises. Therefore, the European Commission took initiatives in order to set standards and operating rules. (Goula, et al., 2020)

1.2. Regulatory Framework, Approval Processes, and the Role of the EMA

The regulatory landscape for ATMPs is complex and can lead to delays and high costs for both manufacturers and healthcare providers. According to Bellino et al. (2023), the time and resources required for these approval processes often slow down the introduction of new therapies to the market. This is a major issue because the journey from drug discovery to the patient is already long and expensive. As noted by Warreth and Harris (2020), it can take more than 12 years and cost over 2.6 billion dollars to bring a new product to market.

Before granting Marketing Authorization, authorities in both the EU and the US require a detailed dossier with quality, non-clinical, and clinical data. While the standard process of MA involves three phases of clinical trials, ATMPs often rely on single-arm, open-label studies. As a result, this creates more uncertainty for regulators and doesn't improve patient access. Therefore, clear guidelines are necessary to make the approval process more efficient and ensure that patients can have benefit without unnecessary delays. (Bellino, et al., 2023; Warreth & Harris, 2020)

At present, the European Medicines Agency (EMA) and the national drug authorities of member states are the main bodies responsible for licensing ATMPs. All advanced therapy medicines are authorized centrally via the EMA. They benefit from a single evaluation and authorization procedure. As with all medicines, the Agency continues to monitor the safety and efficacy of

advanced therapy medicines after they are approved and marketed. The Agency also provides scientific support to developers to help them design pharmacovigilance and risk management systems used to monitor the safety of these medicines. Additionally, the EMA offers scientific advice to companies researching and developing new medicines, prepares scientific guidelines and regulatory guidance to assist pharmaceutical companies in preparing marketing authorization applications, and contributes to the harmonization of regulatory requirements in the EU and internationally. (Kamisetti, 2023)

Following the implementation of Regulation 1394/2007 in 2009, and recognizing the innovative nature of ATMPs, the EMA established the Committee for Advanced Therapies (CAT), a multidisciplinary expert group. To facilitate market access across Europe, the centralized marketing authorization application (MAA) process for ATMPs was made compulsory, benefiting from a unified evaluation procedure. CAT determines whether a product qualifies as an ATMP and classifies it into relevant categories. Furthermore, due to the technical details often involved in these products, CAT provides scientific recommendations on whether they meet the definition of advanced therapies. However, member states are not required to follow these recommendations at the EU level, resulting in different legal frameworks for similar products in each state. Laboratories developing ATMPs frequently express concerns about these classifications, as they may need to halt standard therapy protocols. It is evident that obtaining an EMA license for ATMP production is essential for exporting these products between member states and for their off-the-shelf sales. Additionally, in 2016, the EMA introduced the Priority Medicines (PRIME) scheme to accelerate the development of medicines addressing unmet medical needs, thereby ensuring quicker patient access. This fast-track pathway supports the efficient development of treatments without requiring extensive datasets, balanced by more rigorous post-market safety and efficacy evaluations. (Goula, et al., 2020; Piccchi, et al., 2020)

1.3. Product life cycle of advanced therapies

The product life cycle of advanced therapies, under the oversight of the European Medicines Agency and more specifically by the CAT, includes three key stages for the ease of assessment and post marketing authorizations: Research and Development, Marketing Authorization, and Post Authorization. In the Research and Development stage, EMA provides crucial support for

developers of advanced therapies, ensuring they have the necessary resources and guidance to innovate effectively. The EMA also establishes scientific guidelines that assist developers in their research efforts. During the Marketing Authorization phase, EMA classifies advanced therapies to ensure they meet specific criteria and oversees the procedures for their marketing authorization, making sure they comply with regulatory standards. In the Post Authorization stage, EMA continues to monitor the safety and efficacy of advanced therapies once they are approved and marketed. This ongoing oversight includes supporting developers in designing pharmacovigilance and risk management systems to ensure the continued safety and effectiveness of these therapies. (Kamisetti, 2023)

Table 1: Advanced therapies in the product life cycle through, EMA perspective (Kamisetti, 2023)

I-Research and Development	II-Marketing Authorization	III-Post Authorization
A. Support for Advanced therapy developers	A. Advanced therapy Classification,	A. Pharmacovigilance
B. Scientific guidelines	B. Marketing authorization procedures	

1.4.The Role and Challenges of HTA in the Era of ATMPs

Health Technology Assessment (HTA) is a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. Its primary goal is to inform decision-making in health policy by evaluating the social, economic, and ethical impacts of medical interventions. As healthcare costs rise, HTA plays a central role in balancing these expenditures with the provision of high-quality medical care. (Mentis, 2022)

While HTA traditionally serves as the basis for pricing and reimbursement decisions, its application to Advanced Therapy Medicinal Products (ATMPs) presents unique and complex challenges. Unlike conventional pharmaceuticals, ATMPs are often curative, one-off treatments with high upfront costs and long-term benefits. Standard HTA frameworks, initially developed for non-personalized medicines, frequently struggle with clinical uncertainty and the lack of mature long-term data at the time of marketing authorization. (Drummond, et al., 2019)

Therefore, in the context of this Master's Thesis, HTA is not viewed merely as an evaluative tool, but as a critical mechanism for managing uncertainty. By evolving from traditional static assessments to more flexible frameworks—such as the integration of Real-World Evidence (RWE) and Managed Entry Agreements (MEAs)—HTA processes aim to bridge the gap between early patient access and the long-term financial sustainability of healthcare systems. (Vreman, et al., 2020)

1.5. Hospital Exemption (HE) for ATMPs.

The EU Regulation 1394/2007/EC authorizes the use of non-authorized ATMPs under specific circumstances through a hospital exemption rule, requiring individual applications in each EU Member State. This exemption is intended for exceptional cases where no equivalent authorized ATMP is available, and the product is suitable for the individual patient. Misuse of this exemption could discourage the submission of marketing authorization applications for ATMPs. The ATMP-HE pathway not only allows access to non-approved products but also ensures safety through quality controls and monitoring. Since its inception in 2007, the application of the ATMP-HE pathway has evolved alongside the development of new therapies. The regulation limits manufacturing conditions but does not restrict patient indications, originally justifying HE therapies for “compassionate use” in incurable conditions without authorized treatments. As newer cell and gene therapies like CAR-T have gained market authorization, the ATMP-HE pathway has also been used to provide access to these therapies when standard treatment protocols are not met. Variations in the interpretation and application of the ATMP-HE regulations by each EU member country create discrepancies in the coverage and delivery of therapies, leading to significant differences in which treatments are available and how they are administered. (Gonçalves, 2022; Pachocki & Verter, 2024)

1.6. Early Access Schemes and Named Patient Access

The journey of an ATMP from clinical trials to standard clinical practice is often prolonged due to complex HTA evaluations and price negotiations. However, given that these therapies often target life-threatening or chronically debilitating conditions with no alternative treatments, regulatory

and reimbursement frameworks have evolved to include 'Early Access Schemes' and 'Named Patient Access' programs.

Named Patient Access (or Compassionate Use) refers to the provision of an unauthorized medicine to a specific patient, requested by their physician, under strict clinical conditions. These programs are vital for ATMPs as they provide a 'last-resort' pathway for patients who cannot wait for the formal marketing authorization. (EMA, 2024) While these programs often involve high costs, they represent the first point of entry for many gene therapies into national health systems.

Several European countries have implemented structured frameworks to bridge the gap between EMA approval and national reimbursement decisions (Wenzl & Chapman, 2019). These schemes allow for 'temporary' reimbursement while clinical and economic evidence is still being gathered: In France, the 'Accès Précocé' (formerly ATU) system is a global benchmark, allowing immediate access to innovative drugs with high clinical added value based on criteria of unmet medical need. (Casanova, et al., 2019; Wenzl & Chapman, 2019)

In the United Kingdom, the 'Early Access to Medicines Scheme' (EAMS) and the 'Innovative Medicines Fund' (IMF) provide similar pathways, particularly for oncology and rare disease ATMPs, facilitating earlier availability before NICE recommendations. (NICE, 2024; Wenzl & Chapman, 2019)

In Italy, the '5% Fund' (Law 648/96) and Law 326/2003 serve as specialized mechanisms for financing drugs that are not yet reimbursed but are necessary for patients with no therapeutic alternatives. (Vreman, et al., 2020; AIFA, 2024)

Early access programs serve as a critical data-collection phase. The Real-World Evidence (RWE) gathered during this period is often used to reduce the uncertainty surrounding an ATMP's performance, subsequently informing the negotiation of Performance-based Managed Entry Agreements (MEAs) (Vreman, et al., 2020). By establishing early access, payers can monitor patient outcomes in a real-world setting before committing to long-term high-cost reimbursement models. (Wenzl & Chapman, 2019)

1.7. List of authorized ATMPs.

The table below (Figure 2) provides a detailed overview of various ATMPs that have been authorized in Europe, along with specific information about each product. Currently the ATMPs

with market authorization by EMA are: Holoclax, Imlygic, Strimvelis, Spherox, Alofisel, Yescarta, Kymriah, Luxturna, Zolgensma, Libmeldy, Tecartus, Abecma, Breyanzi, Carvykti, Upstaza, Roctavian, Ebvallo, Hemgenix, Casgevy, Durveqtix. (EMA, 2024)

The following explains the significance of each column in the table:

Name: The commercial name of the ATMP.

Type of ATMP: The classification of the ATMP, which can be Tissue Engineered Product (TEP), Gene Therapy Medicinal Product (GTMP), Cell Therapy Medicinal Product (CTMP), or a combination of these categories.

Authorization Date: The date on which the product received marketing authorization from the relevant regulatory body.

Orphan: Indicates whether the product has been designated as an orphan drug, meaning it is intended for the treatment of a rare disease or condition.

PRIME: Indicates whether the product is part of the EMA's PRIority MEdicines (PRIME) scheme, which aims to support the development of medicines that address unmet medical needs.

Comment: Additional notes or updates about the product, such as if the marketing authorization (MA) was withdrawn or not renewed. (EMA, 2024)

Also, the image (Image 1) illustrates the authorization timeline of the ATMPs for the last 10 years, reflecting the evolving landscape of advanced therapies and their regulatory milestones.

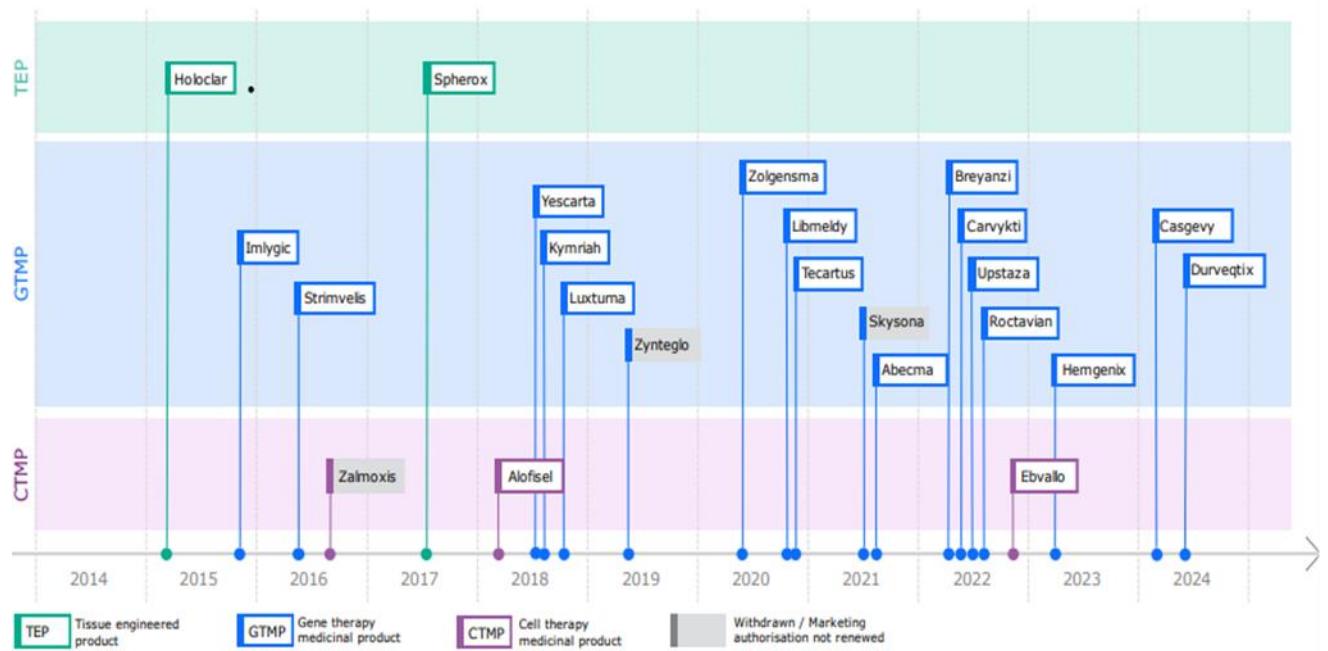


Image 1: The last 10 years of ATMPs. (EMA, 2024)

Table 2: List of authorized ATMPs. (EMA, 2024)

Name	Type of ATMP	Authorization Date	Orphan	PRIME	Comment
Chondroelect	TEP	5/10/2009	No	No	MA withdrawn July 2016
Glybera	GTMP	25/10/2012	Yes	No	MA not renewed (ended Oct. 2017)
MACI	TEP, combined ATMP	27/06/2013	No	No	MA not renewed (ended June 2018)
Provenge	CTMP	6/9/2013	No	No	MA withdrawn May 2015
Holoclar	TEP	17/02/2015	Yes	No	
Imlygic	GTMP	16/12/2015	No	No	
Strimvelis	GTMP	26/05/2016	Yes	No	
Zalmoxis	CTMP	18/08/2016	Yes	No	MA withdrawn Oct. 2019
Spherox	TEP	10/7/2017	No	No	
Alofisel	CTMP	23/03/2018	Yes	No	
Yescarta	GTMP	23/08/2018	Yes	Yes	
Kymriah	GTMP	23/08/2018	Yes	Yes	
Luxturna	GTMP	22/11/2018	Yes	No	
Zynteglo	GTMP	29/05/2019	Yes	Yes	MA withdrawn March 2022
Zolgensma	GTMP	18/05/2020	Yes	Yes	
Libmeldy	GTMP	17/12/2020	Yes	No	
Tecartus	GTMP	14/12/2020	Yes	Yes	
Skysona	GTMP	16/07/2021	Yes	Yes	MA withdrawn Nov. 2021
Abecma	GTMP	18/08/2021	Yes	Yes	
Breyanzi	GTMP	4/4/2022	No	Yes	
Carvykti	GTMP	25/05/2022	Yes	Yes	
Upstaza	GTMP	18/07/2022	Yes	No	
Roctavian	GTMP	24/08/2022	Yes	Yes	
Ebvallo	CTMP	16/12/2022	Yes	Yes	

Hemgenix	GTMP	20/02/2023	Yes	Yes	
Casgevy	GTMP	9/2/2024	Yes	Yes	
Durveqtix	GTMP	24/07/2024	No	Yes	

The following table (Table 3) provides an even more comprehensive view, as it includes the therapeutic indications for each treatment. This added information builds on the details provided in the previous table, offering a deeper insight into the Advanced Therapy Medicinal Products (ATMPs) authorized by the EMA. Out of the 20 ATMPs listed, 16 have been granted orphan drug status.

Table 3: : ATMPs authorized in Europe. (EMA, 2024; VFA, 2024)

Active Ingredient	Indication	Drug / Brand Name	Permit	Company	Classification	Orphan Drug
Autologous CD34+ cells encoding ADA	ADA-SCID	Strimvelis®	May 2016	Fondazione Thelethon	Gene Therapy	Yes
Tisagenlecleucel	Acute lymphocytic leukemia (ALL) / B- cell lymphoma (DLBCL)	Kymriah®	Aug 2018	Novartis	Gene Therapy (CAR-T)	Yes
Eladocagene Exuparvovec	Aromatic L-amino acid decarboxylase deficiency	Upstaza®	July 2022	PTC Therapeutics	Gene Therapy	Yes
Axicabtagene Ciloleucel	B-cell lymphoma (DLBCL and PMBCL)	Yescarta®	Aug 2018	Gilead	Gene Therapy (CAR-T)	Yes
Lisocabtagene Maraleucel CD4 cell component /	Diffuse large B-cell lymphoma (DLBCL), primary	Breyanzi®	April 2022	Bristol Myers Squibb	Gene Therapy (CAR-T)	No

Lisocabtagene Maraleucel CD8 cell component	mediastinal large B- cell lymphoma (PMBCL) / grade 3B follicular lymphoma (FL3B)					
Tabelecleucel	Epstein-Barr virus positive post- transplant proliferative disease	Ebvallo®	Dec 2022	Pierre Fabre	Cell Therapy	Yes
Valoctocogene Roxaparvovec	Hemophilia A	Roctavian®	Aug 2022	BioMarin Europe	Gene Therapy	Yes
Fidanacogene Elaparvovec	Hemophilia B	Bequez® (formerly: Durveqtix®)	July 2024	Pfizer	Gene Therapy	No
Etranacogen Dezaparvovec	Hemophilia B	Hemgenix®	Feb 2023	CSL Behring	Gene Therapy	Yes
Living (cornea) tissue equivalent	Limbal stem cell insufficiency after burns/chemical burns of the eye	Holoclar®	Feb 2015	Holostem	Biotechnologically Processed Tissue Product	Yes
Brexucabtagene Autoleucel	Mantle cell lymphoma, refractory	Tecartus®	Dec 2020	Kite	Gene Therapy (CAR-T)	Yes
Talimogene Laherparepvec	Melanoma (unresectable, metastatic)	Imlygic®	Dec 2015	Amgen	Gene Therapy	No
Atidarsagene Autotemcel	Metachromatic leukodystrophy	Libmeldy®	Dec 2020	Orchard Therapeutics	Gene Therapy	Yes
Ciltacabtagene Autoleucel	Multiple myeloma	Carvykti®	May 2022	Janssen	Gene Therapy (CAR-T)	Yes

Idecabtagene Vicleucel	Multiple myeloma	Abecma®	Aug 2021	Bristol Myers Squibb	Gene Therapy (CAR-T)	Yes
Darvadstrocel	Perianal fistulas in Crohn's disease	Alofisel®	March 2018	Takeda	Cell Therapy	Yes
Spheroids from autologous chondrocytes	Repair of certain cartilage defects	Spherox®	July 2017	Rejuvenate	Biotechnologically Processed Tissue Product	No
Voretigene Neparvovec	Retinitis pigmentosa and Leber's inherited amaurosis	Luxturna®	Nov 2018	Novartis	Gene Therapy	Yes
Exagamglogene Autotemcel	Sickle cell disease, beta-thalassemia	Casgevy®	Feb 2024	Vertex	Gene Therapy	Yes
Onasemnogene Abepravovec	Spinal muscular atrophy type 1	Zolgensma®	May 2020	Novartis	Gene Therapy	Yes

The procedure for an ATMP to be reimbursed involves several key steps. First, the ATMP must receive approval from the EMA, where it is evaluated for safety, efficacy, and quality, with the CAT providing scientific recommendations. Following EMA approval, HTA bodies conduct evaluations on the clinical effectiveness, cost-effectiveness, and overall impact on the healthcare system of the ATMP. A positive recommendation from these HTA bodies supports the reimbursement process. Subsequently, national health authorities make the final reimbursement decision, taking into account the healthcare budget and the product's necessity within the national healthcare system. In some cases, price negotiations between the manufacturer and national health authorities are conducted to agree on a fair price for the ATMP. Once approved, the ATMP is included in the national reimbursement list, allowing healthcare providers to prescribe it to patients. (Drummond, et al., 2008) (EMA, 2024)

2. CHAPTER 2. Problem Statement

2.1. Challenges in Reimbursement

The arrival of ATMPs marks a significant leap in medical science, offering revolutionary treatments for various rare and severe conditions. However, their integration into healthcare systems poses substantial reimbursement challenges that need to be addressed to ensure patient access and sustainable healthcare practices, these challenges include issues related to affordability, uncertainty due to limited evidence, regulatory and administrative hurdles, and opportunity cost.

One of the foremost challenges in the reimbursement of ATMPs is affordability, as ATMPs often come with high upfront costs due to their nature as one-time treatments designed to provide long-term benefits. Payers are facing the critical challenge of ensuring a balance between the financial sustainability of the healthcare systems while encouraging the innovation and development of the new therapies. The financial burden of developing, manufacturing, and administering these therapies creates significant obstacles for traditional payment models. There is a risk that aiming for financial stability in healthcare systems may limit patient access and innovation. To ensure these advanced treatments are accessible to patients, innovative pricing and funding models are necessary. (Gonçalves, 2022)

Another significant hurdle is the uncertainty surrounding the long-term outcomes of ATMPs. Given the relatively recent introduction of many of these therapies, there is limited evidence on their prolonged efficacy and safety. For example, there are potential safety concerns related to the internal characteristics of living cells, including the risk of severe or life-threatening toxicities, such as CAR-T induced neurotoxicity and cytokine release syndrome. (Bellino, et al., 2023) This uncertainty complicates the assessment of their true value and risks, making payers hesitant to commit to high-cost treatments without robust, long-term data. To address this, continuous post-market surveillance and the collection of real-world evidence are essential to build a comprehensive understanding of ATMPs' impact over time. In a study conducted through semi-structured interviews with key informants in US payer organizations, decision-makers highlighted the need for comprehensive evidence to ensure long-term real-world outcomes of curative therapies align with expected benefits. The study emphasized future policies must balance high initial costs with long-term financial benefits. Payers seek robust data to confirm the long-term

efficacy and economic impact of these high-cost therapies. (Yeung, et al., 2019; Gonçalves, 2022; Dolon, 2023)

Payers face the challenge of evaluating the opportunity cost of reimbursing ATMPs. This involves assessing whether the benefits provided by these therapies justify the potential diversion of resources from other treatments. Although especially for orphan medicines, alternative treatments are unavailable. The high price of ATMPs necessitates a careful examination of their overall value to the healthcare system. Payers must balance the allocation of limited resources to ensure that the adoption of ATMPs does not adversely affect the availability of other essential medical services. The value of a good or service, including ATMPs, is determined by what individuals are willing to pay in monetary terms or other resources. For ATMPs, pricing involves defining both the economic justification and the value of the product. Health Technology Assessment (HTA) often determines payer willingness to pay, but calculating the incremental cost-effectiveness ratio (ICER) for many ATMPs is not viable. Traditional value assessments consider factors like improvement in length and quality of life, ease of use, and healthcare cost savings. Additional elements such as insurance value, value of hope, and socioeconomic impact should also be considered. Rare diseases, often targeted by advanced therapies, add complexity to pricing and reimbursement decisions, as generating sufficient clinical evidence and assessing long-term effectiveness can be challenging. Ethical considerations arise when potential cures are available, yet patients may be denied access due to evidence development timelines. (Gonçalves, 2022; Dolon, 2023)

2.2. How are HTA bodies responding to the assessment challenges posed by ATMPs

There is evidence that traditional HTA methodology does not adequately capture the entire value proposition for ATMPs, which have the potential to ‘cure’ rare or ultra-rare diseases. Capturing the lifelong benefit potential of ATMPs could lead HTA bodies and payers to accept a higher level of uncertainty in their decision-making for transformative treatments. HTA methods were initially developed for conventional, non-personalized medicines using randomized clinical trials to demonstrate comparative clinical and economic value. These methods do not anticipate the transformative benefits of ATMPs, which may provide additional value beyond comparative effectiveness, shaped by contextual considerations such as disease severity, availability of other

treatments, and ethical priorities (ARM, 2023). ATMPs often reach the market with immature clinical data due to data generation challenges, leading to high uncertainties in HTA assessments. The high prices required by ATMP manufacturers subject the evidence to intense scrutiny by HTA bodies and payers, balancing significant patient benefits against uncertainties and opportunity costs.

The current HTA processes are evolving to address many of the challenges posed by ATMPs, but there are still areas where they fall short. Much has already been written about the distinctive characteristics of these new therapies and the need for updated HTA methods. Some papers argue for a different approach to the HTA of cell and gene therapies, while most HTA bodies prefer standardized approaches for all health technologies. In this context, (Drummond, et al., 2019) argue that HTA bodies could apply their standardized approach but should pay specific attention to the particular challenges posed by ATMPs. HTA bodies are increasingly accepting surrogate endpoints, recognizing disease severity, incorporating broader value concepts, and using scenario and sensitivity analyses. However, they still rely heavily on single-arm trials with limited comparative evidence, struggle with small sample sizes and generalizability, and face challenges in extrapolating long-term outcomes. Economic evaluations often do not fully account for unique aspects like insurance value (the financial protection a health technology provides against future health risks) and option value (the value of having the flexibility to use a health technology in the future based on evolving evidence). (Drummond, et al., 2023)

2.2. Managed Entry Agreements

2.2.1. A Definition of MEAs

Managed entry agreements (MEAs) are arrangements between firms and healthcare payers that allow for coverage of new medicines while managing uncertainty around their financial impact or performance. These agreements negotiated between manufacturers (firms) and payers, the payer term can include healthcare payers, government departments, national authorities, or health

technology assessment (HTA) bodies. MEAs can also exist between healthcare providers and firms.

The use of managed entry agreements (MEAs) has increased significantly over the past decades. Most OECD countries and EU member states now use MEAs, although to varying extents, to include new medicines in health coverage schemes. The design and implementation of MEAs differ widely across countries, influenced by the intended goals, payer strategies, and technical capacities. While MEAs are praised for accelerating access to new treatments, reducing uncertainty around product performance, and managing budget impact, critics argue they reduce transparency and increase administrative workload. (Wenzl & Chapman, 2019)

2.2.2. Taxonomy of MEAs

Initially, MEAs are divided into financial agreements and performance-based agreements. Financial agreements focus on managing budget impact, often through confidential discounts (price/volume discounts, patient/dose-dependent discount) or rebates, or price capping, without linking to treatment performance. Performance-based agreements require data analysis on product performance, with financial outcomes dependent on achieving specific health outcomes, in other words they link the reimbursement level to clinical outcomes. There are also combination managed entry agreement which rely on both financial and performance considerations to address different issues at the same time, for example, budget impact and use, or access and cost-effectiveness. (Al-Omar, et al., 2021; Wenzl & Chapman, 2019)

Additionally, MEAs are categorized by whether financial mechanisms operate at the patient or population level. Patient-level agreements address individual treatments, while population-level agreements apply to groups of patients. Simple discounts or rebates are included in financial agreements as they condition coverage on the presence of a discount or rebate. (Wenzl & Chapman, 2019)

Finally, MEAs are broken down by specific design mechanisms to control budget impact or manage performance uncertainty, applicable at both patient and population levels. This classification is illustrated in Image 2, with detailed descriptions and examples provided in tables 4 and 5. This taxonomy is only based on how agreements are structured. (Wenzl & Chapman, 2019)

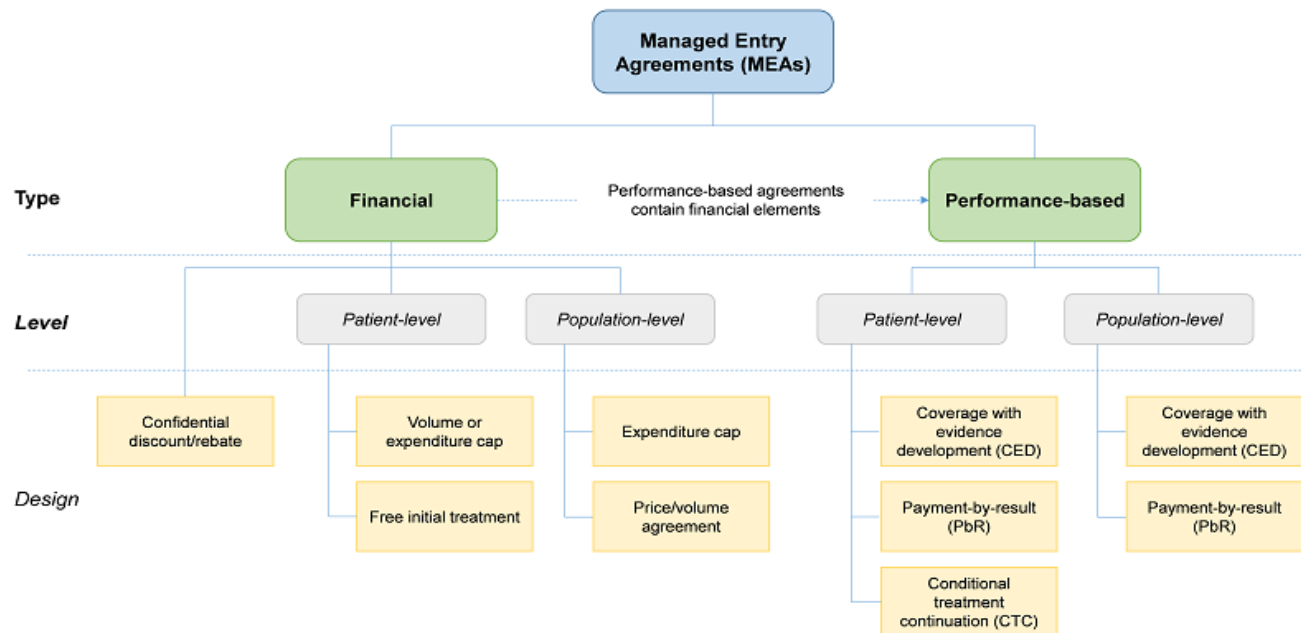


Image 2: Taxonomy of Managed Entry Agreements (MEAs), equivalent of Value Based Contracting. (Wenzl & Chapman, 2019)

Table 4: Examples of types and designs of Financial MEAs

Agreement Level and Design	Description	Example
Confidential Discount or Rebate	An unconditional reduction off the list price is agreed in a confidential contract, taking the form of an up-front discount or an ex-post rebate refunded by the firm.	Lenvatinib (Kisplyx®) for renal cell carcinoma (RCC) in England and Wales (since Jan.2018). A simple discount at the point of purchase or invoice has been agreed confidentially between the Department of Health and the firm.
Patient-level Treatment or Expenditure Cap	A patient-level treatment (number of product, dosage or duration) or expenditure ceiling is agreed on, and the firm	Lenalidomide (Revlimid®) for treating myelodysplastic syndromes in England and Wales (since 2014). The firm is paid for treatment of up to 26 monthly cycles and provides products free

		provides products exceeding the cap free of charge.	of charge for patients who receive more than 26 monthly cycles.
Patient-level Treatment	Initial	The firm provides initial treatment units free of charge up to an agreed level for each patient treated, after which additional units are purchased at an agreed price.	Certolizumab pegol (Cimzia®) for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor in England and Wales (since 2016). The first 12 weeks of treatment (10 pre-loaded syringes of 200mg each) are free of charge. Acquisition costs is GBP 6,793 in the first year of treatment and then GBP 9,295 per year.
Population-level Expenditure Cap		An aggregate expenditure ceiling for all patients/a defined number of patients treated is agreed on, and the firm provides products exceeding the cap free of charge.	Direct-acting antivirals (DAAs) for hepatitis C in Australia (since 2015). The government defined an annual budget cap above which firms provide a rebate for the full treatment costs.
Population-level Price/Volume Agreement		Tiered price are agreed on, which decrease with increasing aggregate volume purchased for all patients treated.	Commonly used in France. Information on specific agreements are not public.

Table 5: Examples of types and designs of Performance based MEAs

Agreement and Design	Level	Description	Example
Patient-level Coverage Evidence Development (CED)	with	The treatment is covered temporarily by the payer only for patients who agree to enroll in a study that evaluated the performance of the treatment. Based on the results of the study,	Clofarabine (Evoltra®) in Korea (2018). Patients must have been enrolled in a clinical trial to receive reimbursement of the medicine. This agreement ended in December 2018 as clinical effectiveness was confirmed and reimbursement maintained.

	coverage is withdrawn or extended, or prices adjusted.	
Patient-level Payment by Results (PbR)	Payment to the firm for treatment provided is contingent on the achievement of pre-specified response to treatment in each patient. Payers may uphold payment partially or entirely for each patient until the results are achieved, receive full or partial refunds for patients who do not achieve the response, or receive free additional products with which to treat subsequent patients.	Alglucosidase alpha for late-onset Pompe disease in Estonia (ongoing). The product is reimbursed when a positive effect is confirmed by a panel of 4 specialist doctors.
Patient-level Conditional Treatment Continuation (CTC)	Coverage of the treatment is continued only for patients who achieve a pre-specified response to treatment: firms provide products free of charge or discounted for patients who do not achieve results.	Several Alzheimer's medicines in Italy (2007). The firm provides products free of charge for the first 3 months of treatment and short-term effectiveness is assessed. If treatment goals are met after 3 months, treatment is continued for a maximum of 2 years and the firm paid by the national health service (SSN).
Population-level Coverage with Evidence Development (CED)	The treatment is covered temporarily by the payer for all treatment-eligible patients while a study evaluates the performance. Based on the results of the study, coverage is maintained, withdrawn or extended, or prices are adjusted.	Axicabtagene ciloleucel (Yescarta®) for B-cell lymphoma in England (ongoing). The Cancer Drugs Fund (CDF) covers the treatment under the condition that further evidence is collected to reduce uncertainty around survival estimates. Evidence includes an ongoing phase II trial and observational data from a cancer registry. At the end of the agreement, the medicine is reappraised and if there is insufficient evidence or the medicine is considered not to be clinically or cost effective,

		the medicine may be removed from the CDF and no longer available on the National Health Service. In this case, patients will continue to receive the drug at the pharmaceutical company's cost until the prescribing physician deems it appropriate to discontinue treatment.
Population-level Payment by Results (PbR)	Payments to the firm for treatments provided is contingent on the achievement of an agreed result in the population treated. Payers may withhold payments partially or entirely until the result is achieved, receive a full or partial refund if the result is not achieved, or receive free additional products.	Interferon beta and glatiramer acetate for multiple sclerosis in England and Wales (2002). Treatments were initially priced at the level demanded by the firm and, based on a 10year cohort study estimating disability using the extended disability status scale (EDSS), prices were expected to be adjusted every 2 years to meet a cost-effectiveness threshold of GBP 36,000/QALY gained.

By comparing the MEAs presented in Tables 4 and 5, it is clear why financial MEAs are usually preferred in practice. The main reason is that they are much simpler to set up and manage. Performance-based MEAs require a lot of work, such as constant data collection and tracking how patients respond to treatment. On the other hand, financial MEAs focus on simple things, like discounts and expenditure caps. Because they don't need complicated monitoring, they create much less administrative work for everyone involved. This makes them a more practical choice for managing costs without the technical difficulties of tracking clinical outcomes.

*Table 6: OECD countries and EU member states in which MEAs are used or were used in the past. **"product/indication pair," means a specific medication or therapy (product) and its intended use (indication). (Wenzl & Chapman, 2019)*

Country	Financial	Performance-based	Comment
UK	yes	Yes	All products in the current Cancer Drugs Fund (CDF) are subject to population-level CED. NICE confirmed existence of

			performance-based MEAs for a number of other product/indication pairs. No data are available on the total number and types of performance-based MEAs outside of the CDF
France	Yes	Yes	France reported that financial MEAs for 3 product/indication pairs and patient-level CED for 1 pair were closed but provided no agreement end dates for the remaining pairs, by 2020. **
Germany	No	No	
Italy	Yes	Yes	
Spain	No data	Yes	
Poland	Yes	Yes	Surveys found that MEAs were used but are confidential

The flowchart in image 3 is a useful tool for understanding how to choose between outcome-based delayed payment models and financial-based reimbursement models for therapies. It helps clarify under which circumstances each model is feasible by guiding through key questions about clinical uncertainties, relevant outcome measures, and available data infrastructure. So, this visual aid supports the text by providing a clear, step-by-step framework for evaluating and implementing these reimbursement models. (Callenbach, et al., 2024)

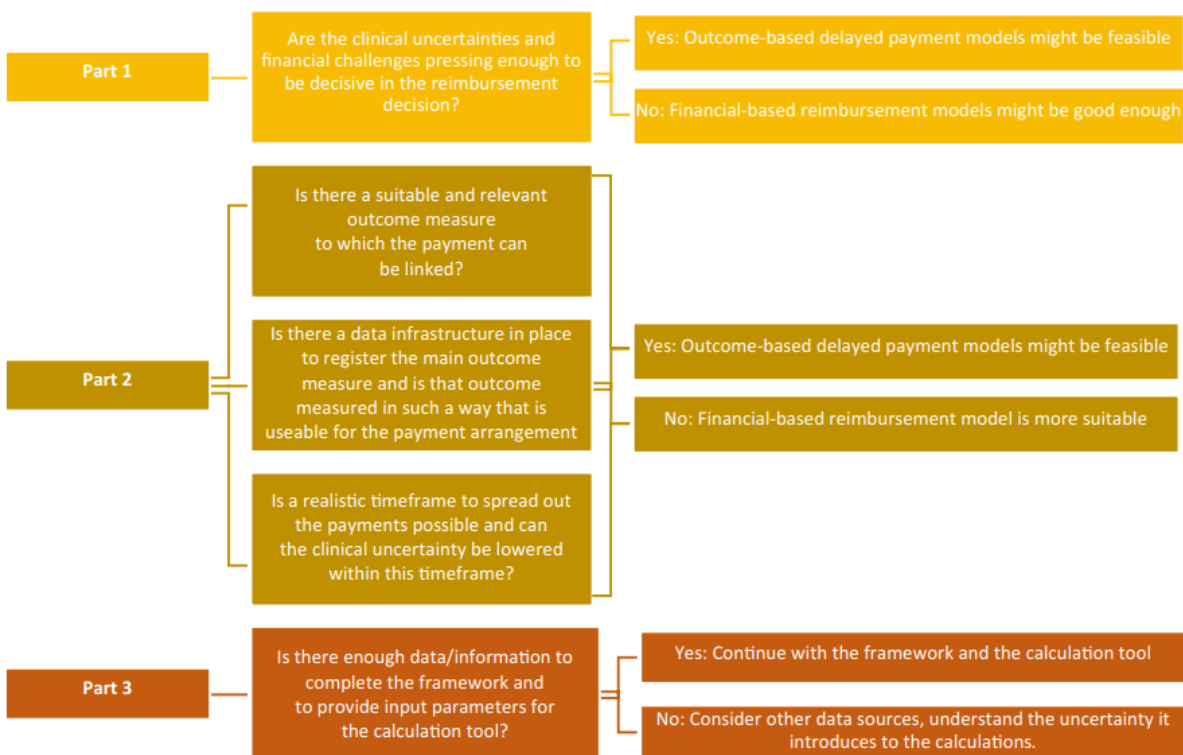


Image 3: Key decision questions for end users per part of the framework and calculation tool. (Callenbach, et al., 2024)

Table 7: Payment Mechanisms (Vreman, et al., 2020)

Payment Mechanisms	Benefits	Limitations
Upfront payment	-Easiest mechanism to implement -Rebates may be able to mitigate some of the risks associated with upfront payment	-High financial burden on payers with high associated risk
Payment after achieved outcomes	-Relatively little risk for payers	-High financial burden on manufacturers with high associated risk
Annuity payments	-Spreading out high costs over longer period of time assures that more patients per year can be treated within the same yearly budgets - Acceptable mechanism for industry and payers	-Does not lower the price of treatment unless combined with other measures, and interest rates may apply, which would make the total price higher -Requirement of diagnostic monitoring may add extra burden to providers

	-Possibility to create a liquid healthcare-loan market with substantial leverage for payers and lenders to negotiate prices -Can be combined with risk-shared contracts to set the duration of payment	-Difficult to implement in healthcare systems with multiple payers between which patients can switch -Unclear where initial financing will come from, especially with smaller insurers
Health leasing/subscription	-Reduces uncertainty for payers and manufacturers -Could prevent high upfront costs -Can facilitate the treatment of large patient populations for drugs with low production but high unit costs -Could reduce manufacturers' incentives to aggressively market drugs	-Does not affect total budget impact of treatment per patient in all cases -Accurate forecasting may be difficult for payers as well as manufacturers, making it hard to establish an appropriate financing limit -For manufacturers, time to return on investment can be increased

2.2.3. Importance of Performance-based MEAs for ATMPs

They provide the short-term advantage of covering new medicines at lower, confidential prices, making them more affordable for healthcare systems, while collecting evidence on their effectiveness and safety. These agreements are designed to reduce uncertainty about the performance of new products in terms of their comparative and cost-effectiveness. Although there have been challenges, the goal remains to gain better insights into how new treatments perform in real-world settings. Performance-based MEAs offer a way to manage the financial risks associated with new treatments. Payment-by-result agreements effectively manage budget impact by limiting payments to only those patients who respond to treatment, ensuring financial resources are used efficiently. Experts also highlight that these agreements enable access to high-priced medicines under public and industry pressure, making them more affordable. These agreements encourage the collection and analysis of data on treatment effectiveness, which can inform future healthcare

decisions and policies. To conclude, performance-based MEAs are essential tools for bridging the gap between the urgent need for value-based approaches and the reality of slow-to-change pricing and reimbursement systems. They are particularly suitable for innovative drugs that meet a medical unmet need but come with substantial uncertainty regarding their clinical effectiveness. (Wenzl & Chapman, 2019; Dolon, 2023)

2.2.4. Challenges on Performance-Based MEAs

Performance-based MEAs face several significant challenges. The quality of the evidence generated often suffers due to poor study design and methodological issues, leading to poorly addressed uncertainties. The administrative burden of implementing these agreements is substantial, as they require extensive resources for data collection and analysis, which can be taxing for healthcare providers and payers. High levels of confidentiality further complicate matters by restricting information sharing with third parties, making coverage decisions more challenging. Additionally, there's a potential risk of firms engaging in risk selection, where they might only treat patients likely to respond positively to ensure payment, though this has not been observed in practice. Experts have mixed views on the effectiveness of performance-based MEAs, they acknowledge their success in accelerating coverage decisions and managing budget impact but express concerns about their ability to reduce uncertainty around product performance, the administrative burden they impose, and the issues surrounding confidentiality. (Wenzl & Chapman, 2019)

2.2.5. Combined Models

Both finance-based and outcome-based MEAs can help to reduce payer uncertainty, aid patient access and form an important part of pricing and market access launch strategy. Finance-based agreements are generally easier to implement, are less complex and are implemented more widely. Outcome-based arrangements are less common and typically have greater complexity due to data collection or administrative issues. The Cancer Drugs Fund in England is a recent example where a government has proactively provided funding whilst additional evidence is being developed. (NICE, 2024; Wenzl & Chapman, 2019)

Another example is Annuity (Financial-based) with Pay-for-Performance (P4P, Performance-based). When annuity payments are combined with P4P, a leasing-style arrangement is created that spread costs over time and only pays when targets are met. This "leasing" approach addresses budget constraints and shares risks between payers and manufacturers. It is especially suitable for ATMPs with long-term health benefits, making it more feasible and accepted than P4P alone. Repayment is tied to direct health outcomes observed in the short-to-medium term following treatment. (Coyle, et al., 2020)

3. CHAPTER 3. ATMP Pricing and Reimbursement Practices: Country Case Studies and Joint HTA Regulation

3.1. Current HTA, Pricing, and Reimbursement practices for ATMPs in scope countries: United Kingdom, Germany, France Italy, Spain and Poland.

3.1.1 United Kingdom

In the UK, the National Health Service (NHS) funds most drugs and health services. The National Institute for Health and Care Excellence (NICE), established in 1999, provides guidance on the use of medicines, devices, and other health interventions in the NHS. Before NICE can recommend a medicine or device through its health technology assessment (HTA) process, it must first receive marketing authorization from regulatory agencies like the EMA, the UK's Medicines and Healthcare products Regulatory Agency (MHRA), or other accredited bodies issuing CE marks. These regulators evaluate company submissions, including lab methods, manufacturing specs, and clinical data, to decide on the safety and efficacy of the products. NICE then takes these regulatory decisions and further assesses the clinical and economic aspects to ensure NHS patients have access to the most effective and cost-efficient treatments. They decide which health technologies get funding and when. If NICE recommends a drug, the NHS must fund it, however a negative recommendation does not automatically mean that there will be no funding. (Osipenko, 2021) (McPhail & Bubela, 2023)

NICE reviews new drugs through a process called Health Technology Appraisal. For the evaluation of ATMPs, two different HTA processes are being used: the Single Technology Appraisal (STA) and the Highly Specialized Technologies Program (HSTP). The STA process is applied to products targeting non-rare diseases and uses cost-effectiveness analysis (CEA), while the HSTP is used for products targeting ultra-rare diseases and allows for a higher Incremental Cost-Effectiveness Ratio (ICER) threshold. Recently, ATMPs such as Kymriah® and Yescarta® have been evaluated through the STA process, whereas Strimvelis®, Luxturna®, Zolgensma®, and Libmeldy® have been assessed through the HSTP. (Ronco, et al., 2021; Iglesias-López, et al., 2023) NICE believes that its standard HTA methods and processes for evaluating clinical and cost-effectiveness are suitable for ATMPs. (Champion, et al., 2021) Although, evaluating ATMPs is more complex than traditional pharmaceutical treatments, making standard appraisal methods by

NICE difficult or unsuitable. Recognizing the need for flexible and adaptable evaluation methods, they are considering significant changes to their health technology assessment processes. (Pinho-Gomes & Cairns, 2022)

NICE usually uses an ICER of £20,000-30,000 per Quality Adjusted Life Year (QALY) to decide if a treatment is cost-effective. The first wave of ATMPs approved by NICE were evaluated through the Cancer Drugs Fund (CDF). When a treatment shows potential for positive recommendation but has certain uncertainties, which requires more investigation while additional data is gathered, it is made available through the CDF, which does not strictly follow the usual ICER range. After a set period, the treatment undergoes a comprehensive review, resulting in a final recommendation. (McPhail & Bubela, 2023; Champion, et al., 2021)

Because ATMPs are innovative and complex, it's hard to determine their ICER accurately, leading to the use of higher thresholds. That's why ATMPs are being assessed under the Highly Specialized Technologies route to have an ICER of up to £300,000 per QALY in certain cases. (Champion, et al., 2021)

The NHS uses managed access schemes to help individuals get quicker access to promising new treatments that might not be recommended yet due to uncertainties about their effectiveness or cost. These treatments are financed through two dedicated funds, each with an annual budget of £340 million: NHS England's Cancer Drugs Fund as already mentioned, and the Innovative Medicines Fund (IMF). This approach ensures that taxpayers receive optimal value for their money and provides pharmaceutical companies with a pathway to secure NHS funding for treatments that are likely to be cost-effective. Under managed access agreements, additional real-world evidence is collected to address any uncertainties about a treatment. Then it can be determined whether the treatment should be made available for routine use within the NHS. (NICE, 2024) The IMF will expand the current CDF and has the potential to be more ambitious than currently envisioned. If implemented effectively, the IMF can facilitate sustainable and earlier access to new medicines, including treatments for rare conditions. The CDF has provided immediate funding for cancer treatments since 2011, and the IMF offers an equivalent route for non-cancer medicines. (NHS, 2024; ABPI, 2023)

Currently, most of ATMPs are purchased through a standard reimbursement method, which involves an upfront payment for the product regardless of the treatment's success or failure. This includes with a basic patient access scheme discount which has been negotiated for all NICE-

approved ATMPs. Upfront payments provide full reimbursement to manufacturers for the ATMP, placing all financial risks on the NHS. (Andrew, et al., 2020)

In the UK, coverage with evidence development (CED) is commonly used, instead of performance-based agreements. Real-world evidence is collected through ongoing patient monitoring and data analysis in clinical settings. While CED can effectively use real-world data to guide coverage and payment decisions, the frequent reassessment of therapies can be burdensome and create uncertainty about future access. As part of the 2024 voluntary scheme, NHS England announced plans to pilot two studies on outcomes-based agreements including innovative payment models for ATMPs. These pilots could initiate a shift away from reliance on CED in the UK. (IQVIA, 2024; ABPI, 2024)

ATMPs currently reimbursed in the United Kingdom

Since 2021, NHS England has commissioned three gene therapies for rare genetic conditions: onasemnogene abeparvovec (Zolgensma®) for spinal muscular atrophy, atidarsagene autotemcel (Libmeldy®) for metachromatic leukodystrophy, and eladocogene exuparvovec (Upstaza®) for aromatic L-amino acid decarboxylase (AADC) deficiency. Additionally, NHS England has introduced groundbreaking CAR-T therapies for five different cancer indications, using the body's own immune system to target cancer cells, such as Axicabtagene Ciloleucel (Yescarta®), Brexucabtagene Autoleucel (Tecartus®), and Tisagenlecleucel (Kymriah®), which are funded by the CDF. These therapies are part of an expanding portfolio of ATMPs. Recently, NHS England began funding etranacogene dezaparvovec (Hemgenix®) through the Innovative Medicines Fund (IMF) making it available to patients with severe or moderately severe haemophilia B, and also eladocogene exuparvovec (Casgevy®) for patients with AADC deficiency, which is a rare genetic disorder (NHS, 2024)

According to NICE, there are currently 12 reimbursed ATMPs in the UK out of the 20 approved by EMA: Hemgenix®, Imlygic®, Kymriah®, Yescarta®, Luxturna®, Tecartus®, Upstaza®, Libmeldy®, Holoclar®, Spherox®, Zolgensma® and Casgevy®. (NICE, 2024)

Table 8: ATMPs reimbursed in the UK. (NICE, 2024)

ATMPs	Reimbursement
Hemgenix	IMF
Casgevy	IMF
Holoclax	Restricted access
Imlygic	Simple discount
Kymriah	CDF
Yescarta	CDF
Luxturna	Simple discount
Spherox	Restricted access
Tecartus	CDF
Upstaza	Simple discount
Libmeldy	Simple discount
Zolgensma	Restricted access

When NICE imposes restricted access for an ATMP, it means that the treatment is not immediately available to all patients through the NHS. Instead, access is limited to specific criteria or conditions, often due to uncertainties about the treatment's effectiveness or cost-effectiveness. (ABPI, 2024)

3.1.2. France

In France, the HTA process and pricing and reimbursement practices involve several key organizations. The final decision to include a medicine for reimbursement falls within the competence of the ministers responsible for Health and Social Security and is published in the Official Journal. The Transparency Committee of the Haute Autorité de Santé (HAS) evaluates medicines that have obtained their marketing authorization (Autorisation de Mise sur le Marché,

AMM), when the laboratory seeks their inclusion on the list of reimbursable medicines. They provide an opinion on the coverage of medicines by Social Security and/or for their use in hospitals and contribute to the proper use of medicines by publishing independent scientific information on medicines and their place in the therapeutic strategy. Created by the Health Insurance reform law of August 2004, the National Union of Health Insurance Funds (UNCAM) defines the scope of services eligible for reimbursement and sets the rate of coverage for care. For medicines, its competence concerns the reimbursement rate, while the registration decision belongs to the ministers responsible for Health and Social Security. The Economic Committee for Health Products (CEPS) contributes to the development of the economic policy for medicines. This interministerial body, created in 2005 and under the aegis of the Ministry of the Economy and Finance, the Ministry of Social Affairs and Health, and the Ministry of Productive Recovery, sets the prices of medicines and medical devices for individual use covered by compulsory health insurance. (HAS, 2024)

In France, medicinal products are assessed and appraised by the Transparency Committee (TC) of the French National Authority for Health (Haute Autorité de Santé, HAS). If the absolute clinical value (Service Médical Rendu, SMR) of a drug is considered sufficient, the medicine can be granted reimbursement and then evaluated for its additional clinical value (Amélioration du Service Médical Rendu, ASMR). The ASMR is a driver for price negotiation with the Committee for Healthcare Products (Comité Économique des Produits de Santé, CEPS). The ASMR rating, assigned by the TC, ranges from I (maximum, revolutionary therapy) to V (minimum, no superiority versus standard of care) and it impacts price negotiations with the CEPS. (Ronco, et al., 2021)

While the SMR determines if a drug is reimbursed, the ASMR determines how much the state is willing to pay for it compared to existing treatments. The table bellow (Table 9) illustrates how the rating translates directly into pricing strategy. The higher the rating (lower the number), the more leverage a pharmaceutical company has to request a higher price.

Table 9: Measure of the clinical added value (HAS, 2014)

Major	Important	Moderate	Minor	No clinical improvement
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ASMR I	ASMR II	ASMR III	ASMR IV	ASMR V
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Medicinal products can be reimbursed temporarily before the conclusion of the regular HTA pathway or even before the Marketing Authorization, via the Temporary Authorization of Use (ATU) on a named patient basis (nominal ATU) or for all patients for a given indication (cohort ATU). Until January 2023, 3 products have received cohort ATU (Kymriah®, Yescarta®, and Luxturna®) and 1 product (Zolgensma®) received nominative ATU and a cohort ATU later in the marketing authorization indication. During the ATU period, the MAH is allowed to set a launch price before the negotiation with the CEPS. Until the Committee for Medicinal Products for Human Use generates a positive opinion, the patients can already have access to the medicine without waiting for European Commission's decision and the HTA full evaluation period. During the ATU validity, the company can set a free price before the negotiation, but subsequently, the ASMR category will be a driver for price negotiation. Formally, the duration of early access cannot exceed 1 year, but it can be renewed with updated product information. If the price negotiation with CEPS extends beyond 90 days after obtaining the evaluation from the HAS, discounts over the list prices can be applied. (Iglesias-López, et al., 2023; HAS, 2024; Ronco, et al., 2021)

If a new medicine receives authorization, it can set its price freely for the entire Early Access Program period, unless the product is provided for free. For new indications of an already approved product, the previously set price is used. Early access contracts include financial managed agreements with volume caps, where the manufacturer covers any excess, and if the final price negotiated is lower than the early access price, the manufacturer reimburses the difference. (Tarantola, et al., 2023) ATMPs, such as Kymriah® , Yescarta® , and Zolgensma® , have benefited from this system. France also guarantees earlier access to non-innovative drugs for unmet medical needs. France covers most ATMPs with confidential price discounts. Details about whether reimbursement arrangements include mandatory evidence collection are also confidential. If evidence collection is mandated, the Technical Agency for Information on Hospitalization (AITH) would be responsible for gathering this data, and the health ministry would analyze it. When an HTA assessment indicates that a therapy provides significant added clinical value, France has a system to allocate additional funding to cover the costs of ATMPs administered in hospitals, beyond the existing diagnosis-related group (DRG) fee. (Rejon-Parrilla, et al., 2023) For CAR-T

cell therapies, France relies on coverage with evidence development (CED) to adjust reimbursement and pricing over time as real-world evidence is generated. (IQVIA, 2024) For example for Kymriah, the Transparency Committee recommended to collect further data through the Lymphoma Academic Research Organization Registry: effectiveness (survival, remission status, disease progression) and adverse events, to be recorded at 28 days, 100 days, 6 months and every subsequent 6 months after injection. (Drummond, et al., 2023)

If the Haute Autorité de Santé does not recommend reimbursement, the manufacturer must provide treatment to patients for one year before cutting off supply. The assumption of innovativeness is crucial for eligibility. To be considered innovative, a medicine should bring significant improvements in efficacy, safety, convenience in use, and organizational impact. It must be backed by a development plan and clinical results showing patient benefits, and it should not have significant unknown factors regarding tolerance or other critical data. Manufacturers apply to the Agence nationale de sécurité du médicament et des produits de santé (ANSM) for safety and efficacy assessment. After ANSM approval, the request goes to HAS, which should complete its analysis within three months. (Tarantola, et al., 2023)

ATMPs currently reimbursed in France

While the EMA has authorized 20 ATMPs, France currently reimburses 11 of them. ATMPs that are currently reimbursed in France are Abecma®, Breyanzi®, Carvykti®, Ebvallo®, Kymriah®, Yescarta®, Luxturna®, Tecartus®, Upstaza®, Libmeldy® and Zolgensma® (Santé, 2024) (HAS, 2024) (VFA, 2024)

While the 11 ATMPs listed above are the ones that have reached a permanent reimbursement, Table 11 shows a longer list that contains 5 more: Alofisel, Hemgenix, Holoclar, Roctavian, Spherox.

This is because Table 11 includes ATMPs that are available through the Early Access scheme, due to their high unmet medical need, and this allows patients to have access to these treatments while their final reimbursement price is still being negotiated with the authorities. So, France provides coverage for 16 of them, but through different regulatory pathways, and the 5 ATMPs funded through the Early Access framework have ongoing pricing and reimbursement negotiations. This distinction explains the broader list of ATMPs shown on Table 11.

In Table 10 presents the financial aspect of Early Access in France and more specifically the maximum compensation for certain ATMPs. For instance, therapies Upstaza and Libmeldy reach up to 3.5 million Euros. However these figures are a temporary payment and not the final reimbursement prices, while the official price is still being negotiated.

Table 10: ATU- Table of maximum compensation (Santé, 2024)

ATU- TABLE OF MAXIMUM COMPENSATION	
1. ZOLGENSMA	1,945,000.00 €
2. BREYANZI	345,000.00 €
3. ABECMA	350,000.00 €
4. YESCARTA	350,000.00 €
5. TECARTUS	360,000.00 €
6. KYMRIAH	320,000.00 €
7. LUXTURNA	345,000.00 €
8. LIBMELDY	2,875,000.00 €
9. EBVALLO	75,000.00 €
10. UPSTAZA	3,500,000.00 €

Table 11 gives a full picture of which ATMPs are available in France as mentioned above.

Table 11: ATMPs under formal reimbursement or Early Access in France (HAS, 2024) (IQVIA, 2024) (VFA, 2024)

ATMPs	Status
Alofisel	SMR Important/ Insufficient ASMR IV
Breyanzi	SMR Important ASMR III EARLY ACCESS RENEWED

Carvykti	SMR Important ASMR V
Ebvallo	SMR Important ASMR IV REFUSED EARLY ACCESS
Hemgenix	SMR Important/ Insufficient ASMR IV
Holoclar	SMR Important ASMR III/IV
Kymriah	SMR Important ASMR III/IV EARLY ACCESS RENEWED
Yescarta	SMR Important ASMR III EARLY ACCESS RENEWED
Luxturna	SMR Important ASMR II
Roctavian	SMR Important ASMR V
Spherox	SMR Insufficient ASMR not applicable REFUSED EARLY ACCESS
Tecartus	SMR Important ASMR V EARLY ACCESS RENEWED
Upstaza	SMR Important ASMR III EARLY ACCESS RENEWED
Libmeldy	SMR Important ASMR III

	EARLY ACCESS RENEWED
Zolgensma	SMR Important ASMR III/ V

3.1.3. Germany

Approximately 90% of the population in Germany is covered by statutory health insurance (SHI: gesetzliche Krankenversicherung), which guarantees access to appropriate healthcare in accordance with German healthcare legislation. SHI funds are obligated to reimburse approved treatments, such as new medications, immediately upon their market authorization, while also ensuring the efficient use of resources. (Köhler & Christoph, 2021)

The Federal Joint Committee (G-BA) is the main decision-making body in Germany's healthcare system, including representatives from statutory health insurance funds, hospitals, physicians, psychotherapists, and dentists, with patient representatives participating in discussions but without voting rights. The decision-making process for HTA is more autonomous compared to France or Spain, where organizations are influenced by their Ministries of Health. The G-BA oversees the early benefit assessment of new drugs, determining their additional benefit. (Fontrier, et al., 2022; Epstein & Espín, 2020)

The Institute for Quality and Efficiency in Health Care (IQWiG) evaluates pharmaceutical and non-pharmaceutical interventions, excluding orphan drugs, under G-BA's direction.

Upon receiving market approval, new drugs must be submitted for health technology assessment within 6-12 months. (Casilli, et al., 2023)

Germany's early benefit assessment process requires pharmaceutical companies to submit detailed dossiers, including clinical study data, to prove the new drug's additional benefit over established treatments. IQWiG evaluates the evidence within 3 months, focusing on criteria such as mortality, survival, disease severity, adverse effects, health-related quality of life, and innovation. The findings are submitted to G-BA for the final decision, which is publicly available for transparency. (Köhler & Christoph, 2021; Ronco, et al., 2021).

The AMNOG process aims to ensure appropriate drug pricing for products entering Germany without restricting prescription volumes. While national-level negotiated prices are public, individual public health insurance funds may negotiate additional confidential discounts with manufacturers. (Casilli, et al., 2023)

Pharmaceutical companies in Germany have the option to opt-out and withdraw their drug product from the market within four weeks of the G-BA's decision if the evaluation or negotiation outcomes are unfavorable. From 2011 to 2016, around 16% of drugs opted out following unfavorable decisions (Staab, et al., 2018). This opt-out option highlights the stringent nature of the G-BA's evaluation process. Cost-effectiveness analysis is not utilized in reimbursement evaluations due to ethical and legal concerns, with the IQWiG opposing the use of QALYs based on these issues (Epstein & Espín, 2020). This stance sets Germany apart from other countries that heavily rely on CEA in healthcare decisions.

While budget impact analysis is mandatory, cost-benefit analysis remains optional and has not been employed so far (Angelis, et al., 2018). The BIA offers a detailed assessment of the financial impact of new treatments on the healthcare budget, ensuring economic feasibility. Despite the availability of CBA, no such analysis has been submitted to date, likely due to the extensive nature of the benefit assessments by IQWiG, making additional economic analysis unnecessary. (Köhler & Christoph, 2021)

The German healthcare system shares similarities with the French system, particularly in the emphasis on clinical outcomes over economic factors. In both systems, the evaluation of the added therapeutic value of a new drug is crucial. In Germany, the concept of additional clinical benefit closely resembles the French ASMR (Amélioration du Service Médical Rendu), which assesses the improvement in medical service provided by the drug. However, a key difference lies in the strictness of the evaluation criteria. While both countries prioritize clinical effectiveness, Germany's approach tends to be more stringent in determining the extent of the additional benefit. (Casilli, et al., 2023)

ATMPs in Germany

The Federal Joint Committee (G-BA) first categorizes the ATMP either as a medicine or a medical procedure. If the ATMP has pharmacologic properties and its clinical outcome is not dependent on the healthcare professional skills, it is categorized as a medicine and undergoes the benefit assessment procedure according to the AMNOG (Arzneimittelmarktneuordnungsgesetz, Medicine Market Reorganization Act), where discounts on list prices determined by the MAH after 1 year of marketing are negotiated on the grounds of different variables, including the added therapeutic value. Otherwise, it is categorized as a medical procedure and is normally assessed by the PEI (Paul-Ehrlich Institute). Spherox and Holoclar were evaluated via the medical procedure, all other ATMPs underwent the AMNOG process. (Ronco, et al., 2021)

Germany and France have implemented extra-cost coverage systems to support the management of ATMPs in hospitals 15,000 € for each DRG. In Germany, if a medicine used in a hospital setting is not fully covered by an existing DRG fee, hospitals can apply for extra-budgetary reimbursement through the NUB (Neue Untersuchungs- und Behandlungsmethoden, new examination and treatment method). A NUB 1 status is awarded to medicines or procedures that are new, innovative, intended for a small patient population, and require higher resource use beyond what is covered by the DRG. This status allows hospitals to negotiate additional coverage for these treatments. (Ronco, et al., 2021)

To better understand how the NUB system works in practice, it is useful to look at which ATMPs have actually received this status. In Germany, most of the cell and gene therapies on the market right now rely on the NUB 1 category to get funded in hospitals. This is because the standard DRG prices are usually not enough to cover the very high costs of these innovative treatments. As shown in Table 12, most of the authorized ATMPs have been granted NUB 1 status. This confirms that the NUB pathway is currently the main tool for hospitals to manage the financial risk and provided these treatments to patients without delays. (Lee, et al., 2023)

Table 12: ATMPs with NUB1 status according to IQWiG and Lee et al. (Lee, et al., 2023)

ATMPs	Status
Abecma	Order withdrawn
Alofisel	NUB1
Breyanzi	NUB1

Carvykti	NUB1
Ebvallo	NUB1
Hemgenix	NUB1
Imlygic	NUB1
Kymriah	NUB1
Yescarta	NUB1
Luxturna	NUB1
Tecartus	NUB1
Upstaza	NUB1
Libmeldy	NUB1
Zolgensma	NUB1

In Germany, there are no special arrangements at national level to finance ATMPs but social health insurers negotiate outcomes-based rebates with manufacturers. (Rejon-Parrilla, et al., 2023)

Novartis arranged an outcome based payment system for Kymriah based on patient survival. Rebates to the health insurers for patients dying after treatment (time horizon for measuring survival, and the magnitude of the rebate not available in public dominion) (Drummond, et al., 2023). This agreement was accepted by many of the larger insurance groups in Germany resulting in 60% of the citizens covered by German statutory health insurance having access to the therapy. (Hennessy, et al., 2023)

Also for Zolgensma, there is a mandatory collection of RWD until 2027 that is considered an outcome-based agreement, as it ensures that the data collected will be used to evaluate the long-term effectiveness and safety. (Drummond, et al., 2023)

The Medical Research Act (MFG), approved by the Health Committee of the Bundestag on 3 July 2024, aims to simplify clinical trials and drug and medical device approval processes in Germany.

The MFG will also amend rules on ATMPs and drug pricing and reimbursement laws (AMNOG). One key provision is allowing pharmaceutical companies the option of confidential pricing if they have significant drug research activities in Germany. Upon completing price negotiations, companies can choose between confidential and transparent pricing, with confidential pricing requiring an additional discount. This legislation is part of Germany's broader Pharma Strategy to enhance its attractiveness to the pharmaceutical industry by improving market access and the pricing environment. While the MFG facilitates drug pricing and reimbursement, it indirectly affects the management of ATMPs by streamlining regulatory processes and promoting local investment in clinical trials and R&D. (Barton, 2024)

Currently 17 ATMPs are positively recommended in Germany, out of the 20 authorized by EMA. Libmeldy, Yescarta, Tecartus, Carvykti, Alofisel, Upstaza, Hemgenix, Abecma, Holoclax, Breyanzi, Zolgensma, Spherox, Ebvallo, Imlygic, Kymriah, Roctavian, Luxturna. (LIF, 2024; VFA, 2024; IQWiG, 2024)

While ATMPs are widely available in Germany, this does not necessarily reflect their actual usage frequency. According to an IQVIA survey conducted in June 2023, regarding CAR-T cell therapies, only 31 percent of patients referred to appropriate centers in Germany receive these treatments. (VFA, 2024)

3.1.4. Italy

HTA and Pricing Framework

In Italy, the evaluation of drugs and medical devices is governed by distinct procedures involving the Ministry of Health and the regional system, which consists of 19 regions and 2 autonomous provinces. Regions receive budgets from the Central Government and are accountable for healthcare expenses, with the ability to use supplementary payments, regional taxes, and cost-containment policies if they exceed their budgets. The Italian Ministry of Health, AGENAS, and the regions oversee the evaluation of medical devices, with a national HTA plan introduced in 2019 and expected to develop between 2023-2025. (Garau & Jommi, 2023)

In Italy, the assessment and appraisal process for drugs is overseen by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA). This process involves the Scientific Technical Committee (Commissione Tecnico Scientifica, CTS) and the Price and Reimbursement Committee

(Comitato Prezzi e Rimborso, CPR). The CTS evaluates the clinical added value, therapeutic positioning, and potential price comparators of new medicines. If the CTS gives a positive opinion, the CPR then negotiates the price and any Managed Entry Agreements (MEAs) with the Marketing Authorization Holder (MAH). Once a product is reimbursed and its price is negotiated at the national level, a request for its inclusion in regional and/or hospital therapeutic lists must be submitted. Additionally, the MAH can apply for the medicinal product to be granted "innovative status" to facilitate quicker market access.

AIFA's HTA and Pharmacoeconomic Department manage the drug evaluation, considering criteria such as disease burden, target population size, unmet medical needs, and added therapeutic value. (Garau & Jommi, 2023; Ronco, et al., 2021)

Innovative Status, Early Access and Timelines for Access

In Italy, pharmaceutical companies can apply for an innovative status, which grants immediate access to regional markets and coverage by a special innovation fund for three years. Introduced in 2017, these funds include EUR 500 million for innovative oncology medicines and another EUR 500 million for innovative non-oncology medicines, available for 36 months. The funds reimburse innovative medicines at the regional level under conditions set by the 2017 Budget Law (No. 232/2016). Only medicines with 'full' innovative status, determined by AIFA based on unmet therapeutic need, therapeutic added value, and quality of evidence, can access these funds. Italy also set up routes for early access to non-repetitive use of advanced therapies, with law 94/98 providing the legal basis for trying other indications without granted approvals.

Main challenges include spending caps, stakeholder participation, evaluation fragmentation, and lengthy reimbursement decision times. In November 2023, Italy passed a law reorganizing AIFA by merging two committees into one Scientific-Economic Committee to streamline the evaluation process. For orphan medicines, there is a fast-track procedure to complete within 100 days of the reimbursement application. Pricing and reimbursement decisions are consistent across outpatient and inpatient settings. (OECD, 2023; Lee, et al., 2023; Garau & Jommi, 2023)

In a study conducted with data from 2006 to 2023, the average time for the P&R assessment for ATMPs was 1.2 years (446 days, n = 12 ATMPs), which is consistent with the time required to appraise new orphan drugs (484 days on average). From the beginning of the EMA evaluation to

the publication of the reimbursement decision in the Italian Official Gazette (OG), the total regulatory time was 3.2 years. The analysis of the time to first patient access, based on available data for 6 out of 12 ATMPs, showed significant variability, with a national average time ranging from 148 to 611 days after the OG publication.

By disaggregating the access time data at the regional level, it is observed that regions like Molise, Sardegna, Marche, Friuli Venezia Giulia, and Abruzzo have longer average patient access times (450–1313 days). The shortest access times were in Lombardia, Emilia Romagna, and Toscana (116–131 days). The highest variability was in Friuli Venezia Giulia and Sardegna. The longest times were for the first treatments with Yescarta and Kymriah (1342 and 1283 days in Molise, respectively), while the shortest were for Tecartus and Zolgensma (4 and 33 days in Umbria and Puglia, respectively). Nationally, the time to patient access averages 340.6 days (median 216.0 days). Northern and central Italy average 281.5 and 290.9 days, respectively, while southern Italy averages 436.8 days. (Rivetti di Val Cervo, et al., 2024)

Also, the data of the study show a significant expansion in the use of ATMPs in Italy, with coverage increasing from a few regions in 2017 and 2019 to 86% of the national territory by 2023. This growth was particularly notable from 2020 onwards, reflecting a progressive spread of ATMPs across the country. In 2023, the highest expenditure was concentrated in the Northern regions, indicating a significant adoption of ATMPs in these areas. (Rivetti di Val Cervo, et al., 2024)

Beyond the financial models, it is also important to consider the time it takes for these therapies to actually become available in the Italian market. Table 13 provides a clear picture of the timeline of clinical development and the regulatory process, showing the average duration from the clinical stages to the final regulatory approval in Italy. Understanding these delays is key, as they affect how fast patients can access these innovative treatments after they are authorized by the EMA.

Table 13: Clinical Development and Regulatory Timelines for ATMPs in Italy. (Rivetti di Val Cervo, et al., 2024) *under ev, under evaluation; Std. Dev., standard deviation; IQR, inter-quartile range

(Figure 13)	Brand Name	Clinical Development Time ¹ (days)	EMA Assessment Time ¹ (days)	Lag Time between EC and AIFA ^{1,2} (days)	AIFA Assessment Time ³ (days)	Regulatory Time ³ (days)	Average Time to First Patient ⁴ Access (days)
	Holoclar	6474	692	367	361	1430	430
	Strimvelis	8447	364	-51	116	431	-
	Spherox	5650	1656	886	682	3256	-
	Kymriah	2787	273	-51	397	627	387
	Yescarta	3084	371	-48	481	816	611
	Luxturna	3605	462	31	709	1241	305
	Alofsel	2452	729	-93	271	928	-
	Zolgensma	1608	564	8	283	863	148
	Tecartus	1522	321	-45	483	773	155
	Libmeldy	3500	385	-13	450	861	-
	Abecma	1591	454	-41	768	1185	-
	Upstaza	1908	902	122	348	1406	-
	Carvykti	2036	370	33	-	-	-
	Breyanzi	1636	627	58	-	-	-
	Roctavian	2141	405	83	-	-	-
	Hemgenix	2827	333	-10	-	-	-
	Ebvallo	9732	386	109	-	-	-
Mean		3588	547	79	446	1151	340.6
Median		2787	405	8	424	896	216
Std.Dev.		2500	333	234	195	729	328.5
IQR		1697	257	128	201	477	425

¹Statistics calculated on n = 17 ATMPs

² For eight ATMPs the dossier was submitted to AIFA before the EC decision

³ Statistics calculated on n = 12 ATMPs

⁴ Statistics calculated on n = 6 ATMPs

Managed Entry Agreements in Italy

To evaluate how reimbursement models are applied in the Italian healthcare system, Table 14 presents specific examples of innovative contracts for several ATMPs. For instance, therapies such as Yescarta and Kymriah utilize payment-by-results schemes, where the total reimbursement is divided into installments based on the patient's clinical response at specific intervals, such as 6 or 12 months after infusion of the ATMP. This approach demonstrates AIFA's strategy to share both clinical and financial risks with manufacturers. According to the data provided below, manufacturers have indicated that for completed contracts, outcomes have generally matched the clinical effect predictions that supported the initial financial projections. (Dolon, 2023) (Lee, et al., 2023) (Drummond, et al., 2023)

Table 14: Publicly available innovative contracting information. (IQVIA, 2024) (Dolon, 2023) (Lee, et al., 2023) (Drummond, et al., 2023)

Publicly available innovative contracting information	
YESCARTA	Payment at results at 180, 270, and 365 days from infusion. Outcome indicator: unknown (confidentiality agreement)
LUXTURNA	Confidential discount; budget cap (21.6Min €/24months)
ZOLGENSMA	Confidential discount; pay per result (Installments at delivery, 12, 23, 36, 48 months) Outcome indicator: unknown (confidentiality agreement)
LIBMELDY	Mandatory Discount
KYMRIAH	Confidential discount (for diffuse large B-cell lymphoma); Installment payment at result, at 6 and 12 months from infusion, both indications Outcome indicator: unknown (confidentiality agreement)
STRIMVELIS	Performance-linked-reimbursement (through Drug Registry)

Since many agreements are still in their early stages, it is too soon for a comprehensive assessment of their longterm impact. However, in one instance, a manufacturer reported that real-world outcomes for their ATMP exceeded expectations, leading to a revision of the financial terms in Italy. Even in a country like Italy, which is experienced in managing outcomes-based agreements,

such cases have prompted payers to occasionally switch to a flat discount model to avoid higher-than-planned payments when outcomes surpass the initial expectations.

(Dolon, 2023)

Reimbursed ATMPs

The final stage of the Italian pricing and reimbursement process is the inclusion of the therapy in the national formulary, making it available to patients through the National Health Service. Table 15 provides a comprehensive list of the ATMPs that have successfully secured a reimbursement agreement with AIFA. This list includes a variety of gene and cell therapies, ranging from CAR-T treatments for hematological malignancies to gene therapies for rare genetic disorders. The successful reimbursement of these products confirms Italy's commitment to providing access to medical innovation, despite the high costs and the complexities involved in their clinical evaluation. (AIFA, 2024)

To better understand the regulatory status of these therapies, the following table organizes the data by identifying the specific brand name and the active biological substance of each treatment. Furthermore, it highlights the innovativeness effectiveness dates, which indicate the specific timeframe during which AIFA grants the innovative status that allows for funding through specialized national funds. Finally, the table confirms the reimbursement status, showing whether each product has finalized its price negotiation and is currently covered for patient use within the Italian public healthcare system.

Table 15: ATMP Innovativeness and Reimbursement Status in Italy (AIFA, 2024)

ATMP	Active ingredient	Innovativeness effectiveness start date	Innovativeness expiration date	Reimbursed
ABECMA	Idecabtagene vicleucel	9/2/2024	8/8/2025	Yes
YESCARTA	Axicabtagene ciloleucel	12/11/2023	11/11/2026	Yes
TECARTUS	Cellule CD3 + autologhe trasdotte anti-CD19	05/12/2023	04/12/2026	Yes
LUXTURNA	Voretigene neparvovec	10/01/2021	9/1/2024	Yes
ROCTAVIAN	Valoctocogene roxaparvovec	23/01/2024	22/07/2025	Yes
ZOLGENSMA	Onasemnogene abeparvovec	14/03/2021	13/03/2024	Yes
UPSTAZA	Eladocogene exuparvovec	2/4/2023	1/4/2026	Yes
LIBMELDY	Atidarsagene autotemcel	8/4/2022	7/4/2025	Yes
STRIMVELIS	Autologous CD34+ cells responsible for ADA encode	-	-	Yes
HOLOCLAR	Human corneal epithelial cells	-	-	Yes
KYMRIAH	Tisagenlecleucel	-	-	Yes
BREYANZI	Lisocabtagene maraleucel	-	-	Yes
EBVALLO	Tabelecleucel	-	-	In price negotiations
CARVYKTI	Ciltacabtagene autoleucel	-	-	In price negotiations
HEMGENIX	Etranacogene dezaparvovec	-	-	In price negotiations

3.1.5. Spain

In Spain, the evaluation of medicinal products is managed by the Ministry of Health (Ministerio de Sanidad) and the 17 regional branches. The Spanish Agency of Medicines and Health Products (AEMPS - Agencia Española de Medicamentos y Productos Sanitarios) performs the clinical assessment of new medicinal products. Following this, the General Directorate for Medicines of the Ministry of Health (DGCBSF - Dirección General de Cartera Básica de Servicios del Sistema Nacional de Salud y Farmacia) prepares a price proposal. Negotiations occur between the Price Committee (CIPM - Comisión Interministerial de Precios de Medicamentos y Productos Sanitarios) and the Marketing Authorization Holder (MAH). The final price, which is the maximum reimbursable price nationwide, can be further reduced by hidden discounts negotiated by the Regions, given the decentralized nature of the Spanish Healthcare System. The Spanish Network for Economic Evaluation of Medicines (REvalMed - Red de Evaluación de Medicamentos) provides economic evaluation reports to AEMPS. The criteria considered by AEMPS and the Interministerial Committee on Drug Prices (CIPM) for the evaluation of medicines include therapeutic benefit, severity and impact of the disease, available alternative treatments (and their prices), unmet medical need, safety, mode of administration, degree of innovation, cost, budget impact and rational use of public funds, cost-effectiveness ratio, additional clinical benefit considering cost-effectiveness, and social benefit. AEMPS conducts clinical assessments and requests REvalMed to perform economic evaluations. AEMPS then advises CIPM on clinical and economic assessments and proposes a drug price. CIPM makes the final decision on the price and reimbursement. Negotiations may involve the General Directorate of Pharmaceuticals of the Ministry of Health and the Marketing Authorization Holder (MAH). Some regional HTA agencies or hospitals can reassess or negotiate hospital drug prices below the maximum official price set by CIPM. (Epstein & Espín, 2020; Ronco, et al., 2021)

In Spain, hospitals receive annual budgets based on past treatment volumes, allocated by the autonomous regions. This often results in funding discrepancies across the country. Supplementary payments for high-cost innovative therapies are provided only in exceptional cases. Hospitals can apply for additional funds from regional authorities, but there are no set criteria for making these decisions. (Jørgensen & Kefalas, 2015)

Special arrangements to finance ATMPs aim to share risk and control expenditure through measures like Pay-for-Performance (P4P) schemes, expenditure caps, and price-volume agreements. Outcome-based payment approaches have been adopted to address clinical uncertainties, with payment protocols allowing for payments months after administration and up to 100% refunds if clinical responses are unsuccessful. (Lee, et al., 2023)

ATMPs in Spain

Currently 6 ATMPs are reimbursed in Spain, out of the 20 authorized by EMA. According to IQVIA those are Kymriah, Yescarta, Zolgensma, Luxturna, Alofisel and Tecartus. (IQVIA, 2024; VFA, 2024; Lee, et al., 2023)

While all six are approved for funding, the specific innovative payment models, such as installments and performance-based criteria, have been publicly detailed for the therapies presented in the table below. So, as shown in Table 16, Spain frequently utilizes outcome based payment models that divide the total cost into installments, often linked to long-term clinical success. For instance, the reimbursement for therapies like Kymriah and Yescarta is split into two payments, with a significant portion being contingent on the patient's survival or complete response after 18 months. This structure, along with the use of expenditure caps for products like Luxturna, demonstrates the Spanish strategy to mitigate clinical uncertainty while ensuring budget predictability. (Jørgensen & Kefalas, 2021) (IQVIA, 2024) (Lee, et al., 2023)

Kymriah	Outcomes-based payments in two installments: one at the time of treatment (52%), and a second payment at 18 months (48%), Outcome indicator: complete response to the treatment
Yescarta	Outcomes-based payments in two installments, at time of treatment (52%), 18 months (48%) Outcome indicator: survival
Zolgensma	Outcomes-based payments in installments with additional data collection

Luxturna	-Ceiling cap (Lee, et al., 2023) -Price agreement with installments with additional data collection (Drummond, et al., 2023)
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Table 14: Payment Models for ATMPs in Spain (Jørgensen & Kefalas, 2021) (IQVIA, 2024) (Lee, et al., 2023)

3.1.6. Poland

In Poland, the Ministry of Health makes reimbursement decisions under the 2012 Reimbursement Act. They decide which medicines are reimbursed and their prices, guided by the Drug Policy and Pharmacy Department and the Economic Committee, which process applications and negotiate prices. The Agency for Health Technology Assessment and Tariff System (AOTMiT) evaluates new molecules, and their data and recommendations assist the Minister of Health in making decisions.

Poland's HTA system was introduced in 2005 and became legally authorized in 2009 with the establishment of AOTMiT. AOTMiT employs numerous experts and has expanded its scope to include health service evaluations and public health policy programs. Submitting dossiers to AOTMiT is mandatory for all medicines seeking public reimbursement, requiring manufacturers to present clinical effectiveness, economic analysis, budget impact, and rationalization analyses. The HTA process in Poland is multicriteria, considering clinical effectiveness, disease severity, unmet medical needs, health-related quality of life, innovation, socio-ethical aspects, and recommendations from other HTA organizations. Mechanisms such as rebates, clawbacks, and risk-sharing agreements are used. After evaluation, dossiers are sent to the Ministry of Health's Economic Committee for negotiations on managed entry agreements, official price, reimbursement level, and indications. The Minister of Health makes the final reimbursement decision. Transparency issues exist in selecting AOTMiT members, and there is a call for creating HTA committees within hospitals. Despite challenges such as long delays in patient access to new therapies and high outpatient drug co-payments, Poland's HTA system is robust and continues to progress, supported by the state. (Dimitrova, et al., 2022; Mela, et al., 2024)

The cost-effectiveness threshold is set at 155,000 PLN (35,000 EUR) per QALY, applied to all medicines, including rare and oncology drugs, leading to more negative decisions for high-cost

treatments. Prices are compared across 26 EU countries. Expensive medicines are reimbursed through drug programs with strict inclusion/exclusion criteria and careful monitoring. The Medical Fund Act of 2020 aims to improve care for oncology and rare diseases, allowing reimbursement for such treatments, like Zolgensma, though its inclusion in Poland remains limited due to restrictive criteria. Funding for the Medical Fund currently comes from the National Health Fund (NHF) reimbursement budget. (Kamusheva, et al., 2021) (Mela, et al., 2024)

The reimbursement process is one of the longest in the EU, typically taking at least two years. Reimbursement decisions are valid for either two or three years, with the first decision always set for two years. Managed Entry Agreements do not exist in Poland, but similar mechanisms, called risk-sharing schemes (RSSs), have been implemented. The most common RSSs involve price-volume agreements and confidential discounts for hospitals, while outcome-based RSSs are rare. However, the introduction of the Medical Fund mandates data collection, which may support the development of risk-sharing agreements once medicines are reimbursed. (Wolf Thesis, 2023)

According to the Reimbursement Act of Poland, there are five types of Managed Entry MEAs designed to ensure innovative drugs are available within the public payer's budget constraints.

These MEAs are:

a) Pay-for-Effect: Reimbursement depends on the drug's effectiveness in achieving the desired outcomes. b) Price Discount: An agreed-upon discount on the drug's price between the manufacturer and the payer. c) Price Volume: Setting a predetermined number of drug packages or the population size for which the drug will be sold at a set price. d) Pay-Back: The drug manufacturer must return part of the reimbursement received from public funds, such as for each reimbursed package or after exceeding a set amount intended to finance a particular active substance. e) Other: Includes additional reimbursement conditions aimed at increasing the availability of guaranteed benefits or reducing associated costs.

These MEAs ensure that patients have access to innovative drugs while staying within the public payer's budget. They create a framework that encourages the effectiveness, affordability, and appropriate use of medications for the benefit of patients and the healthcare system. An analysis of risk-sharing instruments proposed in reimbursement applications for drugs used in oncological diseases (assessed by the Polish HTA Agency from 2012 to 2018) shows a preference for easy-to-implement mechanisms, with rebates or pay-back being the most common choices. (Mela, et al., 2024)

ATMPs in Poland

Currently, 5 ATMPs are reimbursed in Poland out of the 20 authorized by the EMA. These treatments include Yescarta, Kymriah, Hemgenix, Breyanzi, and Ebvallo. Although Poland has a more limited reimbursement portfolio compared to other Western European countries, it has made steady progress in providing access to these advanced therapies, particularly for hematological malignancies.

It is important to note that the reimbursement for these therapies is managed through specialized national drug programs. These programs ensure that patient access is controlled through strict clinical criteria and centralized funding, allowing the Polish healthcare system to manage the high costs while providing innovative treatments to those in need. (AOTMiT, 2024) (Zdrowia, 2021)

3.2. Comparison of National Health Authorities reimbursement recommendations among scope EU countries

The landscape of ATMP reimbursement across the studied European countries shows a significant degree of variation, reflecting the different healthcare priorities and regulatory systems of each nation. While the EMA grants a central marketing authorization for all of Europe, the final decision on whether to fund these therapies is made at a national level, which often leads to differences in patient access. Table 17 provides a consolidated overview of the reimbursement status for the 20 authorized ATMPs in the scope of this study, summarizing which products have secured funding (marked with 'R') or are currently in price negotiations in each country.

Table 15: Consolidated Table of Reimbursed ATMPs in Scope Countries According to the presented Data. (R: Reimbursed) (Jørgensen & Kefalas, 2021; IQVIA, 2024)

Active Ingredient	Brand Name	France	Germany	Italy	Spain	UK	Poland
Atidarsagene autotemcel	Libmeldy		R	R		R	
Autologous CD34+ cells responsible for ADA encode	Strimvelis			R			
Axicabtagene ciloleucel	Yescarta	R	R	R	R	R	R
Brexucabtagene autoleucel	Tecartus	R	R	R	R		
Ciltacabtagene autoleucel	Carvykti	R	R	in price negotiations			
Darvadstrocel	Alofisel	R	R		R		
Eladocagene exuparvovec	Upstaza		R	R		R	
Etranacogene dezaparvovec	Hemgenix	R	R	in price negotiations		R	R
Idecabtagene Vicleucel	Abecma		R	R			
Human corneal epithelial cells	Holoclar	R	R	R		R	
Lisocabtagene maraleucel	Breyanzi	R	R	R			R
Onasemnogene abeparvovec	Zolgensma	R	R	R	R	R	
Spheroids of human autologous matrix-associated chondrocytes	Spherox	R	R			R	
Tabelecleucel	Ebvallo	R	R	in price negotiations			R
Talimogene laherparepvec	Imlygic		R			R	
Tisagenlecleucel	Kymriah	R	R	R	R	R	R
Valoctocogene roxaparvovec	Roctavian	R	R	R			
Voretigene neparvovec	Luxturna	R	R	R	R	R	
Exagamglogene Autotemcel	Casgevy					R	

The reimbursement recommendations among National Health Authorities in the EU vary. France and the UK use reimbursement schemes through Coverage with Evidence Development (CED),

where long-term treatment outcomes inform future pricing. NHS England announced as part of the 2024 voluntary scheme that it will establish two pilots to study outcomes-based agreements for cell and gene therapies, potentially moving away from CED in the UK. Germany, Spain, and Italy base reimbursement on individual patient data, unlike the cohort-based data used in the UK and France. Cohort schemes are cheaper for payers, but if the therapy proves ineffective, individual outcome-based schemes are beneficial as payers are less likely to overpay. Spain and Italy have decentralized Pricing and Reimbursement (P&R) and Marketing Authorization (MA) processes, with regional negotiations affecting adoption and funding.

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Optimal contract time horizons vary from 12 months to 5 years, depending on country preference and the nature of the therapy. In Europe, time horizons for outcome collection are tailored to the clinical evidence needed; for instance, Italy and France often utilize a 12-month horizon for staged payments and annual reassessments. In Spain, this period is typically extended to 18 months for individual patient data collection, while Germany and England may require up to 5 years under CED schemes to inform health technology reassessments.

The selection of the optimal timeframe depends heavily on the incentive structures of different payer segments. In single-payer countries, such as France, Italy, Spain, and England, there is a greater appetite for long-term schemes. In contrast, multi-payer settings like Germany face challenges with such agreements, as patients may switch plans, effectively transferring the long-

term health benefits and cost-savings to a different payer. (Jørgensen & Kefalas, 2021; IQVIA, 2024)

3.3.Economic and Healthcare Expenditure Overview and ATMP Reimbursement

In 2022, the GDP figures for Germany, the United Kingdom, France, Italy, Spain, and Poland varied significantly, with Germany leading at \$4,163.60 billion, and Poland only at \$699 billion. Healthcare expenditure in 2022 also varied, with Germany spending \$561.47 billion and Poland \$51.92 billion. The healthcare expenditure per capita in 2022 was highest in Germany at \$8,011, followed by France at \$6,630, indicating substantial investments in healthcare relative to the population size. Italy, Spain, and the United Kingdom also had notable healthcare spending per capita, reflecting the prioritization of health services across these countries. Poland, although having the lowest expenditure per capita at \$2,973, highlights the diverse economic landscapes and healthcare investments in Europe

In Table 18 , we can see economic figures and information about each country, along with the number of ATMPs that are reimbursed. The numbers used for comparison are from 2022, as apart of the GDP, the rest of the data for 2023 has not yet been published by the official platforms. (WORLDBANKGROUP, 2024; Eurostat, 2024; ONS, 2024; OECD, 2023)

Table 16: Economic and Healthcare Expenditure Metrics (2022-2023) (WORLDBANKGROUP, 2024; Eurostat, 2024; ONS, 2024; OECD, 2023)

Country	GDP (in Billion USD) 2023	GDP (in Billion USD)2022	Healthcare Expenditure relative to GDP, 2022	Healthcare Expenditure (in Billion USD)	Health expenditure per capita, (USD)2022	Number of ATMPs reimbursed
Germany	4,456.08	4,163.60	12.60%	561.47	8011	17
United Kingdom	3,340.03	3,070.66	11.10%	370.74	5493	12
France	3,030.90	2,938.00	11.90%	360.68	6630	13
Italy	2,254.85	2,106.00	8.90%	200.68	4291	12
Spain	1,580.69	1,425.00	9.70%	153.33	4432	6
Poland	811.23	699	6.40%	51.92	2973	5

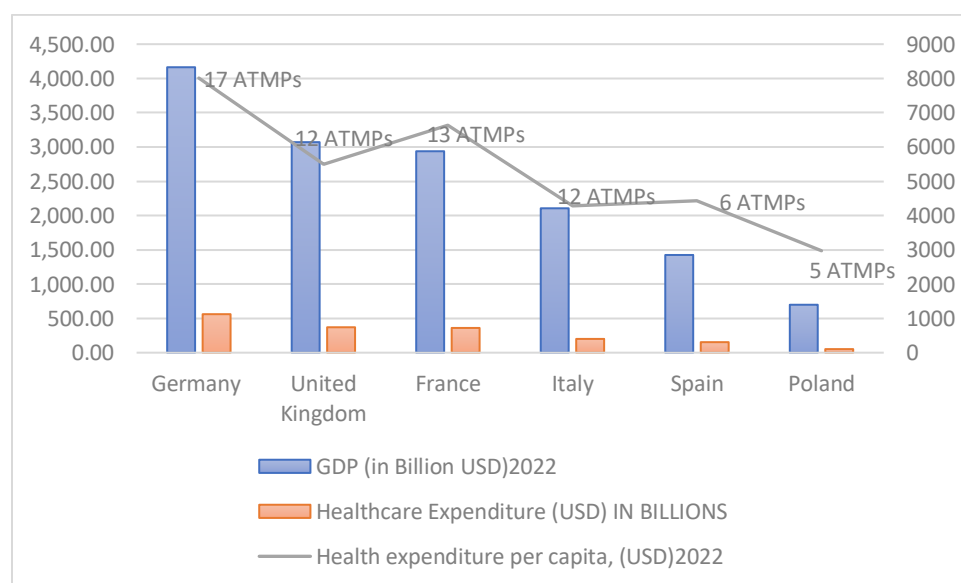


Figure 1: Comparison of GDP, Healthcare Expenditure, Health Expenditure per Capita, and Number of Reimbursed ATMPs in Select European Countries (2022)

Germany leads with the highest healthcare expenditure per capita and total healthcare expenditure, reflecting its strong economic position and substantial investment in healthcare. This correlates with Germany having the highest number of reimbursed ATMPs, indicating that higher financial resources enable better access to advanced therapies. On the other hand, Poland, with the lowest healthcare expenditure per capita and total healthcare expenditure, has the fewest reimbursed ATMPs, underscoring the challenges faced by countries with limited healthcare budgets in providing access to innovative treatments.

Furthermore, the data showcases that countries like the United Kingdom, France, and Italy, despite having lower healthcare expenditure per capita compared to Germany, still manage to reimburse a notable number of ATMPs. This suggests that effective allocation of healthcare resources and prioritization can also play a crucial role in ensuring access to advanced therapies. The variation in healthcare expenditure and ATMP reimbursement across these countries highlights the importance of both financial investment and strategic healthcare planning in achieving equitable access to new medical technologies.

It is worth mentioning that there can be differences in the ex-manufacturer prices of approved cell and gene therapies across various countries. These price variations may affect patient access to these advanced treatments. Higher prices in certain markets, such as the United States, can lead to prioritized launches in those regions, while lower prices or more restrictive reimbursement policies in other countries can delay or limit patient access. Understanding these variations is crucial for comprehensively assessing the global landscape of ATMP accessibility and affordability. (IQVIA, 2024)

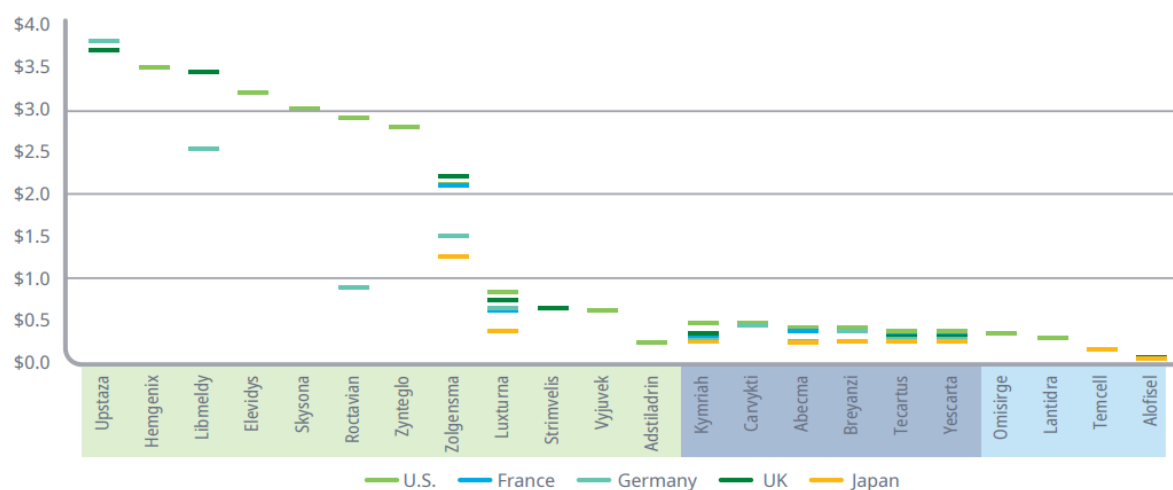


Figure 2: Ex-manufacturer price per patient of approved cell and gene therapies across select markets, US\$ in Millions. (IQVIA, 2023)

Notes for figure 2: Prices converted using exchange rates as of Dec 2023. Prices based on publicly available information and do not reflect net prices paid by payers. Prices do not reflect all discounts and rebates provided by manufacturers. (IQVIA, 2023)

3.4.The Role of Joint Health Technology Assessment

The introduction of the centralized EU HTA process is set to significantly improve access to cell and gene therapies across Europe. This new process aims to accelerate time to market access following approval and reduce the burden of HTA assessments. Scheduled to begin in 2025, the centralized HTA process will initially focus on new cancer medicines and cell and gene therapies (ATMPs). While clinical assessments will be centralized, non-clinical assessments, including economic evaluations, and pricing and reimbursement decisions, will remain managed at the national level. (IQVIA, 2024)

The JCA applies to all new medical products and devices approved by the European Medicines Agency, following this timeline:

2025: Oncology products, ATMPs, and medical devices

2028: Orphan designation products

2030: All central authorized medicinal products (EUnetHTA, 2021)

Why is the JCA important?

- ✓ It is the evidence base that each country will use to set the price, reimbursement and market access
- ✓ The JCA applies to all new medical products and devices approved by the European Medicines Agency from:
 - ✓ 2025: Oncology products, ATMPs and medical devices
 - ✓ 2028: Orphan designation products
 - ✓ 2030: All central authorised medicinal products

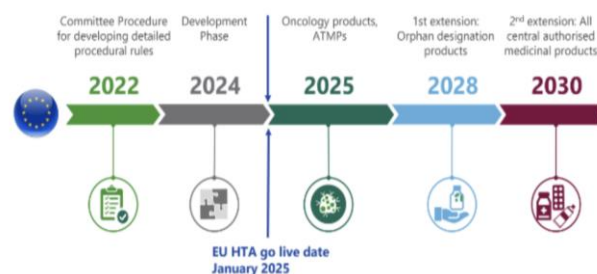


Image 4: Why is JCA important? (EUnetHTA, 2021)

In the coming years, the European Health Technology Assessment Regulation (HTAR 2021/2282) will be implemented, creating a stable framework for evaluating the added value of newer medicines and medical technologies. The HTAR's goal is to accelerate patient access to health technology and establish common clinical evaluations among member states with shared perspectives on clinical study quality. (EC, 2024)

The HTAR regulation establishes a legal framework for ongoing and sustainable cooperation among EU HTA bodies. This cooperation covers four main areas:

- Joint Clinical Assessments (JCA)
- Joint Scientific Consultations (JSCs), where medicine manufacturers can seek advice from HTA bodies and regulators
- Horizon scanning
- Continuing voluntary cooperation in areas not covered by JCAs, such as non-clinical aspects of health technologies and pricing and reimbursement decisions, which remain the responsibility of individual EU countries.

The JCA aims to provide a "scientific analysis of the relative effects of the health technology," considering the "degree of certainty of the relative effects, taking into account the strengths and limitations of the available evidence."

The JCA process is managed by the HTA Coordination Group (HTACG), comprised of representatives from the member states' HTA bodies. The process begins when the HTACG appoints two rapporteurs from different member states' HTA bodies. These rapporteurs are

responsible for conducting the clinical assessment, drafting the report, and consulting with stakeholders. (EMA, 2024)

For the HTA process, the designated experts need to define what exactly they will be assessing. To do this, they use the PICO (population, intervention, comparator, outcomes) framework, which helps them to outline the key components of their research question clearly. A PICO survey is sent to all 27 EU countries, and each country reports the PICOs required for its decision-making. The rapporteurs then consolidate these PICOs, without the involvement of the manufacturer. Due to varying informational requirements among member states, the number of consolidated PICOs may exceed the head-to-head evidence available at launch.

The manufacturer must prepare the JCA dossier following the PICO survey and consolidation, typically at day 120 of the regulatory EMA procedure. Approximately 100 days later, the manufacturer submits the JCA dossier, which must address all identified PICOs. The first draft of the JCA is expected to be ready by the time the Committee for Medicinal Products for Human Use (CHMP) issues its opinion. About three months after the European Commission's decision, the HTACG finalizes the JCA process. According to the HTA regulation, the HTACG should aim to approve the JCA report by reaching a consensus. If consensus cannot be reached, "divergent scientific opinions" should be included in the report. (Schuster, 2024)



Image 5: Timeline of Joint HTA (EC, 2024)

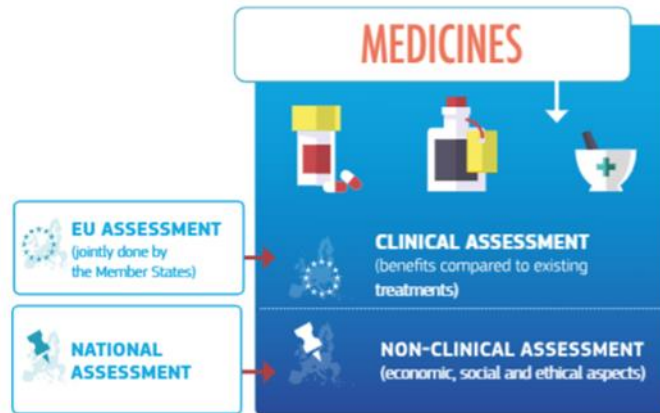


Image 6: Type of assessment and national/centralized level (EC, 2024)



Image 7: Joint HTA process timeline. (Schuster, 2024)

This structure in figure Image 7 is similar to the structure of the German “Arzneimittelmarktneuordnungsgesetz” (AMNOG) dossier. (Schuster, 2024) Although, there is an ongoing debate that the German template is not fit for purpose, as the G-BA has released an updated dossier template in 2020 which imposes even more rigorous requirements. As for the timeline, extensive AMNOG dossiers necessitate lengthy preparation times, spanning approximately 12 months, which is incompatible with the proposed EU HTA timeframe of 2.5 months. (Schweitzer, et al., 2024)

As outlined in the HTAR, the timeline for the JCA process begins when the Health Technology Developer (HTD) submits a dossier for centralized marketing authorization. The process must be completed within 142 days: 45 days before the CHMP opinion, 67 days between the CHMP

opinion and the Commission's decision, and 30 days after marketing authorization to publish the JCA report.

These timelines are based on current regulations, which state that the Coordination Group must adopt detailed procedural steps and a timeframe for conducting JCAs and updating them. It is crucial to avoid delays in patient access, so clearer guidelines are needed, either in the implementing act or as a separate document. This guidance is now available in the form of the Implementing Act on JCAs of Medicinal Products.

All stakeholders emphasize the importance of not delaying patient access, stressing the need for clear and comprehensive guidelines to ensure timely assessments and decisions. (Desmet, et al., 2024)

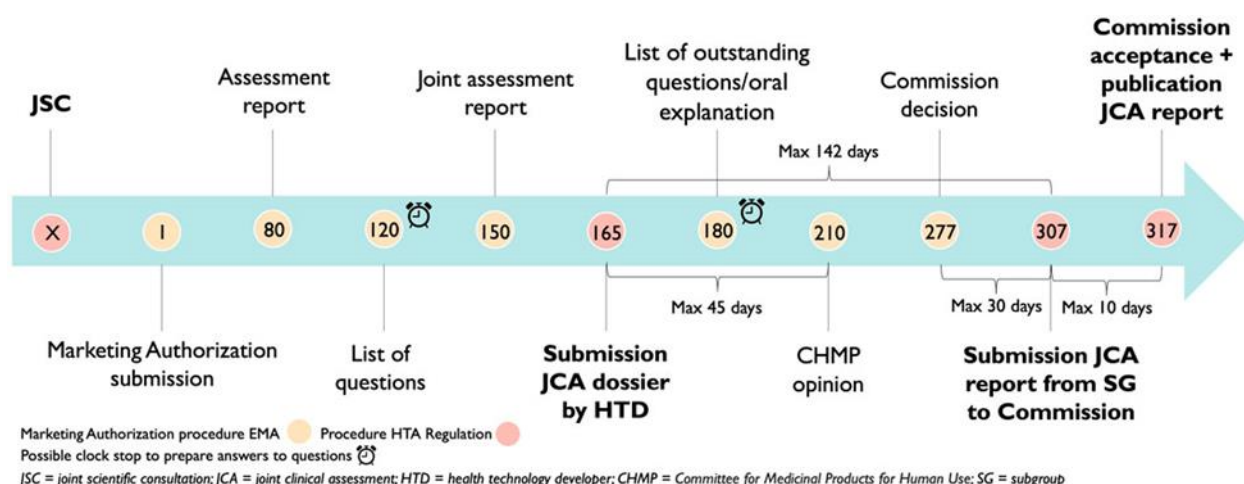


Image 8: Timeline from JSC to publication of JCA report (Desmet, et al., 2024)

Challenges and Opportunities in JCA Implementation

For the purposes of HTAs, evaluating the relative clinical effectiveness of new treatments involves comparing them to the current standard of care. Variations in these standards across member states, especially in central and eastern Europe, necessitate adaptation. JCAs will likely encompass network meta-analyses and conventional meta-analyses of head-to-head clinical trials, given the wide range of alternatives and the limited availability of direct comparative evidence. Additionally, the scarcity of randomized clinical studies for some new therapies, particularly gene therapies and high-risk medical devices, presents significant challenges. The use of surrogate

endpoints, often used in accelerated access programs and for rare diseases, adds complexity to HTAs. Validating these endpoints needs standardized and agreed methods. Generating RWD is crucial, as initial clinical data might be insufficient for ATMPs due to their innovative nature. Incorporating RWD into JCAs is essential for thorough assessments. RWD offers insights into how treatments perform outside clinical trials, filling evidence gaps, especially when RCTs are impractical or raise ethical concerns. HTA methods must adapt to the unique challenges of innovative therapies. This includes guidelines for indirect and mixed treatment comparisons when direct trials aren't available. Ensuring all stakeholders, including HTA bodies, payers, and developers, understand these methods through training and education is key to successful JCAs. Ultimately, the aim is to create a robust and adaptable framework that can handle the complexities of modern healthcare technologies, ensuring that patients across Europe have timely access to effective and innovative treatments. (Desmet, et al., 2024; Schuster, 2024)

3.4.1. Balancing Evidential Uncertainties and Patient Access (EU HTA)

The EU HTA guidance aims to balance the uncertainties in evidence with patient access. Excluding real-world evidence (RWE) and not conducting JCAs for single-arm trials could lead to unfair access to treatments for rare diseases. Stakeholders believe including RWE, as done by NICE, is crucial to reduce bias and use RWE as external controls.

The EU HTA regulation seeks to create a collaborative framework for health technology assessments, promoting transparency and efficiency while reducing redundant work. However, the current guidance on indirect treatment comparisons could prevent this goal. If RWE is excluded and JCAs are not performed for single-arm trials, it could result in unequal patient access.

Including RWE in JCAs is essential for a complete understanding of a treatment's effectiveness, especially when randomized trials are not possible. RWE provides insights into real-world performance, filling evidence gaps. This approach ensures the EU HTA aligns with patient needs and clinical practice realities.

For successful implementation, clear and practical guidelines are needed. This will help member states integrate these processes into their national HTA frameworks effectively, ensuring fair and timely access to new treatments across Europe. (Mueller & Neeser, 2023)

3.4.2. Implementation of the JCA

The JCA will only focus on the clinical assessment of health technologies. Member states need to adjust their timelines and prepare for coordination at the European level to integrate JCA procedures into their national HTA frameworks. The process starts when the Health Technology Developer (HTD) submits a dossier for centralized marketing authorization, with a total of 142 days to complete the JCA report.

Stakeholders see the value in the HTAR, but JCA reports do not have binding power for reimbursement decisions. This could lead HTA bodies to request additional evidence, increasing differences between member states. Clear guidelines are needed to ensure uniformity in JCA reports and prevent misunderstandings. Countries may choose to perform their own clinical assessments to enable patient access if they do not feel that EU HTA aligns with their national process.

Differences in access to medicines across Europe are influenced by GDP per capita, healthcare system features, and pharmaceutical market characteristics. HTA recommendations are crucial for informing pricing and reimbursement decisions, supporting negotiations, and updating national clinical guidelines. Policymakers need to balance cost optimization with timely access to medicines.

The JCA represents a significant step toward harmonizing health technology assessments across Europe. While challenges exist, including variations in standards of care, the use of surrogate endpoints, and the integration of RWE, the joint HTA process aims to improve patient access to innovative therapies. Effective communication, early stakeholder engagement, and clear guidelines are essential for the successful implementation of the JCA and ensuring timely access to life-saving treatments for patients across the EU. In conclusion, the Joint HTA will not currently impact the reimbursement decisions for ATMPs. These reimbursement decisions will continue to be made at the national level based on individual country criteria and processes. (Mueller & Neeser, 2023; Schuster, 2024)

4. CHAPTER 4. Discussion and Conclusions

4.1. Discussion

The integration of ATMPs into healthcare systems reveals diverse strategies and significant challenges across the scope countries. Examining the diverse HTA processes, pricing models, reimbursement practices, and the role of Managed Entry Agreements (MEAs) showcases how each country navigates these complexities.

In the UK, NICE utilizes robust frameworks such as the STA and HSTP. The CDF and the IMF are instrumental in providing timely access to ATMPs while addressing uncertainties through real-world evidence collection. This dual approach of enabling access and gathering post-market data reflects the UK's commitment to patient-centric innovation. MEAs, particularly outcomes-based agreements, are being piloted to transition from reliance on coverage with evidence development (CED).

France employs a multifaceted HTA process involving HAS and CEPS. The ATU mechanism, which allows early access to non-approved medicines, exemplifies France's proactive stance. The extensive use of performance-based MEAs, which integrate mandatory evidence collection, ensures financial sustainability while facilitating access to innovative treatments.

Germany's HTA framework, led by G-BA and IQWiG, emphasizes early benefit assessments through the AMNOG process. The use of outcome-based rebates and the NUB status for hospital-based ATMPs ensures rapid access and financial risk management. MEAs in Germany often involve confidential price agreements and volume-based discounts, which help manage costs while ensuring access to new therapies.

Italy's approach, managed by AIFA, involves stringent assessments of clinical value and price negotiations. The introduction of payment-by-results and annuity payments demonstrates Italy's innovative strategies to mitigate financial risks associated with ATMPs. MEAs are commonly used to ensure that payments are linked to the achievement of specific clinical outcomes. However, regional disparities in patient access times indicate a need for enhanced central coordination to ensure equitable treatment availability.

Spain's decentralized HTA system involves regional authorities and hospitals, facilitating localized decision-making in ATMP management. Implementing outcome-based payment models

and expenditure caps reflects Spain's pragmatic approach to managing clinical uncertainties and controlling costs. The limited number of reimbursed ATMPs, however, highlights challenges related to financial resources and regional differences. MEAs, such as risk-sharing agreements and price-volume agreements, are employed to manage the financial impact of ATMPs.

Poland's HTA process, under the 2012 Reimbursement Act, uses a multicriteria evaluation approach. Despite a robust system, Poland faces significant barriers such as lengthy reimbursement decision times and restrictive cost-effectiveness thresholds. The Medical Fund Act of 2020 aims to address these issues, but its effectiveness remains to be fully realized. MEAs in Poland are still emerging, with efforts focused on introducing outcome-based agreements to enhance patient access to innovative therapies.

The issue of restricted reimbursement for ATMPs is a global concern, affecting numerous healthcare systems worldwide. Carvykti, a recent CAR T-cell therapy launch, began its global rollout in 2022 for patients with relapsed or refractory multiple myeloma. However, the journey to secure reimbursement has been challenging. In Australia, Carvykti initially faced a reimbursement rejection but is currently under re-evaluation. Similarly, the therapy is still undergoing pricing and reimbursement assessments in Canada and Italy. In the UK, Janssen withdrew its reimbursement application for Carvykti, likely due to limited supply issues. This scenario highlights the extensive time and effort required not only to launch a cell and gene therapy globally but also to ensure it is reimbursed, thereby making it accessible to patients. Reimbursement restrictions often stem from payers' scrutiny of the clinical efficacy data, which can limit access to specific patient populations or indications. For instance, Yescarta in Australia received regulatory approval for use in an earlier line of therapy but faced a negative reimbursement decision. Similarly, Zolgensma has seen its reimbursement limited to certain patient populations based on age or weight, reflecting the patient populations evaluated in clinical trials. These examples underscore the widespread challenges within healthcare systems regarding reimbursement for advanced therapies. (IQVIA, 2024)

Reimbursement recommendations for ATMPs differ significantly among these countries, influenced by healthcare expenditure and economic capacity. Germany stands out with the highest number of reimbursed ATMPs, supported by substantial healthcare investment. Conversely, Poland's limited healthcare budgets result in fewer reimbursed ATMPs, underscoring the financial constraints faced by lower-income countries.

Economic analysis indicates that Germany, with its high healthcare expenditure per capita, exemplifies a successful model for integrating ATMPs. In contrast, Poland's lower expenditure highlights the challenges of providing equitable access to innovative treatments within constrained budgets.

The forthcoming centralized EU HTA process, beginning in 2025, presents a promising avenue for harmonizing clinical assessments and improving ATMP access across Europe. The focus on oncology products and ATMPs aims to streamline HTA processes and accelerate market access. Challenges remain, including standardizing care variations, validating surrogate endpoints, and integrating RWE. Nevertheless, the potential for harmonized assessments, expedited patient access, and a collaborative framework among member states offers significant opportunities.

4.1.1. Comparison with the US

There are global variations in the pricing of ATMPs. CAR T-cell therapies generally cost less than gene therapies, with an average price of approximately \$350,000 across different regions. These prices cover only the therapy itself, not additional healthcare costs such as hospital stays, testing, monitoring, or treatment for adverse events. In the US, the list prices for CAR T-cell therapies are typically higher than in other countries, averaging over \$400,000, which is 16% higher than in France, the second-highest priced country. This higher pricing environment in the US has incentivized some cell and gene therapy developers to prioritize launching their products there. Conversely, it has also led to market exits from Europe, as exemplified by Bluebird Bio's withdrawal of Zynteglo. The US offers a different landscape for ATMPs, where the FDA, through its Center for Biologics Evaluation and Research (CBER), oversees the approval of these therapies using a flexible system similar to EMA's PRIME. Programs like Breakthrough Therapy Designation and RMAT expedite the development and approval processes. The US also emphasizes real-world evidence (RWE) and post-market monitoring to track the safety and effectiveness of ATMPs. The reimbursement landscape in the US is complex, involving both public and private payers, which creates a flexible environment for negotiating access and prices. Managed Entry Agreements (MEAs) in the US often use value-based contracts, meaning payments are linked to the therapy's performance and outcomes. However, while Medicare typically covers FDA-approved therapies, reimbursement rates for hospital costs vary, with higher rates for

outpatient treatments. Commercial insurance plans generally cover cell and gene therapies but often require prior authorization and may have restrictions that limit access. These factors highlight the complexities and challenges in the US healthcare system regarding the reimbursement of advanced therapies. (Iglesias-Lopez, et al., 2019; IQVIA, 2024)

4.2. Conclusions

The integration and reimbursement of Advanced Therapy Medicinal Products present complex challenges and opportunities across healthcare systems. This comparative analysis of different countries has revealed several key insights.

Firstly, each country employs unique strategies and regulatory frameworks to manage the adoption and integration of ATMPs. The United Kingdom leverages frameworks like the STA and HSTP, supported by real-world evidence collection through the Cancer Drugs Fund and the Innovative Medicines Fund. France's proactive approach is shown by its ATU mechanism and extensive use of performance-based Managed Entry Agreements. Germany's emphasis on early benefit assessments and outcome-based rebates reflects a balanced approach to financial risk management and rapid access to therapies.

Secondly, economic capacity and healthcare expenditure significantly influence the reimbursement recommendations for ATMPs. Germany stands out with the highest number of reimbursed ATMPs, supported by substantial healthcare investment, making it a model to follow. However, Germany also benefits from its strong economic resources. This study highlights the evolution of AIFA in Italy, which has doubled the numbers of ATMPs since 2023 using innovative payment models. So, focusing on the development and implementation of MEAs, as well as fostering good collaboration among all stakeholders, is crucial to ensuring broader patient access and financial sustainability in other regions.

The forthcoming centralized EU HTA process, starting in 2025, presents a promising opportunity to harmonize clinical assessments and improve ATMP access across Europe. This initiative aims to streamline HTA processes, expedite market access, and foster collaboration among member states. However, challenges remain, including standardizing care variations, validating surrogate endpoints, and integrating real-world evidence. If the timelines for the joint HTA are adhered to, the assessments will be conducted more quickly and efficiently. Furthermore, if the initiative

proves successful, it could provide a solid foundation for a more unified reimbursement framework across the EU, reducing the current fragmentation. This dissertation has several limitations. Firstly, the availability of data is limited, and confidentiality issues can restrict access to comprehensive information. Additionally, the number of patients in each country varies, which can impact the applicability of findings and the implementation of ATMPs. The field of ATMPs is highly dynamic, and significant changes can occur within a few years, particularly with the implementation of the Joint Clinical Assessment (JCA) and potential mechanisms to resolve confidentiality issues, which could lead to greater transparency and broader information availability.

To address the aforementioned challenges, the use of performance-based or combined MEAs is highly recommended, as these agreements help manage financial risks by linking payments directly to the achievement of specific clinical outcomes. However, a key conclusion of this analysis is that the successful implementation of such models is now inseparable from the development of robust Real-World Evidence (RWE) infrastructure. A key conclusion of this analysis is that the successful implementation of performance-based agreements is deeply linked to the development of robust Real-World Evidence (RWE) infrastructure. As ATMPs often enter the market with clinical uncertainty, national registries have become essential tools for Health Authorities to monitor long-term safety and efficacy outside of controlled clinical trials.

In countries like Italy and Spain, the use of sophisticated web-based registries allows for the systematic collection of individual patient data, which then triggers the corresponding performance-based payments. This trend indicates a shift toward a 'lifecycle approach' to drug pricing, where the final value of a therapy is not determined at launch but is continuously reassessed based on real-world performance. Therefore, the future of ATMP access in the EU will depend on the ability of member states to harmonize their RWE collection methods, ensuring that registries are not just administrative burdens but strategic assets that facilitate faster and more sustainable patient access to innovation.

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