Alliance *for* Regenerative Medicine

Getting Ready:

Recommendations for Timely Access to Advanced Therapy Medicinal Products (ATMPs) in Europe

2019

Alliance *for*
Regenerative Medicine

The Alliance for Regenerative Medicine (ARM) is the preeminent global advocate for regenerative and advanced therapies. ARM fosters research, development, investment, and commercialization of transformational treatments and cures for patients worldwide.

By leveraging the expertise of its membership, ARM empowers multiple stakeholders to promote legislative, regulatory, and public understanding of, and support for, this expanding field.

www.alliancerm.org

Preface

Preface

Advanced therapy medicinal products (ATMPs) have the potential to offer life-changing solutions for patients with few or no alternative treatments. However, their complexity and relative novelty present challenges to ensuring these therapies reach those in need.

This report provides an overview of the characteristics and benefits of ATMPs, and the current regulatory market and access frameworks in six European countries: France, Germany, Italy, Spain, Sweden, and the United Kingdom. It also identifies hurdles to adoption and makes EU-wide policy recommendations to address those challenges.

The report brings together the views of a number of European policy makers and experts, ARM member organizations, and other stakeholder groups. The report was funded by the Alliance for Regenerative Medicine (ARM).

Project process — a comprehensive approach

The report draws on extensive research into the environment for ATMPs in Europe, including:

- a targeted literature review on topics related to patient access challenges, HTA methods, and innovative payment models;
- an expert board meeting, held in Paris in September 2018, brought together academics, health technology specialists, investors, and other stakeholders;
- expert interviews;
- a stakeholder meeting, held in Brussels in April 2019.

Project leads

Eve Hanna — Creativ-Ceutical

Annie Hubert — ARM

Paolo Morgese — ARM

Mondher Toumi — Creativ-Ceutical

Participants to expert board meeting held in Paris, 27 September 2018

Meriem Bouslouk — former G-BA, Orphan Drugs/ Innovation expert (Germany)

Serge Braun — Genethon, Treat NMD, Institut de Myologie (France)

Pilar Pinilla-Dominguez — NICE ATMP expert (United Kingdom)

Mira Pavlovic — HAS/EMA adviser, early dialogue expert (France)

Ulf Persson — Health economist (Sweden)

Paolo Siviero — Former AIFA and ATMP investor at Principia (Italy)

Fernando Villar — Regional HTA (Spain)

Stakeholder groups represented at stakeholder meeting held in Brussels, 2 April 2019

Eucope — European Confederation of Pharmaceutical Entrepreneurs

The European Federation of Pharmaceutical Industries and Associations (EFPIA)

The European Haemophilia Consortium (EHC)

EuropaBio — European Association for Bioindustries

Eurordis — Rare Diseases Europe

Interviewed Experts

Frank-Ulrich Fricke — Health Economist; member of the arbitration board on drug prices (Germany)

Jan Geissler — Patient advocate (Germany)

Ulf Persson — Health Economist (Sweden)

Pilar Pinilla-Dominguez — NICE ATMP expert (United Kingdom)

Mira Pavlovic — HAS/EMA adviser, early dialogue expert (France)

Paolo Siviero — Former AIFA and ATMP investor at Principia SpA (Italy)

Fernando Villar — Regional HTA (Spain)

Alliance for Regenerative Medicine member organizations

1 4D Molecular Therapeutics
2 AABB
3 Abeona Therapeutics
4 Accelerated Biosciences
5 Acera Surgical
6 ACF Bioservices
7 Adaptimmune
8 Adicet Bio
9 Adverum Biotechnologies
10 Aegle Therapeutics
11 AGTC
12 Aivita Biomedical
13 Akron Biotechnology
14 Albumedix
15 Aldevron
16 Alpha-1 Foundation
17 American Association of Tissue Banks
18 American Gene Technologies International
19 American Society of Plastic Surgeons
20 Amicus Therapeutics
21 Andalusian Initiative for Advanced Therapies
22 ANEMOCYTE
23 Angiocrine Biosciences
24 Aseptic Technologies
25 American Society of Gene & Cell Therapy (ASGCT)
26 Aspect Biosystems
27 Asset Management Company
28 Association of Clinical Research Organizations
29 Astellas
30 Asterias Biotherapeutics
31 Atara Biotherapeutics
32 Athersys
33 Audentes Therapeutics
34 AusBiotech
35 Autolus Therapeutics
36 Avectas
37 Avery Therapeutics
38 Avita Medical
39 AVM Biotechnology
40 AVROBIO
41 AxoGen
42 Axovant
43 B-MoGen Biotechnologies
44 Baylor College of Medicine, Center for Cell and Gene Therapy
45 Be the Match Biotherapies / NMDP — National Marrow Donor Program
46 Bellicum Pharmaceuticals
47 Benitec BioPharma
48 BioBridge Global
49 BioCardia
50 BioLife Solutions
51 BioMarin
52 BioStage
53 Biotech Mountains
54 BioTime
55 Blood Centers of America
56 bluebird bio
57 BlueRock Therapeutics
58 Bone Therapeutics
59 BrainStorm Cell Therapeutics
60 Brainxell
61 Brammer Bio
62 C3i
63 Caladrius Biosciences
64 Capricor Therapeutics
65 Cardinal Health
66 Caribou Biosciences
67 Carisma
68 Carpenter Consulting
69 Casebia
70 Celgene
71 Celixir
72 Cell and Gene Therapy Catapult
73 Cell Medica
74 Cell Therapies Pty.
75 CellCAN
76 CellGenix
77 Cellular Biomedicine Group
78 Cellular Technology
79 Celsense
80 Center for the Advancement of Science in Space
81 Centre for Commercialization of Regenerative Medicine (CCRM)
82 Cevec
83 Chemelot Campus
84 CIRM (California's Stem Cell Agency)
85 City of Hope (Beckman Research Institute)
86 Cleveland Clinic
87 Cleveland Cord Blood Center
88 ClinicalMind
89 Coalition for Clinical Trials Awareness
90 Cobra Biologics
91 Cognate BioServices
92 CombiGene
93 Cook Myosite
94 Cornell University
95 Covance
96 CRC for Cell Therapy Manufacturing
97 CRC Oncology
98 CRISPR Therapeutics
99 Cryoport Systems
100 CSL
101 CTI Clinical Trial and Consulting Services
102 Cynata Therapeutics
103 Dark Horse Consulting
104 Defined Health
105 DiscGenics
106 Dyno Therapeutics
107 EB Research Partnership
108 Editas Medicine
109 Emerging Therapies Solutions
110 Enochian Biosciences
111 Enzyvant Therapeutics

112 ERA Consulting
113 European Society of Gene and Cell Therapy (ESGCT)
114 EVERSANA
115 EveryLife Foundation for Rare Diseases
116 Evidera
117 ExCellThera
118 Excision Bio Therapeutics
119 Falcon Therapeutics
120 Friedreich's Ataxia Research Alliance (FARA)
121 Fate Therapeutics
122 Fibrocell Science
123 Fight Colorectal Cancer
124 Flexion Therapeutics
125 FloDesign
126 Fondazione Telethon / San Raffaele-Telethon Institute for Gene Therapy
127 Foundation for Biomedical Research and Innovation
128 Fraunhofer Institute for Cell Therapy and Immunology
129 Fred Hutchinson Cancer Research Center
130 Frequency Therapeutics
131 FUJIFILM Cellular Dynamics
132 Gamida Cell
133 GammaDelta Therapeutics
134 GE Healthcare
135 GE2P2 Global Foundation
136 Generation Bio
137 GENETHON
138 Genprex
139 GenSight Biologics
140 Gift of Life Marrow Registry
141 Gilead
142 Giner
143 GlaxoSmithKline
144 Global Genes
145 GPB Scientific
146 Gyroscope Therapeutics
147 Halloran Consulting
148 Healios
149 Histogen
150 Histogenics
151 Hitachi Chemical Advanced Therapeutics Solutions
152 Hogan Lovells
153 Homology Medicines
154 Humanscape
155 Huron Consulting
156 Hybrid Concepts International
157 Immusoft
158 INmune Bio
159 InRegen
160 Institut Clayton de la Recherche
161 Intellia Therapeutics
162 Invetech
163 Invitria
164 Invitrx
165 IO Biosciences
166 Iovance
167 IQVIA
168 International Society for Cell and Gene Therapy (ISCT)
169 International Society for Stem Cell Research (ISSCR)
170 IVERIC Bio
171 Johns Hopkins Translational Tissue Engineering Center
172 Johnson & Johnson
173 Key Biologics
174 Kiadis Pharma
175 Krystal Biotechnologies
176 Kytopen
177 L7 Informatics
178 LabConnect
179 Lake Street Capital Markets
180 Latham BioPharma
181 LatticePoint Consulting
182 Legend Biotech
183 Locate Bio Ltd
184 LogicBio
185 Lonza Biologics
186 Lovelace Biomedical
187 Ludwig Boltzmann Institute for Experimental and Clinical Traumatology
188 Lynch Biologics
189 Lysogene
190 Magenta Therapeutics
191 MaSTherCell
192 MaxCyte
193 Medeor Therapeutics
194 MEDIPOST America
195 Medpace
196 MeiraGTx
197 Memorial Sloan-Kettering Cancer Center
198 Mesoblast Limited
199 MilliporeSigma / EMD Millipore Corporation
200 MiMedx Group
201 Minerva Biotechnologies
202 Miromatrix Medical
203 Missouri Cures
204 MolMed
205 Monarch Biosciences
206 Musculoskeletal Transplant Foundation
207 Mustang Bio
208 Myonexus Therapeutics
209 National Disease Research Interchange (NDRI)
210 National Multiple Sclerosis Society
211 National Stem Cell Foundation
212 Navan Technologies
213 Nebraska Coalition for Lifesaving Cures
214 Neural Stem Cell Institute
215 Neuralstem
216 Neurogene
217 New Jersey Innovation Institute
218 New York Stem Cell Foundation
219 NexImmune
220 Nightstar Therapeutics
221 Nohla Therapeutics
222 Northwestern University Comprehensive Transplant Center
223 Novadip Biosciences
224 Novartis
225 Avexis
226 Novellus
227 Novitas Capital
228 Novo Nordisk
229 NYBC & Comprehensive Cell Solutions
230 Odylia Therapeutics
231 Opsis Therapeutics
232 Orbsen Therapeutics
233 Orchard Therapeutics
234 Organabio
235 Organovo Holdings
236 Orgenesis
237 Orig3n
238 Orthocell
239 Oxford BioMedica
240 Pancella
241 PDC*line Pharma
242 Pfizer
243 Pluristem Therapeutics
244 PolarityTE
245 Poseida Therapeutics
246 Precision Biosciences
247 Prevent Cancer Foundation
248 Promethera Biosciences
249 PTC Therapeutics
250 Recardio
251 Regenerative Patch Technologies
252 ReGenesys
253 Regeneus
254 REGENXBIO
255 REMEDI, the National Centre for Biomedical Engineering Science, National University of Ireland
256 ReNeuron Group
257 RepliCel Life Sciences
258 Rescue Hearing
259 Rexgenero
260 Rocket Pharma
261 RoosterBio
262 Roslin Cell Therapies
263 RxGen
264 SanBio
265 Sanford Health
266 Sanford Stem Cell Clinical Center
267 Sangamo Therapeutics
268 Sanofi
269 Sarepta Therapeutics
270 Sartorius Stedim North America
271 Scinogy
272 SCM LifeScience
273 Scottish National Blood Transfusion Service
274 Semma Therapeutics
275 Senti Biosiences
276 Sentien Biotechnologies
277 Seraxis
278 Sernova
279 Sigilon
280 Skingenix
281 Skyland Analytics
282 Solid Biosciences
283 Spark Therapeutics
284 STEL Technologies
285 StemBioSys
286 StemCyte
287 StemExpress
288 Stop ALD Foundation
289 Student Society for Stem Cell Research
290 Synpromics
291 T-Knife
292 Takeda
293 Talaris Therapeutics
294 Tenaya
295 TERMIS-Americas
296 Terumo BCT
297 Tessa Therapeutics
298 Texas Heart Institute
299 The Michael J. Fox Foundation for Parkinson's Research
300 Thermo Fisher Scientific
301 TikoMed
302 Tmunity Therapeutics
303 TrakCel
304 Trizell
305 Tulane University
306 UCSD Stem Cell Program
307 Ultragenyx
308 UMass Medical School, Horae Gene Therapy Center
309 Unicyte
310 uniQure
311 Unite 2 Fight Paralysis
312 United Spinal Association of Virginia
313 Universidad de los Andes — Cells for Cells
314 University of California at Irvine
315 University of Colorado Gates Center for Regenerative Medicine
316 University of Minnesota Stem Cell Institute
317 University of Pennsylvania, Abramson Cancer Center
318 Unum Therapeutics
319 Vericel
320 VERIGRAFT
321 ViaCyte
322 VidaCel
323 Videregen
324 VINETI
325 ViveBiotech
326 Vivet Therapeutics
327 Voisin Consulting
328 Voyager Therapeutics
329 WiCell
330 WindMIL Therapeutics
331 World Courier
332 Wuxi
333 Xintela
334 Yposkesi
335 Zelluna Immunotherapy

Consensus Report

GETTING READY:
Recommendations for Timely Access to Advanced Therapy Medicinal Products in Europe

Executive Summary

Advanced Therapy Medicinal Products (ATMPs) include cell therapies, gene therapies, and tissue engineered products. These highly complex treatments differ from traditional medicines, both in terms of how they are made and administered and in the type of benefits they may provide. Some gene therapies, for example, address the root cause of disease, offering patients the prospect of a cure after just a single administration. Cell therapies and tissue engeneered products are sometimes manufactured specifically for a given individual, creating a highly tailored medicine with potentially transformative benefits for the patient.

ATMPs' extraordinary potential to offer durable, life-changing solutions for patients with few or no therapeutic alternatives is driving their growing share of the biopharma industry's development pipeline. That growth will accelerate as more products approach the market.

To support timely patient access to these therapies, regulators established specific approval pathways and expert committees to ensure appropriate assessment and expedited approval of ATMPs. The European Parliament formally introduced ATMPs as a class in 2007; the European Medicines Agency's Committee for Advanced Therapies (CAT) was subsequently established to accomodate the specific demands of this class of medicines. However, most payers and health technology assessment (HTA) bodies have not established specific mechanisms to adequately capture the full benefits of ATMPs. Consequently, there are many systematic barriers that may hinder ATMPs from reaching patients in need in a timely manner.

To date, most ATMPs are associated with a high up-front cost compared to traditional treatments, caused in part by complex processes for manufacturing and administration, but primarily due to the long-term value to patients, society, and health systems and administration provided by a one-time treatment. ATMPs are highly novel, with often small patient populations and with benefits that may last for many years, and potentially for the patient's lifetime. Though several HTA bodies demand comparative evidence versus standard of care at time of launch, many ATMPs may not have developed the evidence traditionally required by payers for reasons related to the nature of these technologies.

New payment structures and new approaches to measuring value are required for ATMPs, akin to the new regulatory pathways created over a decade ago. ATMPs potentially bring significant benefit, not only to patients but to their caretakers, families, and to society as a whole. Much of this value may come over time, in terms of savings on treatments and procedures that are no longer necessary, and in terms of quality of life and productivity. Little of this value can be adequately captured in current value-assessment frameworks, mainly due to the gap between feasible evidence generation at launch and the current evidence standards required by HTA bodies.

As such, there is an urgent need for new approaches to patient access offering payers an affordable, risk-mitigated means of funding ATMPs, with evidence-based reassurance that healthcare systems are getting value for money and with the commitment to the generation of long-term evidence.

Recommendations

Payer and HTA experts in Europe were consulted on how to best prepare for providing access to ATMPs in a timely and reasonable manner.

The experts recommended accelerating new payment models like conditional reimbursement, pay-for-performance, and annuity-based payments. Conditional reimbursement is already in use in some countries, such as in England via the Cancer Drugs Fund and in Scotland for ultra-orphan drugs. Under this type of scheme, reimbursement is temporary and conditional on the collection and review of further evidence, allowing for future price re-negotiations. Pay-for-performance deals for traditional drugs have emerged in Europe and the US, linking price or rebates to pre-defined outcomes. They allow payers to hedge financial risk if a product fails in some patients. Annuity models, discussed but not yet implemented, would spread up-front payments over several years, facilitating appropriate resource allocation and affordable access. ATMP-dedicated funds that allow health systems to invest in ATMPs offering the potential of long-term benefits were also proposed.

The group called urgently for better adapted HTA methods, including greater use of real-world evidence (RWE). They recommended further development of the infrastructure required to collect and use high-quality real-world evidence, and expanded opportunities for early dialogue between pharma and payers, supported by increased EU funding.

The experts also recognized the significant challenges in implementing such changes across payment models, evidence collection, and value-assessment frameworks. These require new data collection infrastructure, payment systems, and new kinds of expertise, which must also be adapted to different health system- and country-specific requirements.

Many of these ideas are already being tested. Multiple efforts are underway to accelerate the generation and use of RWE, for instance. The imperative around ATMP access means these efforts must be accelerated. There is unlikely to be a single route for all ATMPs — this is a broad, growing, and highly heterogenous class. Therefore, it is important that new approaches for accelerating access continue to be tested and refined, and, where possible, lessons learned are shared to support future progress.

Recommendation 1: Better adapt Health Technology Assessment (HTA) frameworks to ATMPs:

a) Enhancing acceptability of validated surrogate endpoints to estimate long-term outcomes

b) Conducting further research to improve methodology of indirect comparisons

c) Supporting development, validation, and use of pan-European natural history datasets

d) Leveraging scientific, clinical, and HTA expertise from centers of excellence

e) Adopting changes in economic modelling, such as improving methods for extrapolation

Recommendation 2: Favor wider application of conditional reimbursement schemes:

Conditional reimbursement schemes have the potential to mitigate uncertainty on duration of effect based on data available at time of regulatory approval. This approach is in use in several countries and a wider application in Europe for ATMPs is recommended.

Recommendation 3: Develop pan-European initiatives to create:

a) *Real-World Evidence infrastructure*

Real-World Evidence (RWE) development is instrumental in addressing uncertainties on long-term effect, safety, health-related quality of life, and use of healthcare resources. There is a need to develop RWE infrastructure and a common framework at the European level to support long-term evidence generation and procedures to enhance the quality of evidence collected specifically for ATMPs.

b) *New early dialogue opportunities*

There is a need for more opportunities for early dialogue activities through additional EU and national funding considering the specific needs of ATMPs and the patient populations they are targeting. This would offer developers (and, in particular, SMEs) early insight on ways to address product specific uncertainties and how to mitigate them.

c) *Timely and effective access to cross-border ATMP treatment for all EU patients*

Despite existing legislation to facilitate cross-border treatment in Europe, there are still barriers limiting access to ATMPs as they are most often delivered through centers of excellence, which are not always present at the country or regional level. In particular, there is an urgent need for measures to coordinate and fund access to cross-border ATMP treatment at the European level.

Recommendation 4: Favor wider application of innovative access and funding arrangements such as:

a) Pay-for-performance

b) Annuity payments

c) Special funds for transformative treatments

New payment models are needed to ensure timely patient access to innovation while preserving sustainability of healthcare systems. Without the adoption of these new models, some transformative therapies may not reach patients in some or all European countries and some may be at risk of withdrawal from the market.

The Alliance for Regenerative Medicine hopes that continued dialogue and debate, supportive policy decisions, and a willingness among all stakeholders to create a fair and equitable environment for patient access to ATMPs will help overcome existing hurdles.

Contents

List of tables

List of figures

1. CONTEXT

1.1. What is an Advanced Therapy Medicinal Product (ATMP)?

Advanced Therapy Medicinal Products (ATMPs) are a transformative new category of medicines whose full potential is only just beginning to emerge. ATMPs include cell therapies, gene therapies, and tissue engineered products. These highly complex treatments differ from traditional oral and injectable drugs, both in terms of how they are made and administered and in the type of benefits they may provide.

Cell and gene therapies can involve direct application through infusion or injection or can be delivered by extracting cells, protein, or genetic material (DNA) from a patient or donor and altering them outside the body to create a highly personalized therapy that is then re-infused or injected. Most medicines available today — chemical compounds (like paracetamol tablets) or injected biologics — are one-size-fits-all. All patients take the same pill or injection for a particular condition. These treatments are produced in a standardized fashion, and most are relatively short-lived within the body.

Cell and gene therapies are designed to have longer-lasting effects than most traditional medicines. Many target the underlying biology of disease, rather than its symptoms. This means they can dramatically improve health outcomes and potentially offer a cure. ATMPs can also address complex diseases for which there are no effective conventional treatments.

Gene therapies deliver a corrected copy of a faulty or missing gene, typically using a vector or carrier molecule. The new gene allows cells to function correctly again, alleviating all or some disease symptoms and potentially offering a long-term cure. Gene-therapy products are already available to treat inherited disorders including retinal dystrophy, which causes vision loss, and adenosine deaminase deficiency, which leads to severe immune system damage. Other applications are based on genes encoding new or enhanced functions that would be applicable to a variety of non-genetic disorders. This includes suicide genes, enzymes, growth factors genes or optimized antigens in indications such as cancer, cardiovascular disorders, neurodegenerative disorders, or infectious diseases.

Cell-based therapies involve transplanting substantially manipulated cells or cellular material into a patient. In some cases, the genetic material in the cells may be genetically modified. For example, some of the most exciting new cell therapies involve extracting and re-programming patients' immune cells to equip them to more effectively fight disease from within.

Tissue engineered products are cells or tissues that have been specially engineered *ex vivo* to regenerate, repair, or replace damaged human tissue. For example, cartilage cells taken from patients with osteoarthritis can be grown and expanded on special scaffolds and used to repair painful cartilage defects. This engineered tissue or cells may be used as a standalone ATMP, or it may be integrated into a biodegradable matrix or other medical device, creating what is known as a 'combined therapy medicinal product.'

ATMPs' extraordinary potential to offer life-changing solutions for patients with few or no alternatives is driving their growing share of the biopharma industry's development pipeline. That growth will accelerate as more products successfully reach the market.

Regulators have established dedicated pathways and expert committees to help ensure appropriate, expedited marketing authorization of ATMPs. The European Parliament introduced the concept of ATMPs in 2007, triggering the creation of the European Medicines Agency's Committee for Advanced Therapies (1). The US FDA's Center for Biologics Evaluation and Research (CBER) includes a tissues, cellular, and gene therapy advisory committee.

As of June 2019, 14 ATMPs have been granted marketing authorization in Europe (2): seven gene therapies, three cell therapies, and four tissue engineered products, targeting several diseases in different therapeutic areas. Marketing authorizations for the first four approved ATMPs have been withdrawn by their sponsors for commercial reasons (3).

TABLE 1. ATMPs approved in Europe

	Brand name	INN	MA indication	MA date	Current status
Gene Therapies	Glybera®	Alipogene tiparvovec	Lipoprotein lipase deficiency	10/2012	× 10/2017
	Imlygic®	Talimogene laherparepvec	Regionally or distantly metastatic unresectable melanoma	12/2015	✓
	Strimvelis®	Autologous CD34+ cells transduced to express ADA	Adenosine deaminase deficiency (ADA)	05/2016	✓
	Kymriah®	Tisagenlecleucel	Patients ≤25 years old with B-cell ALL refractory, in relapse post-transplant or in second or later relapse Adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy	09/2018	✓
	Yescarta®	Axicabtagene ciloleucel	Adults with relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma, after two or more lines of systemic therapy	09/2018	✓
	LUXTURNA®	Voretigene neparvovec	Patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells	11/2018	
	Zynteglo®	Autologous CD34+ cells encoding βA-T87Q-globin gene	Beta thalassaemia in patients 12 years and older who require regular blood transfusions	06/2019	✓
Cell Therapies	Provenge®	Sipuleucel-T	Asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer adults in whom chemotherapy is not yet clinically indicated	09/2013	× 05/2015
	Zalmoxis®	Allogeneic T cells genetically modified	Adjunctive treatment in HSCT of adult patients with high-risk hematological malignancies	08/2016	✓
	Alofisel®	Darvadstrocel	Complex perianal fistulas in adult patients with non-active/mildly active luminal Crohn's disease, with no response to at least one conventional or biologic therapy	03/2018	✓
	Chondrocelect®	Characterized viable autologous cartilage cells	Repair of single symptomatic cartilage defects of the femoral condyle of the knee (grade III or IV) in adults	10/2009	× 01/2017
Tissue-Based Therapies	MACI®	Matrix-applied characterized autologous cultured chondrocytes	Repair of symptomatic cartilage defects of the knee	06/2013	× 09/2014
	Holoclar®	*Ex vivo* expanded autologous human corneal epithelial cells	Adults with moderate to severe limbal stem cell deficiency, unilateral or bilateral, due to physical or chemical ocular burns	02/2015	✓
	Spherox®	Spheroids of human autologous matrix-associated chondrocytes	Repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee	07/2017	✓

MA: Marketing authorization, ×: withdrawn, ✓: authorized, ALL: acute lymphoblastic leukemia, DLBCL: diffuse large B-cell lymphoma

1.2. ATMPs are different from other pharmaceuticals

ATMPs have unique attributes which differentiate them from standard pharmaceuticals and biologics.

Curative potential: ATMPs address underlying genetic or cellular mechanisms of disease, meaning they can have a dramatic and long-lasting positive impact on health. These therapies have the potential to transform patients' quality and length of life; in some circumstances, they may even be curative.

One-time treatment: ATMPs are often administered just once, or perhaps a handful of times within a short period. Therefore, they do not present the adherence challenges faced by many taking traditional medicines for chronic conditions.

High upfront cost: These transformative therapies are typically paid as a one-time, up front cost. Despite often small patient populations, ATMPs can present an affordability challenge to certain payers restricted by current budgetary constraints and payment systems.

Complex manufacturing: ATMPs are complex products that may require highly specialized manufacturing equipment, processes, and skills. Some cell-based gene therapies, like CAR-T cell therapies used to treat certain blood cancers, are manufactured individually for each patient: cells are collected from the patient's blood using a process called apheresis, modified and expanded in the laboratory, and then re-infused into the patient hours later. Specialist centers and highly trained individuals are required to carry out these processes. Allogeneic cell therapies and cell-based gene therapies, which use donor cells, can be manufactured more efficiently, in bigger batches. However, scale up can still be tricky for certain cell types.

Scale up can also present challenges in the manufacturing of viral vectors used to carry gene therapies into the body. Different viruses behave in different ways, often requiring highly specific conditions and processes in order to be scaled up and purified in a consistent fashion that meets stringent quality control standards. Ensuring consistent standards and adequate characterization across starting materials, processes, and infrastructure is a common challenge for ATMP manufacturers.

Storage: Some ATMPs are living cells with short shelf lives. Beyond the challenges of procuring appropriate cells and starting materials, these therapies may have highly specific storage requirements, making transportation difficult in some cases (4, 5).

Specific regulatory and pharmaco-vigilance demands: ATMPs are regulated by a specific set of laws due to their uniquely complex characteristics and their differences from traditional pharmaceuticals, biologics, and medical devices. The European Union's Advanced Therapies Regulation EC 1394/2007 defines ATMPs and outlines specific requirements for the evaluation of their quality, safety, and efficacy. These medicines also fall under the overarching EU Medicinal Products Directive 2001/83/EC.

Safety monitoring is critical for all medicines, including ATMPs. This relatively new group of therapies includes living cells and genes, whose potentially profound, durable beneficial effects must be accompanied by rigorous pharmaco-vigilance. The European Medicines Agency has recently drafted updated guidance around ATMP safety and risk-monitoring, building on experience gained using these products since the original guidelines from a decade ago. The guidance covers a range of risks associated with ATMPs, including some that are specific to this category, such as long-term immunogenicity (e.g. for donor-derived cell therapies), insertional mutagenesis (e.g. for some gene therapies), and risks linked to product storage or distribution.

Since many ATMPs treat only small populations, the safety (and indeed efficacy) data available prior to approval may be very limited. Close patient follow-up and disease registries are therefore vital in order to build up long-term efficacy and safety data supporting ATMPs. EMA recommends planning for registries early on in development, allowing all the necessary stakeholder agreements and data privacy/consent structures to be in place when the product is approved. The EMA guidance includes a series of measures for early risk-detection, adverse event reporting, and product-specific monitoring, taking into account the need for tailored approaches depending on the therapy in question (6-8).

It is important to note that advanced therapies that are not produced for "routine use" are exempt from the Regulation EC 1394/2007 and do not require central marketing authorization. The interpretation of "routine use" varies among EU member states. In most member states, these "hospital exemption" products do not need to demonstrate quality, efficacy, and safety and can be commercialized even if there is an authorized product in the respective indication. This report focuses on ATMPs produced by research-based manufacturers that fall under Regulation EC 1394/2007 and are subject to marketing authorization by EMA.

FIGURE 1. Conventional therapy vs. ATMPs

	Conventional Therapy	ATMP
Degree of personalisation	+ Prepared and prescribed for a broad population	+++ Custom-made cell and gene therapies
Length of administration	+ Majority are given as long-course or lifetime treatment	+++ Usually administered once
Cost distribution	+ Cost spread over time of administration	+++ Upfront cost
Outcomes durability	+ Outcomes observed after administration	+++ Outcomes observed on the long term

1.2.1 ATMPs in development

Rapid progress across molecular and cellular biology, driven by the genomics revolution and accurate, accessible, and rapid gene-editing tools, has translated into a growing number of approved ATMPs and an expanding ATMP pipeline. As of January 2019, there were more than 1,000 clinical trials of ATMPs ongoing worldwide, according to the Alliance for Regenerative Medicine (ARM). Over two-thirds were in mid- or late-stage development (Phase II or III) (Table 2) (9).

More than half of all ATMPs in development are in oncology, where a clear genetic component has enabled the development of highly personalized therapies such as CAR-T cells. But development candidates target multiple indications, including many rare conditions, across the cardiovascular, musculoskeletal, central nervous system, endocrine, and dermatological domains (Table 3).

1.3 Value delivered by ATMPs

Some ATMPs have the potential to cure disease, rather than only treat its symptoms. Many offer transformative benefits that are unavailable with traditional pharmaceuticals. The extent of ATMPs' value to patients depends upon the product and condition in question.

TABLE 2. Number of ATMP clinical trials

	Gene Therapy	Gene-Modified Cell Therapy	Cell Therapy	Tissue Engineering
Phase 1	123	160	55	11
Phase 2	217	197	182	22
Phase 3	32	17	31	13
Total	**372**	**374**	**268**	**46**

Source: Alliance for Regenerative Medicine, Q1 2019 Global Sector Report

TABLE 3. ATMP clinical trials by indication

Indication	Number of Clinical trials
Oncology (excluding hematology)	618 (58.3%)
Cardiovascular	67 (6.3%)
Musculoskeletal	60 (5.7%)
Central nervous system	56 (5.3%)
Endocrine, metabolic, and genetic disorders	44 (4.2%)
Dermatology	38 (3.6%)
Hematology	36 (3.4%)
Immunology & inflammation	36 (3.4%)
Ophthalmology	35 (3.3%)

Indication	Number of Clinical trials
Infectious diseases	21 (2.0%)
Genitourinary disorders	15 (1.4%)
Gastroenterology	14 (1.3%)
Respiratory	10 (0.9%)
Surgery	3 (0.3%)
Lymphatic diseases	3 (0.3%)
Ear diseases	2 (0.2%)
Geriatric diseases	2 (0.2%)

Total 1,060 (100%)

Source: Alliance for Regenerative Medicine, Q1 2019 Global Sector Report

TABLE 4: ATMPs in development by geographic area

	Europe	North America	Asia	Oceania	South America	Africa	Total
Phase 1	61	215	105	12			**393**
Phase 2	259	358	143	18	2		**780**
Phase 3	177	79	41	8	3	4	**312**
Total*	**497**	**652**	**289**	**38**	**5**	**4**	**1,485**

*totals larger than overall total as some trials run in multiple locations

1.3.1 ATMPs' value to patients

ATMPs have already delivered significant value to patients suffering from a range of life-threatening conditions, many caused by genetic mutations. These therapies can change lives by significantly reducing the burden of patients' diseases and chronic treatments. ATMPs may also save health system costs over the long term by removing or minimizing the need for regular treatment or procedures and reducing everyday care demands on families and caregivers.

Below are examples of the impact that ATMPs are having on the health and quality-of-life of patients suffering from vision disorders, advanced blood cancers, musculoskeletal and neuromuscular diseases, and blood clotting disorders. Some of the therapies are approved; others have shown strong signs of efficacy in late-stage trials.

Treating ADA-SCID

The gene therapy Strimvelis® was approved in Europe in 2016 for children with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID) who lack a matching bone marrow donor. The treatment was developed by the San Raffaele Telethon Institute for Gene Therapy in Milan, Italy in partnership with GlaxoSmithKline and manufactured by the Italian biotech MolMed. The therapy involves collecting patients' bone marrow-derived CD34+ cells and modifying them to produce functional copies of the adenosine deaminase enzyme. A clinical trial (10) suggested that a majority of patients on the treatment no longer require the enzyme replacement therapy necessary for ADA-SCID patients either as a temporary measure prior to transplant or, for those with no donor, indefinitely.

Strimvelis is only approved for manufacture and administration at a single site, the San Raffaele Hospital in Milan; however, it is available to several EU patients, provided that the patient travels to the specialized clinical center in Milan. In 2018 (11), NICE recommended reimbursement for a small population of English patients being treated with Strimvelis in Italy. The same year, GSK sold the rights to Strimvelis to Orchard Therapeutics, a UK-based biotech focused exclusively on rare diseases.

Restoring sight

LUXTURNA® (voretigene neparvovec) is a one-time gene therapy product used for the treatment of patients with inherited retinal disease due to mutations in both copies of the RPE65 gene, which can only be confirmed through genetic testing. Patients must also have enough remaining cells in their retina, as determined by a healthcare professional, before receiving treatment.

Without treatment, most patients with RPE65-mediated inherited retinal disease progress to blindness. LUXTURNA is the only gene therapy product approved in both the US (2017) and in Europe (2018). Brought to market by Spark Therapeutics and marketed by Novartis outside the US, the drug delivers a functioning copy of the RPE65 gene to act in place of the mutated gene, with the potential to make a patient's visual cycle work again.

By slowing or halting retinal degeneration, LUXTURNA vastly improves vision and the ability to do tasks of daily living that depend on vision. For example, according to news reports (12), Jack, a 13-year-old in the US who was treated at Massachusetts Eye and Ear Hospital in Boston in Spring 2018, had improved night-time vision and improved visual acuity (ability to read fine print) after a single treatment with LUXTURNA. Similar stories are emerging (13) for other patients after receiving the therapy.

Providing options for advanced cancer patients

Cell therapies are also providing options for some patients with advanced, hitherto-untreatable forms of blood cancer. Novartis' Kymriah® (tisagenlecleucel), developed in collaboration with the University of Pennsylvania, was approved in the US in August 2017 (14) for patients up to 25 years old with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) and for adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). A similar drug, Gilead's Yescarta® (axicabtagene ciloleucel) was approved (15) the same year for advanced forms of DLBCL as well.

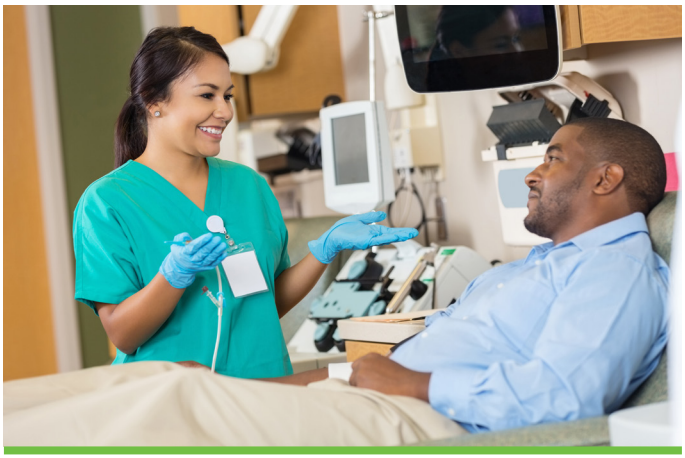
These drugs involve collecting and modifying patients' own T-cells, a type of immune-system cell. The cells are engineered *ex vivo* to target a protein that is specific to cancer cells. The re-infused cells then target and kill the offending cancer cells. CAR-T therapy administration is complex and time-consuming, both for patients and specialists. There are considerable risks associated with the treatment. However, it has also proven to be remarkably effective in some patients, with a few cases of complete response (no signs of cancer at all) up to a year later. CAR-T therapies will likely continue to advance: Kymriah has since been approved for other blood cancers (16), and there are multiple programs in development, including some that modify donor T-cells rather the patient's own cells.

Towards a potential cure for hemophilia

Several gene therapy options are in late-stage development for patients with hemophilia, a typically inherited blood clotting disorder that can be dangerous and, in its severest forms, can significantly impact quality of life. People with hemophilia lack, or have very low levels of, a protein needed for the blood to clot properly. They currently need to regularly administer replacement versions of these clotting factors, to reduce the risk of uncontrolled bleeding, which could arise from just a simple scratch. Most patients have hemophilia A, and therefore need to take clotting factor VIII. Those with a rarer form, hemophilia B, need clotting factor IX.

Gene therapies may offer a one-time treatment that removes the need for patients to undergo regular injections or infusions, allowing them to lead close to normal lives. BioMarin's Phase III hemophilia A candidate, valoctocogene roxaparvovec, delivers the missing gene needed to produce factor VIII. It may, after a single administration, eliminate the need for ongoing factor VIII treatment. This would free patients from the burden of receiving infusions two to three times per week, and associated risks, such as development of antibodies against the protein, preventing it from working. Thus, gene therapy may also reduce the long-term costs of treating hemophilia patients.

Other later-stage hemophilia gene therapy candidates include Spark/Pfizer's Phase III hemophilia B program (17), fidanacogene elaparvovec, and Spark's hemophilia A program, which is on the cusp of Phase III. Competition could help reduce prices and provide a broader range of treatment options.



Extending the lives of patients with SMA and XLMTM

Spinal muscular atrophy (SMA) is an inherited neuromuscular disorder caused by a defective or missing SNM1 gene. Infants born with a particularly severe form of the condition (SMA Type 1) rapidly lose muscular function, limiting their life expectancy to 24 months or less. Novartis' gene therapy product Zolgensma® (onasemnogene abeparvovec) recently approved by the US FDA (18), delivers a replacement copy of SNM1, tackling the root cause of the condition. Young patients in a small (n=15) Phase I pivotal clinical trial showed significant improvements in overall survival and in motor function, compared to untreated patients (19). Novartis acquired the program through its $8.7 billion acquisition of AveXis in April 2018 (20); the therapy was initially developed with support from the patient-funded rare diseases-research institute Genethon and is aimed for all SMA patients.

Gene therapy may also provide a treatment option for children with X-linked myotubular myopathy (XLMTM), another rare genetic neuromuscular disorder that causes breathing, swallowing, and feeding difficulties and which limits life expectancy to months or days. California-based Audentes Therapeutics' Phase I/II candidate, initially developed with Genethon, delivers a functional copy of the MTM1 gene, which encodes the myotubularin protein critical to skeletal muscle function. In October 2018 (21), the company reported encouraging interim efficacy and safety data in eight patients.

New options for beta thalassemia sufferers

Transfusion-dependent beta thalassemia (TDT) is a serious genetic disease that limits the blood's ability to carry oxygen throughout the body. Patients suffer from severe anemia, require life-long blood transfusions, and are at risk of serious co-morbidities. Bone marrow transplant is an option for some patients but can lead to complications.

Zynteglo®, a gene therapy developed by bluebird bio using their LentiGlobin vector technology, delivers a type of hematopoietic (blood) stem cell with a gene encoding part of the oxygen-carrying protein, hemoglobin, that is absent in TDT patients. Phase III data released in December 2018 (22) showed that patients began to produce near-normal levels of gene therapy derived hemoglobin. Ten out of 16 patients were no longer receiving blood transfusions three to 18 months after treatment. In June 2019, the EU gave a conditional marketing authorization for Zynteglo in Europe (23). bluebird bio's LentiGlobin technology was developed at Harvard University, at France's Alternative Energies and Atomic Energy Commission (CEA) and the French research institute INSERM; one of the clinical trials (24) is underway at Necker Children's Hospital and INSERM in Paris.

Improving health-related quality of life (HRQoL)

The profound impact of ATMPs on disease pathology can hugely improve patients' quality of life and health status in the long run (25). This is particularly the case for diseases

with no or few alternative treatment options — true of most conditions for which ATMPs are in development — where patients are forced to endure regular, often time-consuming and uncomfortable procedures that frequently offer only symptom relief.

Improvements to patients' HRQoL translate into similar benefits for families and caregivers. For example, a child with Duchenne Muscular Dystrophy (DMD), an inherited muscle weakness disorder that can lead to severe disability, may not be able to walk or breathe unassisted. An ATMP that addresses the genetic causes of condition could mean these patients no longer require 24-hour care, relieving the emotional, physical, and financial stress on caregivers as well as on the patient. Several gene and gene-based therapies are in development for DMD and similar conditions.

1.3.2 ATMPs' value to healthcare systems

Reduced hospital, therapy, and nursing costs

ATMPs' potentially transformative effects on the health outcomes and treatment requirements of many serious diseases could generate significant cost savings for health systems. Fewer patients would require multiple rounds of expensive, intrusive, and often risky procedures, such as enzyme replacement therapy or blood transfusions, throughout their lives. This could reduce therapy and hospital equipment costs and cut the costs of trained medical and nursing support staff required to carry out or oversee these sometimes lengthy procedures. It would also reduce the costs of home nursing.

Fewer hospitalizations, co-morbidities, and associated treatments

Patients benefiting from ATMPs would also be less likely to suffer the serious complications associated with their conditions, such as the joint damage endured by many hemophilia patients. That would mean fewer emergency hospitalizations, generating significant financial and resource savings. Healthier, more able patients with a higher quality of life are less likely to suffer co-morbidities requiring further, potentially expensive, therapies or support.

1.3.3 ATMPs' value to society

Increased productivity

Beyond their value to patients and healthcare systems, ATMPs are likely to have broader societal benefits. By decreasing the burden of disease on patients and caregivers, they may generate increased workforce productivity, limiting sick leave and freeing up non-healthcare resources, such as community support structures or special educational programs in schools and nurseries.

Healthier, more engaged elderly citizens

Many ATMPs are currently in development to promote healthy aging. For instance, regenerative medicines can alleviate or cure age-related conditions such as osteo-arthritis and may in future offer solutions for degenerative diseases such as Alzheimer's and Parkinson's. This could lead to more active, independent, and engaged older citizens who can remain in the workforce for longer and maintain mental and physical strength. This will be critical to the economic and social wellbeing of all age groups: Europe's working population is expected to shrink from 333 million in 2016 to 292 million in 2070 (26), but will have to support an expanding number of retired citizens.

A wider revolution in medicine

ATMPs have emerged from the extraordinary scientific and technological progress of the last three decades. Their success, and their positive impact on patients, health systems, and society will drive further innovation, both in the life sciences and beyond. In future, ATMPs may not be a special category of medicines. They may become the norm, as happened with monoclonal antibodies.

1.4 HTA frameworks are not always best adapted to ATMPs

ATMPs' potentially transformative impact has given them a special status among regulators. Expedited approval pathways help ensure these treatments reach those in need as quickly and safely as possible.

Yet few payers or health technology assessment (HTA) bodies have established specific pathways or requirements for assessing ATMPs *per se*, challenging patients' timely access to these treatments.

Several European Union countries have special processes (27), cost-effectiveness thresholds, or exemptions for orphan drugs — those intended to treat debilitating or life-threatening conditions that affect no more than five in the 10,000 people (about 250,000 individuals) in Europe (Table 5). Eight out of 13 ATMPs registered in the EU qualify as orphan drugs. In some countries, like Germany, orphan drugs are assumed to bring an added benefit, unless and until they surpass €50 million in sales within a 12-month period (28), and therefore benefit of relative lower burden of evidence compared to other medicines.

Such pathways, however, do not offer a long-term solution to the challenges of valuing ATMPs appropriately. Assessing the full benefit of such drugs requires systematic consideration of a wider range of potential benefits and cost savings than conventional treatments, including for example societal benefits and long term system savings. It also requires new methods for dealing with uncertainty over treatment duration and data limitations often associated with smaller patient populations.

TABLE 5. European HTA Processes for Orphan Drugs

Country	Policy specific to orphan drugs
Germany	Orphan drugs are assumed to have some kind of added benefit following EMA approval. They therefore face an assessment by the G-BA based on evidence available at time of marketing authorization, without a comparison over an appropriate comparator determined by the G-BA. This incentive ends when revenues surpass €50 million (incl. VAT) in a given 12-month period, orphan drugs then undergo the usual assessment procedure.
England & Scotland	**NICE:** In addition to the traditional **Single Technology Appraisal (STA)**, NICE has introduced a **Highly Specialised Technologies (HST)** route for "ultra-orphan" conditions. This process (29) grants decision makers some discretion in considering case-specific evidence, and also takes into account savings or benefits incurred outside of the health and social services systems. It also considers longer-term benefits to the NHS of innovative technologies and takes into account the views of affected patients and caregivers. **SMC:** Orphan drugs — lower levels of clinical trial evidence are accepted, but with possible requirement for additional data (e.g. surrogate markers and QoL data). Higher levels of uncertainty are accepted in economic evaluations of orphan drugs. Ultra-orphan drugs (for conditions affecting <1 in 50,000 people in Scotland). If the medicine meets the new definition of an ultra-orphan medicine and the SMC considers it clinically effective, it will be made available on the NHS for at least three years while information on its effectiveness is gathered. The SMC will then review the evidence and may make a final decision on its routine use in NHS Scotland.
France	France offers early access of orphan drugs through the temporary licensing system (ATU) (30) before marketing authorization. There is no specific orphan reimbursement pathway (31), but the reimbursement authority, HAS, places strong emphasis on innovative technologies, unmet clinical need, added therapeutic benefit, target population size, and forecast sales volumes, all of which can be helpful in gaining access to orphan drugs. There are also examples of conditional reimbursement linked to post-marketing evidence gathering.
Sweden	TLV assessment principles (32) take into account orphan status; the agency has the flexibility to consider a higher cost-effectiveness threshold based on unmet need, severity of condition, and limited budget impact due to small populations.
Italy	AIFA's process considers the innovation status of new drugs, taking into account unmet need, therapeutic added benefit, and evidence quality. Orphan drugs are fully or partly exempted from the evidence quality criterion. New rules (2017) (33) for assessing innovation are designed to provide faster, more streamlined access across the country. Drugs classed as 'innovative' may be paid for by a separate fund, exempted from budget caps and included immediately in regional formularies.
Spain	Spain's Ministry of Health introduced a rare diseases strategy in 2009 to expedite reimbursement of orphan drugs. It was updated in 2014, however, access to orphan drugs remains slow, according to the Spanish Association of Orphan and Ultra Orphan Medicines Companies.

NICE: National Institute for Health and Care Excellence, SMC: Scottish Medicines Consortium, UK: United Kingdom, ODs: Orphan Drugs, QoL: Quality of Life, NHS: National Health Services. IQWiG: Institute for Quality and Efficiency in Healthcare; G-BA: Gemeinsamer Bundesausschuss; AIFA — Italian Medicines Agency; HAS — Haute Autorite de Sante, France; TLV — Dental and Pharmaceutical Benefits Agency, Sweden.

Different HTA processes lead to variations in ATMP access

All HTA bodies seek value-for-money from medicinal products. Yet individual EU HTA agencies have different priorities and methods (34), linked to their health system funding model and the weighting of economic/budget impact versus broader clinical or societal impact (Table 6). HTA agencies vary in the methods they use, and the degree to which they are able to influence negotiated prices. The variation across HTA decision making in Europe is arguably more visible when considering access to orphan drugs and ATMPs (35) than conventional pharmaceuticals.

Some HTA bodies are more willing than others to accept new kinds of evidence beyond randomized controlled trials, or to consider economic models that involve extrapolating longer-term benefit from limited existing data. Germany, for instance, frowns upon such extrapolation, making it challenging to recognize and quantify long-term cost or outcomes benefits.

In England, the National Institute of Care and Health Excellence (NICE) has a higher cost-per-quality-adjusted life year (QALY) threshold for drugs which may extend the lives (normally for a minimum of three months compared with established practice in the NHS) of those considered to have short life expectancy of less than 24 months (36).

TABLE 6. Overview of HTA decision frameworks in 6 European countries

Country/ HTA Agency	Method driving HTA recommendations	HTA perspective (economic analysis)	Value judgement			Degree of influence on price/rebate
			Clinical benefit	Cost-effectiveness analysis	Budget impact	
France/ HAS (TC, CEESP)	Mixed model: usually clinical, in some cases health economic	Payer (collective perspective)	High	High*/[1]	High [1]	Moderate (benefit tier determines reimbursement level)
Germany/ IQWiG (consultative), G-BA	Clinical model (G-BA)	Payer (only drug budget impact)	High	Low [1]	Low	High (decision influences pricing negs.)
Italy/AIFA, regions	Mixed model: clinical for national decisions, sometimes health economic at regional level	Payer	High	Low	High/ Moderate	High — AIFA and regions negotiate prices
Spain/ SGCMPS, regions	Mixed model: clinical for national decisions, sometimes health economic at regional level	Payer	High	Low	High	High — central and regional negotiations; ref. pricing
Sweden/TLV	Health economic model	Societal	High / Moderate	High*	Low / High [2]	High (TLV sets price)
UK/NICE (England), SMC (Scotland)	Health economic model[3]	National health system and personal social services	High	High	Low	Moderate-High[3]

*No formal threshold; 1) only in certain cases/products; 2) Low at national level and high for county councils; 3) clinical aspects are taken into consideration during the process and fed into the HE model; 4) NICE is 'price taker' its assessments are based on sponsor's price, sponsor may need to reduce its price or sign confidential discounts in order to receive a NICE positive guidance.

HAS:Haute Authorité de Santé, IQWIG: Institute for Quality and Efficiency in Health Care, G-BA: Federal Joint Committee, AIFA: Italian Medicines Agency, SGCMPS: General Subdirectorate of Quality of Medicines and Health Products, TLV: Dental and Pharmaceutical Benefits Agency, NICE: National Institute for Health and Care Excellence, SMC: Scottish Medicines Consortium

For ultra-orphan drugs, under the Highly Specialised Technologies (HST) process, NICE applies a higher ICER threshold of £100,000 per QALY gained, and that can be higher in certain circumstances. Some agencies (such as Sweden's TLV or Italy's AIFA) (37), consider the degree of innovation in a technology. Variations also result from the extent to which HTA bodies can influence price and/or discounts, and the tools they have at their disposal to modulate budget impact. Patient access schemes in the UK (typically straightforward discounts) have helped make treatments more widely available there; Italy's use of managed entry agreements is another way to ensure access under certain conditions.

In Spain and Italy, where many reimbursement decisions are made regionally, budget impact often outweighs other considerations in the evaluation of ATMPs.

2. CURRENT CHALLENGES FOR TIMELY ACCESS TO ATMPS

2.1. Uncertainty on magnitude and duration of effect may limit value perceived by HTA and payers

The types of uncertainties identified through literature search and expert input are:

- Uncertainty around efficacy and clinical benefits due to the trial designs used for some ATMPs, which may be deemed inappropriate (e.g. single arm trial, inappropriate choice of endpoint, inappropriate comparator) by HTA bodies, or no data on long-term benefits (5, 7, 27, 46).
- Uncertainty around safety and risks in the long term (7, 47, 48).
- Uncertainty around incremental cost-effectiveness ratios (6, 7).
- Uncertainty around the durability of treatment effect: The long-term efficacy of an ATMP may be considered as uncertain in some cases, which may result in the need for re-treatment in the future (7, 46, 47). The safety and efficacy of a second or subsequent administration may not have been studied at time of approval and may significantly impact costs.
- Uncertainty around a combination therapy, such as symptomatic or replacement therapies combined with gene or cell therapies, with additional costs and no evidence supporting the benefit of such combinations.

In the case of ATMPs, the gold standard of head-to-head comparisons — randomized clinical trials (RCTs) to characterize the efficacy and the safety profile of a medicinal product — may not always be feasible. This is due to technical specificities, such as those associated with autologous treatment; ethical considerations; complex administration of the ATMP; and the rarity of the condition. As a result, products may receive regulatory approval based on open-label, single-arm, and/or small-scale studies.

Regulators have historically shown flexibility in accepting these trials and have focused on the risk/benefit ratio rather than the exact effect size of the new therapy, which is typically the focus of payers. In addition, regulators have developed specific pathways, including EMA Priority Medicines scheme (PRIME), to ensure faster approval of promising therapies (Table 7).

Whilst regulators acknowledge the potential value of such products and recognize their benefit by ensuring their accelerated assessment and/or providing early access to patients, Health Technology Assessment (HTA) bodies and payers often use different metrics to evaluate coverage and reimbursement. Payers usually put more emphasis on uncertainties around long-term benefit, demonstration of efficacy and safety on validated clinical outcomes and perceived affordability (5, 44).

Additionally, unlike EMA's special Committee for Advanced Therapies (CAT), which was set up to ensure regulators have dedicated expertise in ATMPs when evaluating these innovative therapies, HTA bodies do not have a similarly specialized committee. Therefore, there is a lack of dedicated ATMP expertise at the HTA level.

According to developers, current HTA frameworks are not always appropriate for ATMPs, in terms of managing uncertainties around long-term data on safety and efficacy, including the need and/or the possibility for re-treatment.

So far, several HTA bodies appear to be reluctant to acknowledge the limitations in the applicability of their current reference cases (decision analytic framework) to ATMPs (44). HTA bodies tend to consider this new class on a case-by-case basis. As they gain experience, they may develop some specific methodology dedicated to ATMPs; however, it seems unlikely to be on the agenda in the short time horizon in some countries.

As a result, some HTA bodies and payers, especially those driven by clinical evidence, may be reluctant to provide access based on the data available at the time of launch, with the consequence that patients in need will not be able to access these new treatments in a timely manner (e.g. the cases of Glybera® and Chondrocelect®, which

were denied reimbursement in France due to uncertain clinical evidence). The collection of post-marketing evidence will be very challenging for manufacturers under such circumstances if the product's reimbursement is delayed.

Summary and conclusion:

The value of an ATMP at time of launch may likely be associated with uncertainty regarding the long-term efficacy and safety due to limited comparative data and lack of long-term evidence.

There is a paradox between regulators' approaches in providing early access for ATMPs for patients' benefit and HTA/payers' reluctance to provide access until the long-term profile has been fully characterized. This challenge is faced in all the six countries examined in this report.

Previous experience in the HTA of ATMPs

A review of ATMP HTA reports in select geographies available thus far shows heterogeneity in decisions and uptake in the EU. Some countries, where managed entry agreements are already used (e.g. Italy and the UK), have ensured faster ATMP assessments and market access than other EU countries. However, other countries have delayed ATMP assessments, due to the lack of tools to cope with uncertainties (e.g. Sweden and Spain) or possibly due to lack of experience or expertise. Conversely, orphan ATMPs benefit from special regulations in Germany where they are automatically granted an added benefit by law if annual sales do not exceed €50 million.

To date, Germany is the country with the highest number of ATMPs that are or were reimbursed, with a total of six, four of which are still on the market.

NICE England recommended the reimbursement of five, all of them currently available to patients. Four ATMPs were recommended for reimbursement by HTA bodies in France, while in Italy three are reimbursed and currently available to patients. Only Chondrocelect®

TABLE 7. Accelerated regulatory pathways

EMA Priority Medicines scheme (PRIME) scheme (e.g. Kymriah®, Yescarta®)
› Through PRIME, the European Medicines Agency offers early and proactive support to developers to optimize the generation of robust data on a medicine's efficacy and safety and enables accelerated assessment of a medicine's applications; developers of a medicine that benefitted from PRIME can expect to be eligible for accelerated assessment at the time of application for a marketing authorization (39).
Conditional approval (e.g. Zalmoxis®, Holoclar®)
› Conditional approvals are granted for therapies that satisfy an 'unmet medical need' and indicated for a disease for which no treatment is available. The Committee for Medicinal Products for Human Use (CHMP) bases its positive opinion on data which, while not yet comprehensive, indicates that the medicine's benefits outweigh its risks.
› The company is given obligations to fulfill, such as the performance of further studies.
› The approval is renewed on a yearly basis until all obligations have been fulfilled, and is then converted from a conditional approval into a normal approval (40).
Exceptional circumstances (e.g. Glybera®)
› Marketing authorization under exceptional circumstances is granted when the applicant can show that they are unable to provide comprehensive data on the efficacy and safety of the therapy, due to the disease rarity, limited scientific knowledge in the area concerned, or ethical considerations.
› This route normally does not lead to a standard marketing authorization (41).
Accelerated assessment
› It reduces the timeframe to 150 days instead of 210 days if the applicant provides sufficient justification for an accelerated assessment (42).
Compassionate use
› Under strict conditions, products in development can be made available to groups of patients or to a single patient (Named Patient Program — NPP) who have a disease with no satisfactory authorized therapies and who cannot enter clinical trials (43) but for which at least phase II or phase III data are available.

EMA: European Medicines Agency

TABLE 8. HTA review

	France	Germany	UK	Italy	Spain	Sweden
Glybera®	Not recommended*	Non-quantifiable added benefit*	NA	NA	NA	NA
Imlygic®	NA	No added benefit	Recommended with restriction	List Cnn, not reimbursed	NA	NA
Strimvelis®	NA	NA	Recommended	List H	NA	NA
Kymriah®	Recommended	Non-quantifiable added benefit	Funded via CDF with CED scheme	NA	NA	**
Yescarta®	Recommended	Non-quantifiable added benefit	Funded via CDF with CED scheme	NA	NA	***
Luxturna®	Recommended	Ongoing G-BA assessment	Ongoing NICE HST assessment	NA	NA	NA
Provenge®	NA	Non-quantifiable added benefit*	Not recommended*	NA	NA	NA
Zalmoxis®	Not recommended	Non-quantifiable added benefit	NA	List H	NA	NA
Alofisel®	Recommended	Non-quantifiable added benefit*	Not recommended	NA	NA	NA
Chondrocelect®	Not recommended*	Not eligible to early benefit assessment	Recommended	NA	Recommended	NA
MACI®	NA			NA	NA	NA
Holoclar®	Recommended with restriction		Recommended with restriction	List H	NA	NA
Spherox®	NA	NA	Recommended	NA	NA	-

NA: not assessed or no published decision, CDF: cancer drugs fund; CED: coverage with evidence development; HST: Highly Specialised Technology; ACI: autologous chondrocytes implementation; ALL: Acute lymphoblastic leukemia; Cnn list: not yet assessed, H list: hospital only, UK: United Kingdom

*Decision no more effective as product withdrawn from the market

**Kymriah was assessed by TLV in Sweden. TLV concluded that benefits are associated to high uncertainty and follow-up should be carried out continuously. TLV advice will be considered by county councils for decision making.

***Yescarta was assessed by TLV in Sweden. TLV concluded that benefits are associated to high uncertainty and follow-up should be carried out continuously. TLV advice will be considered by county councils for decision making.

****Luxturna was assessed by TLV in Sweden. TLV concluded that benefits are associated to high uncertainty and follow-up should be carried out continuously. TLV advice will be considered by county councils for decision making.

*****Alofisel was assessed by TLV in Sweden. TLV concluded that benefits especially in the long term are associated to very high uncertainty. TLV advice will be considered by county councils for decision making.

was reimbursed in Spain before its withdrawal and no ATMPs have been reimbursed in Sweden.

Table 8 summarizes the HTA recommendations for ATMPs available as of June 2019.

2.2. Affordability and financial sustainability

Health gains provided by transformative therapies usually come at high upfront costs, thereby posing budget and sustainability challenges to healthcare systems (48). Budget impact and affordability are not considered as key elements of the value of a new drug, but they constitute important criteria for access-related decision making in several countries (49).

Budget impact

Payers are increasingly using budget impact analyses when determining access for a particular therapy. Budget analyses usually compare care paradigm costs associated with the new intervention versus the current standard of care. Typically, the budget impact depends on (50):

- **The target population size**: the number of people affected by the disease and treated (disease prevalence and incidence). It can remain stable or evolve over the time horizon.
- **The market share**: the market share should reflect how the market is supposed to evolve over the time horizon in case a new intervention arrives on the market.
- **The cost of the interventions *(both new and existing interventions)*:** all costs related to the acquisition and administration of the interventions.
- **The resource utilization** and the costs associated with the corresponding intervention (hospital, ambulatory, co-medication, among others).
- **The time horizon**, generally up to five years.
- **The perspective**: it defines whose costs and resources should be examined (for example, public payer, individual, society).

A budget impact analysis describes the therapy's short-term costs and savings from the payer's perspective (51). The current budget impact analysis may not be adapted for ATMPs' specificities: the time horizon may be too short to integrate the one-off administration of the ATMP and not sufficiently factor in the potential long-term cost benefit.

Affordability

Affordability concerns arise when healthcare systems are unable to finance ATMPs in the short or long term despite their potential high value, due to their high budget impact. Despite being cost-effective, some ATMPs may not be affordable (51).

Because paying for innovative therapies requires an allocation of resources from the healthcare/pharmaceutical budget (52), it could necessitate tighter budget constraints for some of the existing healthcare technologies, especially the less effective and cost-effective. ATMPs have the potential to dramatically change the way healthcare is provided and, therefore, to drive reallocation of significant resources. As a result of these expected changes, many stakeholders are concerned about overall affordability and potential negative effects on healthcare budgets.

One of the key factors that determine affordability is budget availability. Most public and private healthcare financial systems are built on annual budgets, defined by political decisions which only have short- or medium-term vision. Therefore, it is important to note that the concern surrounding affordability of ATMPs varies between EU countries depending on the pharmaceutical spending defined in each country, and on the political decisions that may not consider the long-term benefits of ATMPs.

In addition to budget impact, many considerations may impact budget decision making, including balancing competing priorities and equity (51).

Budget impact and affordability in decision making

Budget impact and affordability are considered in different ways in decision making processes. They can be considered within the HTA processes or assessed separately by payers (49):

- Budget impact may be one of HTA's decision criteria. This is the case in Italy, for example.
- The payer may make decisions on affordability independently of HTA. In this case, the HTA assessment is the first step of a two-stage process; the second step is a price negotiation. This system has been used in France and Germany.
- The decision can be based on the interaction between HTA bodies and payers. The HTA body assesses evidence on budget impact and other criteria and passes these to the payer for decision making. This process could include a budget impact threshold, which, if exceeded, leads to a different payer process once the HTA decision is received, involving further interaction between the HTA body and payers (e.g. England).

EXAMPLE:
NICE budget impact threshold to manage affordability

In April 2017, the National Health Service (NHS) implemented a budget impact threshold of £20 million. If the budget impact of a drug exceeds this threshold within the first three years, NHS England may engage in negotiations with the manufacturing company (53). This measure improves the payers' ability to predict future expenditure, however, it may negatively impact the revenue of innovative, highly effective therapies, such as in the case of curative ATMPs (54). It does not take into account the long-term benefits of the ATMPs.

Payers sometimes focus on prices of potential comparators, such as Hospital Exemption products, which may not have same therapeutic benefits or the same indication, in order to drive down potential prices of ATMPs with the goal of mitigating the potential budget impact. Another issue is the concentration of spending in terms of timing and geographic location. A national payer may formally approve a price of an ATMP, but a local hospital or sick fund may be hesitant to assume the costs of such a drug if there is no pass-through funding from a national or regional payer. Long-term cost savings may be accrued by other stakeholders in the healthcare system but not necessarily by the local hospital or sick fund that initially paid for the drug.

Financial sustainability

Financial sustainability is an important concern for both governments and ATMP developers. Discounts are not necessarily a threat to commercial sustainability and will depend on the size of the target population, the initial price, and the level of discount. Several gene therapy products target a small number of patients and are often one-off treatments; therefore, price will need to be set at a level that makes product financially viable for the developer.

Summary and conclusion:

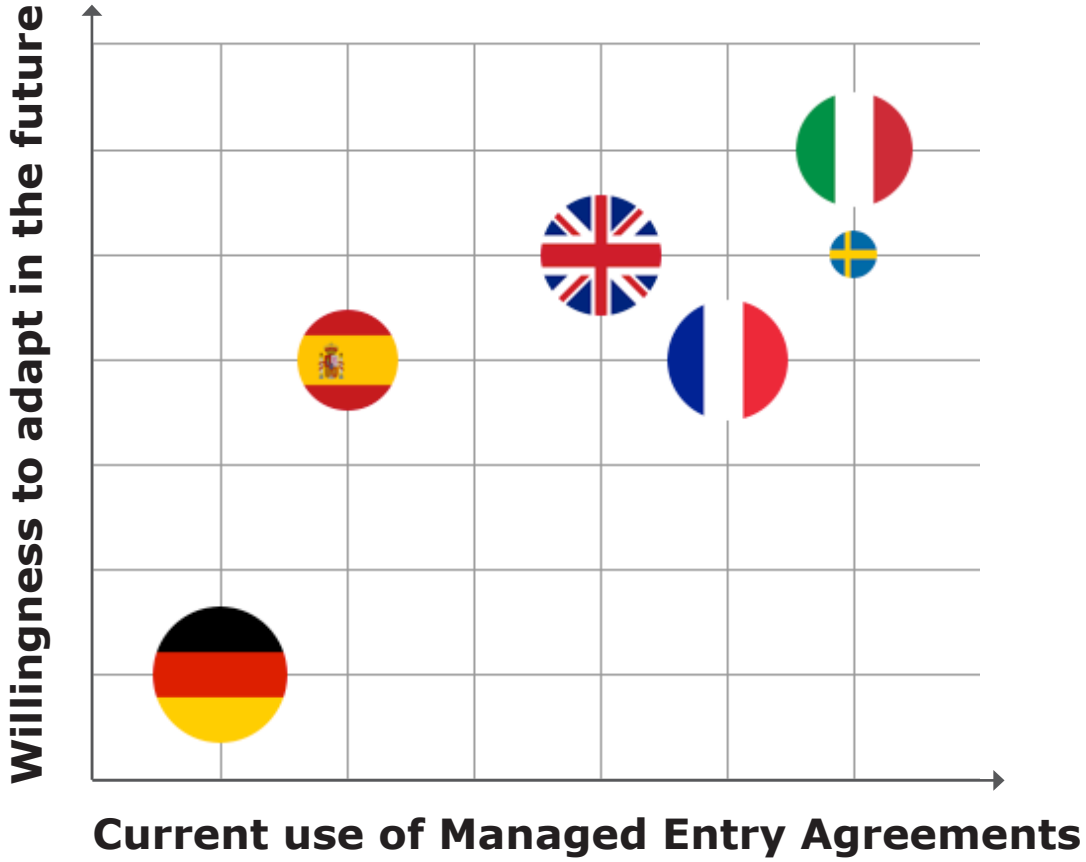
- Budget impact analyses — as currently done — are not best adapted to an ATMP paradigm (short-term administration, long-term benefits and savings) as they often consider short-term time horizons and do not consider impact on societal costs (50).
- Four ATMPs have been pulled from the market due to non-commercial viability. Value to patients/society needs to balance with financial sustainability for both payers and manufacturers. Focusing on one single aspect such as upfront price without considering the long-term value and savings will likely have a negative impact on society as patients may not benefit from a new, effective treatment. Potential transformative treatments' market access failures will have a tremendous opportunity cost on patients and society.

TABLE 9. Financial measures and MEAs in EU5 + Sweden

Country	Financial measures and MEAs
France	Price-volume agreements and rebates are routinely negotiated for new medicines in France. Payment-by-result are rare, limited to drugs in areas of unmet clinical need when evidence at launch is not sufficient by usual HTA standards. If CEPS and the developer do not reach an agreement on price, either CEPS or the manufacturer can propose to establish a conditional price while further post-marketing data is collected. Depending on the outcome, the price of the drug may remain unchanged or be reduced.
Germany	Prices are negotiated at national level and discounts may be agreed on between developers and payers. Rebates are usually used for new drugs, but outcomes-based MEAs are rare. The Act on the Reform of the Market for Medicinal Products (AMNOG) (56) introduced a requirement for manufacturers of new medicines launched after 1 January 2011 to negotiate reimbursed prices with the National Association of Statutory Health Insurance Funds. Developers are free to conclude voluntary discount agreements with individual health insurers or associations of health insurance funds including risk-sharing agreements and capitation agreements. The German health insurance service company GQW and Novartis have signed a risk-sharing agreement according to which Novartis will partially pay back the cost if the patient dies of his blood cancer within a defined period of time after treatment.
UK	Patient Access Schemes (PAS) are routinely used in the UK, they are more often confidential discounts and in rare cases outcome-based agreements. NICE and the NHS have recently closed conditional reimbursement agreements for CAR-Ts with Novartis (Kymriah®) and Gilead (Yescarta®). Under the conditional reimbursement agreements, English patients will get timely access to CAR-Ts while real world evidence will be collected for the next three to five years and will inform future NICE assessments. Discount agreed in the PAS is used for: Imlygic®, Holoclar®, Kymriah®, Yescarta®.
Italy	AIFA uses MEAs to control spending on expensive and innovative products (including oncology drugs). AIFA manages the data required to administer MEAs via the Registry of Pharmaceuticals Subject to Monitoring. MEAs take one of three main forms: payment by results, cost-sharing, risk-sharing. The gene therapy Strimvelis® and Holoclar® are currently available under a payment-by-results scheme in Italy. Zalmoxis® has a flat cost per patient, i.e. treatment cost is the same for all patients, irrespective of dosage.
Spain	Outcomes-based agreements may be used sometimes, and expenditure cap agreements can also be reached between the national (and regional) authorities and pharmaceutical companies.
Sweden	Rebates are used in Sweden: Swedish county councils and companies have agreed, via MEAs for certain pharmaceuticals, that companies refund a certain amount of the pharmaceutical costs to the county councils.

UK:United Kingdom, CEPS: Comité Economique des Produits de Santé, MEA: Managed Entry Agreements, AIFA: Italian Medicines Agency

FIGURE 2. Managed Entry Agreements use and willingness to adopt



Source: ARM primary research

2.3. Current cost-containment measures and Managed Entry Agreements (MEAs)

Strategies to contain the growth rate of the national pharmaceutical expenditure vary between countries. In some European countries, payers manage pharmaceutical spending by applying cost-control initiatives (55). Various policies currently exist, sometimes concomitantly, in order to control the level of spending on particular products (e.g., product-specific rebates), on a therapeutic class (e.g., expenditure cap for a whole therapeutic class), or on pharmaceuticals generally (e.g., claw-backs, patient cost-sharing) (55).

These measures may be applied to ATMPs due to their significant short-term budget impact associated with substantial uncertainty around the long-term benefits. The most common MEAs include:

- **Price-volume agreements:** Agreements where drug prices are reduced if sales volumes exceed given thresholds.
- **Rebates:** Payments refunded by the manufacturer to the payer.
- **Cost-sharing:** The manufacturer grants a percentage discount on either the first cycle of treatment or throughout the treatment, for all eligible patients.
- **Payment-by-result:** The payer only pays the cost of the therapy cycles for responsive patients.
- **Risk-sharing:** The manufacturer gives a percentage discount on the price of initial therapy cycles for non-responsive patients.

2.4. Main country-specific challenges from developers' and experts' perspectives

Multiple hurdles exist in the EU countries that limit ATMPs' market access.

From developers' perspectives, the top challenges in each selected country were collected via a survey completed by ARM members.

To explore potential challenges from HTA bodies/payers' perspective, an advisory board meeting was organized by ARM on 27 of September 2018. The meeting participants were HTA representatives, HTA experts, and former payers, referred to as "experts," from France, Germany, UK, Italy, Spain, and Sweden, in addition to a patient representative and pharmaceutical company representatives. The challenges from experts' perspectives were collected during this meeting and individual phone interviews conducted prior to the meeting.

Table 10 and Table 11 summarize the key challenges in the EU5 countries: France, Germany, UK, Italy, and Spain from developers' and experts' perspectives.

TABLE 10. Country-specific challenges from developers' perspectives

	Germany	France	UK	Italy	Spain	Sweden
1 **Legislative or regulatory barriers**	+++	++	++	+	++++	+++
2 **Limitations of non-comparative data acceptability for long-term value demonstration**	++++	+++	++	++	++	+
3 **Focus on ATMPs' high cost, disconnected from value and price capping**	+	+++	++	++	+++	+
4 **Not adapted pricing processes**	+++	+++	+++	++	+++	++++
5 **Funding and affordability issues**	+	+++	++++	++++	++++	+++
6 **Double hurdle with regional access delay**	++	+	++	++++	++++	++++
7 **Deterministic statistic requested**	+++++	+++++	+	+++	+++	+
8 **Unpredictability of HTA assessment**	+	++++	+++	++++	++++	+
9 **Time to access/Delayed access**	+	+++++	+++	++	+++++	+++

HTA: Health technology assessment, ATMP: advanced therapy medicinal products; UK: The United Kingdom, +: minor challenge; +++++: major challenge
1. Legislative or regulatory barriers to implement new payment models such as annuity payment and outcomes-based payment
2. Not adapted HTA methods not allowing valorization of long-term effects based on non-comparative data: current HTA frameworks do not allow to assess ATMP value based on non-comparative data
3. The countries focus on the high price of ATMPs without considering the long-term value
4. Not adapted pricing processes: Pricing processes that are not flexible, outcomes-based agreements rarely used
5. Affordability issues due to budget constraints
6. Double hurdle in the countries where decisions are made at national and regional level
7. Deterministic statistic is requested by HTA bodies, no room for Bayesian statistic and statistical modelling
8. HTA decision is unpredictable
9. Countries delay the access of ATMPs, few ATMPs were reviewed by these HTA bodies
Source: ATMPs developers survey

Experts' perspective

The main challenges identified are common in the EU countries of scope. Italy and the UK have been identified as the countries with fewer access-related challenges for ATMPs as both have ensured patient access to more ATMPs than the other EU countries, as shown in Table 11.

TABLE 11. Country-specific challenges from experts' perspective

	Germany	France	UK	Italy	Spain	Sweden
Cost and budget impact	++	++++	++++	+++++	+++++	+++
Effect size	+++++	+++++	++	+++	+++	++
Lack of long-term clinical evidence	+++++	+++++	++	+++	+++	++
Not open to the combination of data from RCTs with data from historical cohorts	+++	++	+	++	++	+
Uncertainty	+++	+++	+++++	++	++	++++
Financial sustainability	+	+++	+++++	+++++	+++++	+++

RCT: randomized clinical trials; UK: the United Kingdom, +: low importance challenge in this country; +++++: high importance challenge in this country

Source: ARM primary research and advisory board

3. SOLUTIONS

The potential solutions to challenges presented in Section 2 were discussed in an expert meeting held September 2018. The solutions proposed in this report are based on the outcomes of the expert meeting and on ongoing dialogue with stakeholder groups.

3.1. Solutions to mitigate the uncertainty and valuation challenge

ATMPs face a valuation challenge within current HTA frameworks, particularly with data available at time of launch. HTA bodies and payers have the responsibility of solving the trade-off between ensuring early access to potentially transformative therapies with uncertain patient benefit and delaying access while further data are collected. They consider that current HTA frameworks are adapted to ATMPs and uncertainty is the main challenge; this was recognized by NICE in the mock appraisal conducted to test whether changes to its methods were needed to assess the ATMPs (44).

3.1.1. Better adapted evidence requirements and HTA frameworks

RATIONALE:

In the case of ATMPs, therapies with important long-term benefits for patients and society, there is a need to show more flexibility in evidence requirements and reconsider some aspects in economic evaluation, especially budget impact evaluation.

SOLUTIONS:

Some tools are recommended by experts to ensure better demonstration of ATMPs value at the time of launch:

- Enhance use and validation of surrogate endpoints for early detection of significant and clinically relevant treatment effect.
- Adapt outcome metrics to be fully integrated into continuous RWE development and in HTA assessment processes.
- For indications where control trials are not feasible, increase use of indirect comparisons and generate methodological guidance in collaboration with stakeholders.
- Improve methods to extrapolate shorter-term data into longer term and to update models based on RWE data.
- Improve methods for measuring cost of disease and direct cost of treatment, include costs incurred by patients, payers, caregivers, and society.
- Development and use of pan-European natural history datasets to perform indirect comparisons.
- Leverage scientific, clinical, and HTA expertise from centers of excellence. Due to the complexity of manufacturing and patient management, ATMPs are often administered in a very limited number of centers.
- Consider long-term benefits to patients and society, e.g. by making use of lower discount rates in health economic models if there is an indication that the product is disease-modifying.

RECOMMENDATION 1:
Better adapt Health Technology Assessment (HTA) frameworks to ATMPs:

a.) Enhancing the acceptability of validated surrogate endpoints and indirect comparisons

b.) Supporting development and use of pan-European natural history datasets to perform indirect comparisons

c.) Leveraging scientific, clinical, and HTA expertise from centers of excellence

d.) Adopting changes in economic modelling, such as improving methods for extrapolation

e.) Adapting outcome metrics to be fully integrated into continuous RWE development and in the HTA assessment processes

3.1.2. Conditional reimbursement

RATIONALE:

Conditional reimbursement was proposed as a solution to cope with the uncertainty around the efficacy of ATMPs and to bridge the gaps perceived between clinical trial results and promised real-life results. Conditional reimbursement is a type of performance-based agreement consisting of reimbursement linked to the collection of post-launch evidence, such as Real-World-Evidence (RWE) (58). After collecting prospective population-level evidence from a pre-specified study, the reimbursement is reassessed and

there is a possibility to expand or withdraw the coverage. This type of agreement helps to address the uncertainty existing at the time of regulatory approval (57). A price re-negotiation occurs if the product does not meet real-world expectations.

This policy is usually applied when novel medical technologies are promising, yet additional evidence is required to make an informed decision. According to Lexchin study (59), conditional reimbursement needs to be considered for:

- expensive drugs with available data on intermediate endpoints
- drugs with the potential for widespread use but efficacy and/or safety is disputed
- drugs where RCTs' patient populations are small and are not representative of the target population

These criteria match the ATMP features and conditional reimbursement may become more frequently used by all payers in the future.

Particularly for ATMPs, conditional reimbursement will help to collect evidence on long-term effects that — by definition — are unlikely to be available at launch. This approach helps to facilitate a consensus between patients' demands for early access to innovative technologies, particularly therapies with strong potential to address important unmet needs, and important uncertainties on efficacy, safety, and/or costs for payers, which may induce a reluctance to broadly fund these innovative products.

England applies the concept of conditional reimbursement via the Cancer Drugs Fund (CDF) (described in section 3), and the ultra-orphan pathway in Scotland. The CDF ensures access to promising new treatments, via managed access arrangement, while further evidence is collected to address clinical uncertainty. Conditional reimbursement has been applied in England for the two CAR-T cells approved in the EU so far, Kymriah® and Yescarta® (60). They have been recommended for use in England via the CDF. Similar to the CDF, an Advanced Therapies Fund (ATF) could be established to support both access to breakthrough therapies and use of conditional reimbursement schemes.

In France, the Senate proposed in June 2018 to the government an implementation of conditional reimbursement in order to accelerate innovative therapies market access.

LIMITATIONS AND POTENTIAL SOLUTIONS:

Table 12 summarizes the obstacles that may complicate the implementation of conditional reimbursement and the potential solutions.

RECOMMENDATION 2:
Favor wider application of conditional reimbursement schemes

Conditional reimbursement schemes have the potential to mitigate uncertainty on magnitude/duration of benefits at time of regulatory approval. This approach is in use in several countries and a wider application in Europe for ATMPs is recommended.

3.1.3. Coordinated European HTA activities

a) Develop pan-European Real-World Evidence (RWE) infrastructure

RATIONALE:

RWE is the clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from the analysis of real-world data collected, either prospectively or retrospectively, from observations of routine clinical practice (61). RWE may offer the opportunity for early access to innovative therapies (mainly conditional reimbursement and pay-per-performance schemes) linked to RWE generation (62). HTA bodies may reconsider coverage in light of product performance in the target population in real life. RWE and

TABLE 12. Conditional reimbursement limitations and potential solutions

Limitations	Solutions
Administrative burden for healthcare system	Public-private partnership investment in IT infrastructure
One-off treatments, high upfront costs	Identify most suitable technologies and indications
Budgetary uncertainty	Framework budget agreements
Uncertainty: risk for healthcare system if follow-on evidence is disappointing	Possibility to reduce price, revoke coverage

clinical trials long-term follow-up data help developers to provide evidence on the clinical and economic value of the new product that was not evaluated during drug development (61).

Innovative Medicines Initiative (IMI) related projects in the RWE field (61):

- IMI GetReal: IMI, an EU consortium of industry, academia, HTA agencies, regulators, and patient organizations, launched GetReal to look at RWE generation, which may be adopted earlier in the development and decision making processes to supplement RCT data.
- EMA Adaptive Pathways Pilot and IMI ADAPT SMART: EMA tried to develop an adaptive pathway in the EU via the IMI ADAPT SMART initiative. However, payers taking part in the policy discussion seemed reluctant in accepting a conditional reimbursement approach. The main reason was the lack of "methodologically sound strategies of real-world evidence collection to support the assessment of both efficacy and effectiveness" (63).

On 5 November 2018, EMA published a discussion paper prepared by the Cross-Committee Task Force on patient registries where the use of patient disease registries for regulatory purposes are discussed with methodological and operational considerations. It aims to facilitate the use of patient registries to support regulatory decision making (64). This recent initiative can be instrumental in the adoption of standards for RWE.

EUnetHTA JA2 has launched an initiative under the Work Package 5 (WP5) called Post-launch Evidence Generation (PLEG) that aims to improve post-launch evidence generation. PLEG is further developed under EUnetHTA JA3 WP5.

LIMITATIONS AND SOLUTIONS:

Several challenges may limit the acceptance of RWE. The main limitation is the perceived lack of quality of RWE (63) data as described below:

- Bias and confounding: There are internal validity concerns due to potential selection bias and reporting bias (65). Reporting bias may lead to the overestimation of efficacy and the underestimation of safety risks.
  - In order to mitigate the impact of selection biases, RWE studies need to be rigorously designed and evaluated. A mandatory national registry for studies, such as those available for RCTs, could help mitigate this problem.
  - Reporting bias may be mitigated if the registries are co-managed by payers/EMA.
  - In their recent discussion paper, EMA defines the best practices for the use of registries (64).
- Lack of universally accepted methodological standards: To date, there are no universal, harmonized standards for the design, conduct, analysis, and/or reporting of RWE.
  - EMA is working on disease specific registries for defining RWE standards for regulatory purposes in indications like hemophilia, cystic fibrosis, blood cancers, and multiple sclerosis. The expansion of this initiative to HTA purposes and to other indications is recommended.
  - Lack of investigator expertise: Not all investigators have the background needed to be able to interpret RWE without omissions or integration of confounding biases.

Despite the challenges above, all experts, including the developers and payers at the advisory board, recognized the need for robustness of RWE approach.

The potential solutions suggested during this project to ensure the implementation and use of RWE are:

- The development of EU natural history datasets in key indications/disease areas
- The improvement of methods for indirect detection of meaningful effect,
  - When a direct comparison with an active treatment or with placebo is not feasible, indirect comparisons to relevant natural history or treated patient cohorts (historical control design) are needed.
  - There is a need to further develop these techniques in particular to identify standard comparable populations and relevant endpoints.
- The development of RWE registry infrastructure that can be used for conditional reimbursement, performance-based agreements, and for price adjustments over time
  - A potential barrier that may limit payer access to data is the new General Data Protection Regulation (GDPR). The aim of the new GDPR put in place May 2018 is to protect all EU citizens from privacy and data breaches. In registry studies, the principles of data ownership, informed consent, and data security should be applied in accordance with the GDPR. Under the GDPR, the patient can withdraw consent and request their data to be removed from the data holder files and to not be used or disseminated. This may complicate the collection of data in registries. The EU Commission and Member States must take responsibility for GDPR implications and may include exceptions for tracking patient data in GDPR regulation.
  - Data development infrastructure to be built around EMA's registries framework. Registries' interoperability must be ensured, avoiding country-specific, stand-alone registries.
- The exploration of the potential to further develop existing IMI initiative with ATMP-specific activities

- An international collaboration is important to avoid fragmentation of RWE collection, preventing pooling and analysis of data
- Development of a framework or guidance of how RWE is used in the context of HTA report and pricing & market access negotiations with payers

"We need to invest in infrastructures for long term evidence generation and to invest in methods to analyze those long-term evidence development plans. If we don't have comparative data why don't we conduct a study on the natural history of disease, which in many cases is still lacking? Why don't we investigate appropriate registries of relevant clinical outcomes to patients that we can use? We need to invest in proper methods to analyze, synthetize, and interpret observational data."

—EXPERT AT ADVISORY BOARD MEETING

RECOMMENDATION 3A:
Develop pan-European initiatives to build Real-World-Evidence infrastructure

Real-World Evidence (RWE) development is instrumental in addressing uncertainties on long-term effect, safety, health-related quality of life and use of healthcare resources. There is a need to develop RWE infrastructure and a common framework at the European level to support long-term evidence generation and procedures to enhance quality of evidence collected specifically for ATMPs.

b) Create more opportunities for early dialogue activities

RATIONALE:

ATMP developers need to engage with payers and regulators at an early clinical development stage to ensure that clinical trials are designed to maximize the chance of successful reimbursement, to optimize non-clinical elements of the appraisal process, and to begin early negotiations for a mutually agreeable reimbursement strategy (5, 44, 66). Early dialogue may allow developers to gain critical insights from HTA bodies and regulators early in the development of a therapy, generally before the initiation of phase III clinical trials (66). This could help developers to ensure appropriateness of the evidence development plan, optimization of the evidence generation as well as to address HTA bodies/payers' needs (67). As HTA methods are often not well adapted to ATMPs, early dialogue activities can help addressing any potential evidence issues at an early stage and to put remedies in place, including changes in HTA methods.

Different routes for early advice currently exist:

- Parallel consultations EMA-HTA: As of July 2017, EMA offers consultations in parallel with European Network for Health Technology Assessment (EUnetHTA) to help generate optimal and robust evidence that satisfies the needs of both regulators and HTA bodies. This initiative replaces the previous parallel scientific advice procedure by EMA and HTA bodies, which required medicine developers to contact Member States' HTA bodies individually.
- Multi-HTA early advice: Early dialogues may be held with a consortium of HTA bodies in the EUnetHTA and developers. According to EUnetHTA Work Package 5 lead partner in 2017, EUnetHTA budget is limited: five early dialogues were scheduled for Year One and 10 for Year Two. A fee for service system may be put in place to ensure sustainability (68).
- National HTA advice: A developer can engage in early dialogue with a single HTA body. Several countries have put in place HTA early advice for clinical development plan of health technologies, e.g. UK, Germany, France, and Sweden.

LIMITATIONS AND SOLUTIONS:

A limited number of early dialogue activities are currently conducted and timelines are not aligned with the fast pace of the development of ATMPs. For example, the HTA body in the Netherlands, the National Healthcare Institute (ZIN), provides early advice on six to 10 products per year through EUnetHTA. EUnetHTA has also a limited number of EMA/EUnetHTA Parallel Consultations that can be conducted per year due to budgetary constraints.

There is a need to increase the number of coordinated early dialogues at European level, to increase the active participation of HTA bodies and payers, and to strengthen the trust between regulators and HTA bodies. Additional funding from EU governments is required to improve number and accessibility to early dialogues from all interested developers. This will ensure that the industry uses early dialogue and scientific advice procedures to agree on evidence generation. Evidence generation plans should not be exclusively for pivotal trials; instead, the discussion can be more holistic, with plans for post-approval evidence generation outlined when seeking advice. Furthermore, HTA early dialogue activities are product-specific. There is a need for broader, indication-specific, early dialogue activities. These would be helpful in defining suitability of existing natural history dataset, relevant comparators, endpoints, and in designing pan-European post approval evidence generation platforms.

RECOMMENDATION 3B:
Develop pan-European initiatives to create new early dialogue opportunities

There is a need for more opportunities for early dialogue activities through additional EU and National funding considering the specific needs of ATMPs and the patient populations they are targeting. This would offer developers (and in particular SMEs) early insight on ways to address product specific uncertainties and how to mitigate them.

c) Timely and effective access to cross-border healthcare for all European patients

RATIONALE:

The EU Social Security Regulations 883/2004 and 987/2009, and EU Directive 24/2011 on patients' rights in cross-border healthcare constitute the legal framework for direct and indirect assistance of EU patients in third countries within the European Union. The Regulations and the Directive have allowed abroad treatment of hundreds of thousands of patients. As an example, in the year 2015, 2 million patients received and were reimbursed for unplanned treatment abroad under Regulation 883/2004, while in the same year approximately 180,000 patients received and were reimbursed for unplanned treatment under Directive 24/2011, for an estimated expenditure below 0.005% of total EU healthcare spending (69). Due to the complex science and manufacturing, combined to rarity of treated conditions, ATMPs are subject to be administered in highly specialized centers, and possibly available only in a limited number of countries or, within countries, only in certain regions. These characteristics of ATMPs make them particularly suitable for cross-border treatment. As an example, Orchard Therapeutics' Strimvelis for ADA-SCID is solely manufactured and administered in the San Raffaele Hospital in Milan (Italy) and patients travel from other European countries for treatment and follow up. The NICE in England has assessed Strimvelis and recommended NHS reimbursement to English patients receiving the treatment in Italy (70).

LIMITATIONS AND SOLUTIONS:

Despite current legislation has allowed cross-border treatment for millions of EU patients, including a few treated with ATMPs, there are still many barriers limiting cross-border access, including:

- The EU Directive 24/2011 requires patients or their families to pay the treatment center upfront before being reimbursed by the national payer. Given the high cost of ATMPs, this provision makes the Directive inapplicable.
  - A suggested solution is to establish through the Health Programs a European mechanism and fund to manage cross-country payments and at the same time release patients from upfront payments.
- Due to EU Directive 24/2011 requirement for home country payers to reimburse up to the cost of the same treatment in the home country (71), reimbursement and therefore feasibility of cross-border healthcare depends very much on home country definition of 'same treatment' and related costs. Given that the need for cross-border treatment is expected to be due to unavailability in certain countries or regions, it seems unlikely that these countries will be able to define a local cost for the same treatment. The European Commission and European Parliament have identified practices at the Member State level aiming at restricting cross-border access through this provision and recommended remedies (69, 71).
  - A potential solution is to define acquisition and ancillary costs of ATMP treatments based on an EU average. This could be part of broader HTA coordination at the EU level and validated through early dialogue activities.
- Similar access barriers are expected also within countries with regionalized healthcare systems like Italy, Spain, and Sweden where ATMPs are likely to be available in a limited number of centers/regions. The lack of mechanisms to ensure funding and access across regions could potentially limit access and generate inequalities.
  - European and national mechanisms and funds could address or at least mitigate regional barriers to patient access.

RECOMMENDATION 3C:
Develop pan-European initiatives to create timely and effective access to cross-border ATMP treatment for all EU patients

Despite existing legislation to facilitate cross-border treatment in Europe, there are still barriers limiting access to ATMPs as they are most often delivered through centers of excellence which are not always present at the country or regional level. In particular, there is urgent need for measures to coordinate and fund access to cross-border ATMP treatment at European level.

3.2. Solutions to mitigate the affordability and sustainability challenge: innovative payment models

Various payment models for innovative therapies have been suggested in the literature over the past years (6, 38, 45, 46, 48, 49, 50, 51, 52, 53, 54, 57, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85). These payment models can be divided into two categories, not mutually exclusive: financial-based agreements and health outcomes-based agreements. The financial-based agreements are budget-driven, aiming to reduce the budget impact of the innovative therapies, whereas health outcomes-based agreements aim to link the payment to the value delivered by the novel therapy.

Some payment models are already commonly used in some countries, e.g. discounts and rebates, while others are used in certain cases, such as payment-by-results, and other innovative payment models have been suggested for innovative therapies.

FIGURE 3. Payment models for innovative therapies suggested in the literature

Payment Models	Definitions & Main Advantages
Annuity payment	• Periodic payments over time rather than a one-time, upfront payment.
Pay for performance	• Performance in a defined patient population is tracked over a specified time period; the amount or level of reimbursement is based on outcomes.
Price control, discounts	• Discounts: Price reductions granted to payers, usually confidentially, under specific conditions without affecting a drug's list price. • Price control/caps: methods used to control and limit pharmaceutical prices and payer expenditure for a given drug.
Price-volume agreement	• Agreements where drug prices are reduced once reach certain sales volume.
Healthcare loans	• Governments facilitate better credit instruments for public payers or contracting arrangements between payers and pharmaceutical companies.
Fund based payment: silo funds	• National funds for specific conditions or diseases: for example, the Cancer Drugs Fund in the United Kingdom that pays for new cancer drugs rejected by NICE.
Pooled funding	• The high aggregate costs of drug treatment for an individual patient are borne by a risk pool of multiple payers. • This pool reimburses payers for the portion of claims incurred by high-cost patients.
Bundling*	• An all-inclusive payment per-enrollee for a defined scope of services, regardless of the quantity of care provided. • It allows better predictability of budget spending and can yield savings for payers.
Healthcoin*	• It converts the incremental outcomes produced by curative treatments to a common currency, such as life-year equivalents. Healthcoin can be exchanged for US dollars in the marketplace. Medicare would pay the private payer for a beneficiary who is transitioning to Medicare at the age of 65 years, if the private payer had previously paid a cure for diabetes for this beneficiary for example. • Healthcoin incentivizes private payers to invest in breakthrough treatment.
Specific fund	• ATMP-specific fund* separate from the traditional existing reimbursement path and independently funded that ensures the sustainability of health systems.

*Bundling and Healthcoin have been proposed for the US

3.2.1. Pay-for-performance (P4P) schemes should be an available option to address uncertainty at launch

RATIONALE:

Experts considered that existing tools are not sufficient to handle one-off high-cost therapies. Therefore, an expert discussion was facilitated on the proposed models in order to identify a potential solution.

Each of the proposed models had advantages and disadvantages for the payers. It was agreed that Pay-for-Performance (P4P) was considered a promising and feasible option to address the uncertainty related to ATMPs' value. P4P is a type of MEA, which consists of linking the payments of a product to clinical milestones achieved by the new therapy in a pre-defined target population in the real world.

LIMITATIONS:

The main hurdles identified by experts in the adoption of the P4P model are of an administrative nature:

- Data infrastructure must be established for measuring health outcomes/performance and this is likely to require significant upfront investment.
- In the absence of a dedicated IT infrastructure, considerable human resources are required to collect and manage outcome data compared to more traditional volume-based discount schemes.
- Country-specific regulations or the way the healthcare system is organized may make introduction of these schemes challenging.

PROPOSED SOLUTIONS:

- The administrative burden of data collection and reporting by healthcare professionals should be alleviated (potential fix for the UK and Spain but also other countries). A possible and recommended measure would be to reduce the financial burden to healthcare systems through Public-Private Partnership (PPP) investment in dedicated IT infrastructure. As already mentioned in paragraph 3.2, an important PPP inititiative in this respect is IMI.
- Standardized, validated outcome measures and methods would help reduce the burden of setting up P4P schemes at local level.
- In Germany, the National Association of Statutory Health Insurance Funds (GKV-SV) could play a positive role in negotiating framework pay-for-performance agreements with individual or multiple companies.
  - *"Performance-adjusted one-off payments and performance-dependent instalment payments are possible models,"* said the National Association of Statutory Health Insurance Funds (GKV-SV) head of medicines Antje Haas at a conference organised by the German society for market access in Berlin (82).
  - In March 2019, Novartis and the German statutory health insurance GWQ ServicePlus AG signed a pay for performance agreement according to which Novartis will pay back part of Kymriah's price in case patient survival will not reach an agreed threshold (83).
- In France, CEPS may agree on performance contracts for ATMPs with the developers.

TABLE 13. Expert-reported barriers to adopting P4P measures in EU5 countries and Sweden

Country	Obstacles
Germany	Germany is a multi-payer system. MEA /P4P agreements would need to be done with every single payer in Germany, therefore MEAs are not considered easy to implement.
France	Outcomes-based agreements are rare in France due to the perceived administrative burden and the possible lack of payer trust in this approach. Eventually under exceptional circumstances, conditional reimbursement with escrow agreements may be used.
UK	Resistance from department of health because they are seen as burdensome to manage and financial schemes are preferred and can be revised when more data are available.
Italy	No obstacles perceived; payer open to such arrangements.
Spain	Historically, rarely done at national level due to perceived administrative burden, and more frequent at regional level. However, CAR-T therapies and other innovative therapies in Spain have been approved based on outcomes-based agreements. Payers are looking at short term performance assessment that may not match ATMP features.
Sweden	Conditional reimbursement used to be the most frequent at national level, however financial agreements are progressing, and at county level P4P are possible. Resistance for administrative burden.

MEA: Managed Entry Agreements, P4P: Pay for Performance. Source: ARM primary research

3.2.2. Annuity payment: a medium-term solution

RATIONALE:

Another solution widely proposed is the annuity payment model; however, this would require a transformation of health insurance systems. The annuity payment model consists of installment payments spread over a pre-determined time period (e.g. monthly payment, annual payment). This helps payers spread out the high upfront costs of a transformative therapy over years, during which the benefits (and cost savings) of ATMPs will be realized by both patients and payers (84-86).

PROPOSED SOLUTIONS:

Substantial efforts are required to implement the P4P and annuity payment:

- Special committees for P4P agreements are needed both at pan-European and country levels. Committees can set-up and supervise the execution of these agreements: definitions of the clinical outcomes must be considered as milestones for payment, including the thresholds of outcomes, the frequency of data collection, and the payment amount.
- Infrastructure for data collection is needed: in order to establish patient registries to facilitate the collection of real-world evidence.
- Develop clear guidelines for the implementation of agreements.
- Introduce legislative and regulatory changes to allow and support P4P and annuity-based schemes implementation on a country-specific basis as existing laws and regulations differ by country.
- The EU commission will need to work with the EU Member States to implement procedures to protect patients' personal data in respect of the GDPR directive.

3.2.3. Special Fund

RATIONALE:

An additional solution suggested by experts in some countries is a specific fund for ATMPs. It is already applied in the UK and Italy for particular drugs. The implementation of a fund for ATMPs may be a solution to ensure patient access to innovative drugs and equity between regions in regional policy countries.

LIMITATIONS:

TABLE 14. Experts' perspectives on country-specific hurdles for annuity payment implementation

Country	Obstacles
Germany	The system is **multi-payer**, it may be complicated to deal with annuity payments if patients switch to another sick fund, even though this is not a frequent event.
France	The service or therapy may need to be budgeted in the year of treatment even if the payment will be spread over years. Therefore, the financial advantages of annuity payment may not immediately translate into healthcare budgets.
UK	There are some concerns about applicability in the UK due to EU accounting law. These concerns could be much less relevant after Brexit.
Italy	Administrative constraints and bureaucratic burden at regional and hospital level are expected to limit opportunities to run annuity payment schemes. Theoretically, annuity is applicable, but the problem is in its implementation. Collaboration and discussion with regional payers and hospital representatives may improve administrative aspects.
Spain	Current regulation does not allow committing for long-term spending for drugs, it is only used for other types of investments (e.g. equipment). New legislation needs to be introduced to frame new instruments for annuity payment.
Sweden	National healthcare system is not used to annuity payment and there are legal restrictions for payments of consumables above three years. Pharmaceuticals are not classified as investment products.

ENGLAND'S CANCER DRUG FUND (CDF) EXPERIENCE:

A drug is eligible for funding from the CDF when NICE considers there to be plausible potential for the drug to satisfy the criteria for routine commissioning, yet significant clinical uncertainty remains. Further data will be collected while the drug is included in the CDF. The timeframe will be as short as possible, normally up to two years, but could be longer depending on the issues of uncertainty and the rarity of the cancer. The CDF Managed Access Agreement contains a data collection arrangement and a CDF Commercial Agreement (60). NICE makes a final decision after the predefined period based on the evidence collected. More than 7,500 patients in the past two years benefited from drugs through the new CDF. And recently, the two CAR-T cell therapies are funded through CDF in England.

Limitations: This solution may be easy to implement and may not have administrative burden. The main hurdle is in defining the source of the fund and the amount of healthcare spending dedicated to this fund. In addition, it is important to fix eligibility criteria for this fund.

SOLUTIONS:

- Define clear eligibility criteria limiting the access to this fund to promising innovative therapies indicated for indications with high unmet medical needs.

RECOMMENDATION 4: Favor wider application of innovative access and funding arrangements such as:

a) Pay-for-performance

b) Annuity payments

c) Special funds for transformative treatments

New payment models are needed to ensure timely patient access to innovation while preserving sustainability of healthcare systems. Without the adoption of these new models, some transformative therapies may not reach patients in some or all European countries and some may be at risk of withdrawal from the market.

CONCLUSIONS

The pipeline of ATMPs in development and prices of some ATMPs have stimulated stakeholder dialogue on affordability and financial sustainability challenges. Concerns around financial sustainability impact both payers and developers and are of major importance for a broader set of stakeholders including patients, governments, and healthcare providers. If the stakeholder community fails to identify viable solutions to the structural challenges identified in this report, there is a risk that a number of potentially transformative treatments will never reach patients, with the negative individual, healthcare, societal, and economic effects that this could imply.

The Alliance for Regenerative Medicine is committed to facilitating an inclusive and solution-driven dialogue with all interested stakeholders and consider the following recommendations as a starting point in a journey that will hopefully lead to timely and sustainable access to a large number of transformative treatments.

ATMPs promise great clinical value for patients, society, and healthcare systems. Access to ATMPs should become a public policy priority.

These recommendations provide balanced, fair, and effective solutions at the EU level to ensure EU countries' readiness for the adoption of ATMPs. These recommendations would improve potential for:

- Timely patient access to ATMPs that may treat chronic, severe disabling or fatal conditions with high unmet medical needs,
- Reduction of patient, societal, healthcare system, and health insurance burden in some health conditions,
- Having a positive economic impact in the European Union and in individual European countries,
- Addressing some of the financial sustainability challenges of health systems and developers.

The challenges and solutions presented in this report were identified in a selected group of countries but may potentially be useful and explored in other EU countries.

BIBLIOGRAPHY

1. Regulation (EC) No 1394/2007 of the European parliament and of the council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, (2007).
2. European Medicines Agency website [Available from: https://www.ema.europa.eu/.
3. Celis P. Advanced therapy medicinal products (ATMPs) and ATMP Regulation. 2nd International Awareness Session – The EU medicines regulatory system and the European Medicines Agency2018.
4. Robert Dream JO. Impact of ATMP Manufacturing on Process Equipment and Facility Design. BioPharm International2018. p. 30-4.
5. Abou-El-Enein M, Elsanhoury A, Reinke P. Overcoming Challenges Facing Advanced Therapies in the EU Market. Cell stem cell. 2016;19(3):293-7.
6. Carr DR, Bradshaw SE. Gene therapies: the challenge of super-high-cost treatments and how to pay for them. Regenerative medicine. 2016;11(4):381-93.
7. Corbett MS, Webster A, Hawkins R, Woolacott N. Innovative regenerative medicines in the EU: a better future in evidence? BMC medicine. 2017;15(1):49.
8. Prasad V. Immunotherapy: Tisagenlecleucel – the first approved CAR-T-cell therapy: implications for payers and policy makers. Nature reviews Clinical oncology. 2018;15(1):11-2.
9. Quarterly report: Q2 2018. ARM website: Alliance for Regenerative Medicine; 2018.
10. European Medicines Agency website [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/strimvelis]
11. NICE website [Available from: https://www.nice.org.uk/guidance/hst7/resources/strimvelis-for-treating-adenosine-deaminase-deficiencysevere-combined-immunodeficiency-pdf-1394905926085]
12. https://focus.masseyeandear.org/two-months-after-gene therapy-jack-sees-a-little-brighter-more-clearly/
13. https://www.aao.org/eye-health/patient-stories-detail/creed-gene therapy
14. Food and Drug Administration website [Available from: https://www.fda.gov/biologicsbloodvaccines/cellulargenetherapyproducts/approvedproducts/ucm573706.htm]
15. Food and Drug Administration website [Available from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm581216.htm]
16. https://www.novartis.com/news/media-releases/kymriahr-tisagenlecleucel-first-class-car-t-therapy-from-novartis-receives-second-fda-approval-treat-appropriate-rr-patients-large-b-cell-lymphoma
17. Novartis web-site [Available from: http://sparktx.com/scientific-platform-programs/
18. Food and Drug Administration website [Available from: https://www.fda.gov/vaccines-blood-biologics/zolgensma]
19. Novartis web-site [Available from: https://www.novartis.com/news/media-releases/novartis-enters-agreement-acquire-avexis-inc-usd-87-bn-transform-care-sma-and-expand-position-gene therapy-and-neuroscience-leader]
20. Shell R. et al. AVXS-101 phase 1 gene therapy clinical trial in SMA Type 1: decreased need of ventilatory and nutritional support at End-of-Study Neuromuscular Disorders, Volume 27, S208 – https://www.nmd-journal.com/article/S0960-8966(17)30986-0/fulltext
21. Audentes web-site [Available from:http://investors.audentestx.com/news-releases/news-release-details/audentes-therapeutics-presents-new-positive-interim-data-aspiro]
22. http://investor.bluebirdbio.com/news-releases/news-release-details/bluebird-bio-presents-new-data-lentiglobin-gene therapy
23. bluebird bio website [Available from: http://investor.bluebirdbio.com/news-releases/news-release-details/bluebird-bio-announces-eu-conditional-marketing-authorization]
24. https://presse.inserm.fr/en/new-gene therapy-success-in-beta-thalassemia-22-patients-treated-in-france-united-states-thailand-and-australia/31149/
25. Yu TTL, Gupta P, Ronfard V, Vertès AA, Bayon Y. Recent Progress in European Advanced Therapy Medicinal Products and Beyond. Frontiers in bioengineering and biotechnology. 2018;6:130.
26. 2018 Ageing Report: Europe's population is getting older. 2018.
27. https://www.sciencedirect.com/science/article/pii/S0168851017300842
28. http://www.english.g-ba.de/benefitassessment/information/faq/
29. NICE website [Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly-specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf]
30. https://ansm.sante.fr/Activites/Autorisations-temporaires-d-utilisation-ATU/ATU-nominative-Liste-des-specialites-autorisees/(offset)/5
31. http://ec.europa.eu/health/ph_threats/non_com/docs/policies_orphan_en.pdf
32. https://www.tlv.se/download/18.1d85645215ec7de284611ebd/1510316381520/ppri_pharma_profile_
33. http://www.agenziafarmaco.gov.it/sites/default/files/Determina_519-2017.pdf
34. https://link.springer.com/article/10.1007/s10198-016-0823-0
35. https://www.sciencedirect.com/science/article/pii/S109830151830189X

36. NICE website [Available from: https://www.nice.org.uk/process/pmg9/chapter/the-appraisal-of-the-evidence-and-structured-decision-making]

37. http://www.agenziafarmaco.gov.it/sites/default/files/Determina_519-2017.pdf

38. Macaulay R. Advanced Therapy Medicinal Products – Transformational Patient Benefits But Destined for Commercial Failure? Value in Health. 2017;20(9):A702.

39. EMA. PRIME: priority medicines [03/03/2019]. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines.

40. EMA. Conditional marketing authorisation [08/03/2019]. Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation.

41. EMA. Exceptional circumstances [08/03/2019]. Available from: https://www.ema.europa.eu/en/glossary/exceptional-circumstances.

42. Detela G, Lodge A. EU Regulatory Pathways for ATMPs: Standard, Accelerated and Adaptive Pathways to Marketing Authorisation. Molecular Therapy – Methods & Clinical Development. 2019;13:205-32.

43. EMA. Compassionate use [Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/compassionate-use.

44. Hettle R, Corbett M, Hinde S, Hodgson R, Jones-Diette J, Woolacott N, et al. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. Health technology assessment (Winchester, England). 2017;21(7):1-204.

45. Driscoll D, Farnia S, Kefalas P, Maziarz RT. Concise Review: The High Cost of High Tech Medicine: Planning Ahead for Market Access. Stem cells translational medicine. 2017;6(8):1723-9.

46. Kent A, Spink J. Will rising prices and budget constraints prevent patients from accessing novel gene therapies? Gene therapy. 2017;24(9):542-3.

47. Zheng PP, Kros JM, Li J. Approved CAR T cell therapies: ice bucket challenges on glaring safety risks and long-term impacts. Drug discovery today. 2018;23(6):1175-82.

48. Hayden E. Promising gene therapies pose million-dollar conundrum. Nature. 2016;534(7607):305-6.

49. Grace Marsden ATaCH. Assessing value, budget impact and affordability to inform discussions on access and reimbursement: principles and practice, with special reference to high cost technologies. HTAi Asia Policy Forum Meeting; Kuala Lumpur, Malaysia2016.

50. Mauskopf JA, Sullivan SD, Annemans L, Caro J, Mullins CD, Nuijten M, et al. Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices--budget impact analysis. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2007;10(5):336-47.

51. Bilinski A NP, Cohen J, Thorat T, McDaniel K, Salomon JA When cost-effective interventions are unaffordable: Integrating cost-effectiveness and budget impact in priority setting for global health programs. 2017. Contract No.: e1002397.

52. Hollis A. Sustainable Financing of Innovative Therapies: A Review of Approaches. PharmacoEconomics. 2016;34(10):971-80.

53. NICE. Budget impact test 2017 [Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/budget-impact-test.

54. Macaulay R, Shaw S, Dave K, Tang M. Nice's New Budget Impact Threshold – What Proportion Of Drugs Is This Likely To Affect? Value in Health. 2017;20(9):A660.

55. WHO. Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research.; 2015.

56. German Bundestag. Gesetzesentwurf: Drucksache 17/2413, July 6, 2010.

57. Hanna E, Toumi M, Dussart C, Borissov B, Dabbous O, Badora K, et al. Funding breakthrough therapies: A systematic review and recommendation. Health policy (Amsterdam, Netherlands). 2018;122(3):217-29.

58. Hutton J, Trueman P, Henshall C. Coverage with evidence development: an examination of conceptual and policy issues. International journal of technology assessment in health care. 2007;23(4):425-32.

59. Lexchin J. Coverage with evidence development for pharmaceuticals: a policy in evolution? International journal of health services : planning, administration, evaluation. 2011;41(2):337-54.

60. England N. National Cancer Drugs Fund list 2019 [05/03/2019]. Available from: https://www.england.nhs.uk/publication/national-cancer-drugs-fund-list/.

61. ICER. Real world evidence for coverage decisions: opportunities and challenges. 2018.

62. Husereau D, Henshall C, Sampietro-Colom L, Thomas S. CHANGING HEALTH TECHNOLOGY ASSESSMENT PARADIGMS? International journal of technology assessment in health care. 2016;32(4):191-9.

63. EMA. Final report on the adaptive pathways pilot. 2016 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/08/WC500211526.pdf.

64. Registries TC-CTFoP. Use of patient disease registries for regulatory purposes – methodological and operational considerations. EMA website: EMA; 2018.

65. Garrison LP, Jr., Neumann PJ, Erickson P, Marshall D, Mullins CD. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2007;10(5):326-35.

66. Mahalatchimy A. Reimbursement of cell-based regenerative therapy in the UK and France. Medical law review. 2016;24(2):234-58.

67. Advanced therapies investment report 2017

68. EUnetHTA activities on Early Dialogues / Scientific advice (ED/SA) [Internet]. 2017.

69. Euroopean Commission: Report from the Commission to the European Parliament and the Council on the operation of Directive 2011/24/EU on the application of patients' rights in cross- border healthcare (21/09/2018) [Available from: https://eur-lex.europa.eu/resource.html?uri=cellar:bc5ac6d2-bd7c-11e8-99ee-01aa75ed71a1.0019.02/DOC_1&format=PDF]

70. NICE Evaluation Determination for Strimvelis (December 2017) [Available from: https://www.nice.org.uk/guidance/hst7/documents/final-evaluation-determination-document]

71. European Parliament: Report on the implementation of the Cross-Border Healthcare Directive (29/01/2019) [Available from: http://www.europarl.europa.eu/doceo/document/A-8-2019-0046_EN.html#title1]

72. Brennan, T. A., & Wilson, J. M. (2014). The special case of gene therapy pricing. Nature Biotechnology, 32(9), 874-876. doi:10.1038/nbt.3003

73. Jørgensen, J., & Kefalas, P. (2015). Reimbursement of licensed cell and gene therapies across the major European healthcare markets. Journal of Market Access & Health Policy, 3(1), 29321. doi:10.3402/jmahp.v3.29321

74. Jørgensen, J., & Kefalas, P. (2017). Annuity payments can increase patient access to innovative cell and gene therapies under England's net budget impact test. Journal of Market Access & Health Policy, 5(1), 1355203. doi:10.1080/20016689.2017.1355203

75. Schaffer, S. K., Messner, D., Mestre-Ferrandiz, J., Tambor, E., & Towse, A. (2018). Paying for Cures: Perspectives on Solutions to the "Affordability Issue". Value in Health, 21(3), 276-279. doi:10.1016/j.jval.2017.12.013

76. Yeung, K., Suh, K., Basu, A., Garrison, L. P., Bansal, A., & Carlson, J. J. (2017). Paying for Cures: How Can We Afford It? Managed Care Pharmacy Stakeholder Perceptions of Policy Options to Address Affordability of Prescription Drugs. Journal of Managed Care & Specialty Pharmacy, 23(10), 1084-1090. doi:10.18553/jmcp.2017.23.10.1084

77. Macaulay, R., & Hettle, R. (2017). Innovative Pricing and Reimbursement Schemes – The What, Why, Which, and How. Value in Health, 20(9). doi:10.1016/j.jval.2017.08.034

78. Spark, Y., Sear, R., & Hutchings, A. (2017). Paying For Gene Therapies: Approaching A Sustainable Solution. Value in Health, 20(9). doi:10.1016/j.jval.2017.08.1729

79. Wang, G., & Macaulay, R. (2017). Trucs And CAR-TS – The Emergence Of Io Cell Therapies. Value in Health, 20(9). doi:10.1016/j.jval.2017.08.421

80. Montazerhodjat, V., Weinstock, D. M., & Lo, A. W. (2016). Buying cures versus renting health: Financing health care with consumer loans. Science Translational Medicine, 8(327). doi:10.1126/scitranslmed.aad6913

81. Hanna, E., Remuzat, C., Auquier, P., Dussart, C., & Toumi, M. (2017). Could Healthcoin Be A Revolution In Healthcare? Value in Health, 20(9). doi:10.1016/j.jval.2017.08.1648

82. Ohlenbusch S. German payers ready for pay-for-performance schemes – umbrella group. conference on gene therapies and one-off innovative treatments organised by the German society for market access (DFGMA)2018.

83. Novartis press release [Available from: https://www.novartis.de/news/media-releases/novartis-pharma-gmbh-und-gwq-serviceplus-schliessen-vertrag-ueber-ein]

84. Edlin R, Hall P, Wallner K, McCabe C. Sharing risk between payer and provider by leasing health technologies: an affordable and effective reimbursement strategy for innovative technologies? Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2014;17(4):438-44.

85. Touchot N, Flume M. The payers' perspective on gene therapies. Nature biotechnology. 2015;33(9):902-4.

86. Kleinke JD, McGee N. Breaking the Bank: Three Financing Models for Addressing the Drug Innovation Cost Crisis. American health & drug benefits. 2015;8(3):118-26.

Alliance *for* Regenerative Medicine

ALLIANCE FOR REGENERATIVE MEDICINE
Contact: Paolo Morgese, Director
EU Market Access & Member Relations
pmorgese@alliancerm.org
www.alliancerm.org