ATMP Market Access

Overcoming cross-border restrictions

Annie Hubert,
Senior Director European Public Policy

26 February 2020, CAR-TCR Summit Meeting, London

Alliance for Regenerative Medicine

About ARM

- **International advocacy organization**
  - Dedicated to realizing the promise of safe and effective regenerative medicines for patients around the world
  - Cell and gene therapy, tissue engineering
- **350+ members**
  - Small and large companies, non-profit research institutions, patient organizations, and other sector stakeholders
  - Across 25 countries
- **Priorities:**
  - Clear, predictable, and harmonized **regulatory** pathways
  - Enabling market access and value-based **reimbursement** policies
  - Addressing industrialization and **manufacturing** hurdles
  - Compile sector data, **educate** media and other stakeholders

Alliance *for* Regenerative Medicine

350+ ARM Members

***Members in bold are publicly traded companies*

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4BIO Capital 4D Molecular Tx AABB **Abeona Tx** Accelerated Bio ACF Bioservices **Adaptimmune** Adicet Bio **Adverum Bio AGTC** Aivita Biomedical Akouos Akron Bio Albumedix Aldevron Alpha-1 Foundation Ambys American Association of Tissue Banks American Gene Technologies International American Society of Plastic Surgeons **Amicus** Andalusian Initiative for Advanced Therapies ANEMOCYTE Angiocrine Bio apceth Biopharma Archbow Consulting Artiva Bio Aruvant Aseptic Technologies ASGCT AskBio Aspect Biosystems Asset Management Company Association of Clinical Research Organizations **Astellas Atara Bio Athersys Audentes Tx** AusBiotech **Autolus** Avectas Avery Tx **Avita Medical** AVM Bio **AVROBIO AxoGen Axovant** B-MoGen Barkey Baylor College of Medicine Be the Match Biotherapies Beam Tx **Bellicum Pharma** BioBridge Global **BioCardia BioLife Solutions BioMarin BioStage** Biotech Mountains Blood Centers of America **bluebird bio** BlueRock Tx **Bone Tx BrainStorm Cell Tx** Brainxell Brammer Bio C3i **Cabaletta Bio Caladrius Bio Capricor Tx Cardinal Health** Caribou Bio Carisma Carpenter Consulting Cartherics Celavie Bio **Celgene (BMS)** CEO Council for Growth CGT Catapult Cell Medica Cellatoz CellCAN **Cellect Bio** CellGenix Cello Health **CBMG** Cellular Technology Limited Celonic Celsense Center for the Advancement of Science in Space CCRM Century Tx Cevec Chemelot CIRM City of Hope Cleveland Clinic Cleveland Cord Blood Center ClinicalMind Coalition for Clinical Trials Awareness Cobra Bio Cognate Bio **CombiGene** Cook Myosite Cornell University Covance **CRISPR Tx Cryoport Systems CSL** CTI Clinical Trial and Consulting Services CureDuchenne **Cynata Tx** Dark Horse Consulting DiscGenics EB Research Partnership **Editas Medicine** Elevate Bio Emerging Therapy Solutions Encoded Tx Enzyvant Tx ERA Consulting ESGCT EVERSANA EveryLife Foundation for Rare Diseases Evidera ExCellThera Exogrades Falcon Tx FARA **Fate Tx Fibrocell Science** Fight Colorectal Cancer **Flexion Tx** Fondazione Telethon Foundation for Biomedical Research and Innovation Fraunhofer Institute for Cell Therapy and Immunology Fred Hutchinson Cancer Research Center Frequency Tx **Fresenius Kabi FUJIFILM Cellular Dynamics** G-CON Manufacturing GalbraithWight **Gamida Cell** GammaDelta Tx G-CON Manufacturing **GE Healthcare** GE2P2 Global Foundation Gemini BioProducts Generation Bio GENETHON **Genprex GenSight Biologics** Gift of Life Marrow Registry **Gilead / Kite** Giner **GlaxoSmithKline** Global Genes GPB Scientific Gyroscope Tx Halloran Consulting **Healios K.K.** Histogen **Hitachi Chemical Advanced Tx Solutions** Hogan Lovells **Homology Medicines** Humanscape Huron Consulting Hybrid Concepts International ICON Immusoft InRegen InsightRX **Intellia Tx** Invetech Invitria Invitrx **Iovance IQVIA** ISCT ISSCR **IVERIC Bio** Johns Hopkins **Johnson & Johnson** Key Biologics **Kiadis Pharma** Kimera Labs Kytopen L7 Informatics LabConnect Lake Street Capital Markets Latham BioPharma LatticePoint Consulting Legend Biotech Locate Bio LogicBio **Lonza Biologics** Lovelace Biomedical Ludwig Boltzmann Institute **Lysogene Magenta Tx** Mammoth Bio MaSTherCell **MaxCyte** MEDIPOST America **Medpace MeiraGTx** MSK Cancer Center **Mesoblast Limited MilliporeSigma MiMedx** Minerva Bio Miromatrix Medical Missouri Cures **MolMed** Musculoskeletal Transplant Foundation **Mustang Bio** National Disease Research Interchange National Multiple Sclerosis Society National Stem Cell Foundation Nebraska Coalition for Lifesaving Cures NeoProgen Neural Stem Cell Institute Neurogene New Jersey Innovation Institute New York Stem Cell Foundation NexImmune NIIMBL Nkarta Northwestern University Comprehensive Transplant Center Novadip Bio **Novartis / Avexis** Novitas Capital **Novo Nordisk** NYBC Obsidian Odylia Tx OIRM Oisin Bio OncoSenX Opsis Tx **Orchard Tx** Organabio **Orgenesis** Orig3n **Oxford BioMedica** panCELLa Parent Project Muscular Dystrophy PDC*line Pharma SA **Pfizer Pluristem Tx PolarityTE** Polyplus-transfection **Poseida Tx** Precigen **Precision Bio Prevail Tx** Prevent Cancer Foundation Project 8p Project Farma Promethera Bio **PTC Tx** Recardio Recombinetics Regenerative Patch Technologies ReGenesys **Regeneus** REGENXBIO REMEDI ReNeuron RepliCel Life Sciences Rescue Hearing Rexgenero Rigenerand **Rocket Pharma** RoosterBio Roslin CT Rousselot RxGen **SanBio** Sanford Health Sanford Stem Cell Clinical Center @ UCSD **Sangamo Tx Sanofi Sarepta** Sartorius Stedim North America SCM LifeScience Scottish National Blood Transfusion Service Semma Tx Seneca Bio Senti Biosiences Sentien Bio Seraxis Sernova Sigilon Sirion Biotech Skyland Analytics SmartPharm Tx **Solid Bio Spark Tx** StafaCT Starfish Innovations STEL Technologies StemBioSys StemCyte StemExpress Stempeutics Stop ALD Foundation Student Society for Stem Cell Research Sven Kili Consulting Synpromics T-Knife Tacitus Tx **Takeda** Talaris Tx Tenaya TERMIS-Americas Terumo BCT Tessa Tx Texas Heart Institute The Michael J. Fox Foundation Theradaptive **Thermo Fisher Scientific ThermoGenesis** TikoMed Tmunity Tx TrakCel TreeFrog Tx Tremont Tx LLC Trizell Tulane University UCSD Stem Cell Program **Ultragenyx** UMass Medical School Unicyte **uniQure** Unite 2 Fight Paralysis United Spinal Association of VA Universidad de los Andes University of Colorado University of Pennsylvania **Unum Tx** VERIGRAFT ViaCyte VidaCel Videregen Vigene VINETI ViveBiotech Vivet Tx Voisin Consulting **Voyager Tx** WiCell WindMIL Tx World Courier **Wuxi Xintela** Xyphos Bio Yposkesi Zelluna **Ziopharm Oncology**

Why is cross-border relevant & important for ATMPs?

More Than Half of Clinical Trials With ATMPs Are in Rare Diseases

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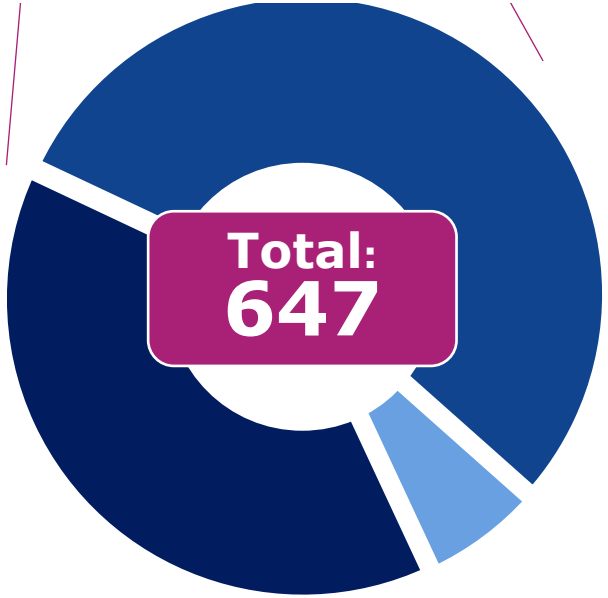
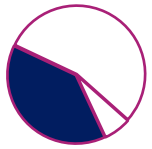
Clinical Trials ATMPs

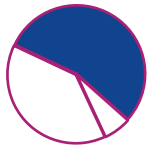
ATMPs in rare diseases





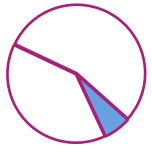
Phase 1: 252
across all tech types
in rare disease

Gene Therapy: 62
Gene-Modified & Cell-Based IO: 174
Cell Therapy: 14
Tissue Engineering: 2



Phase 2: 353
across all tech types
in rare disease

Gene Therapy: 134
Gene-Modified & Cell-Based IO: 168
Cell Therapy: 49
Tissue Engineering: 2

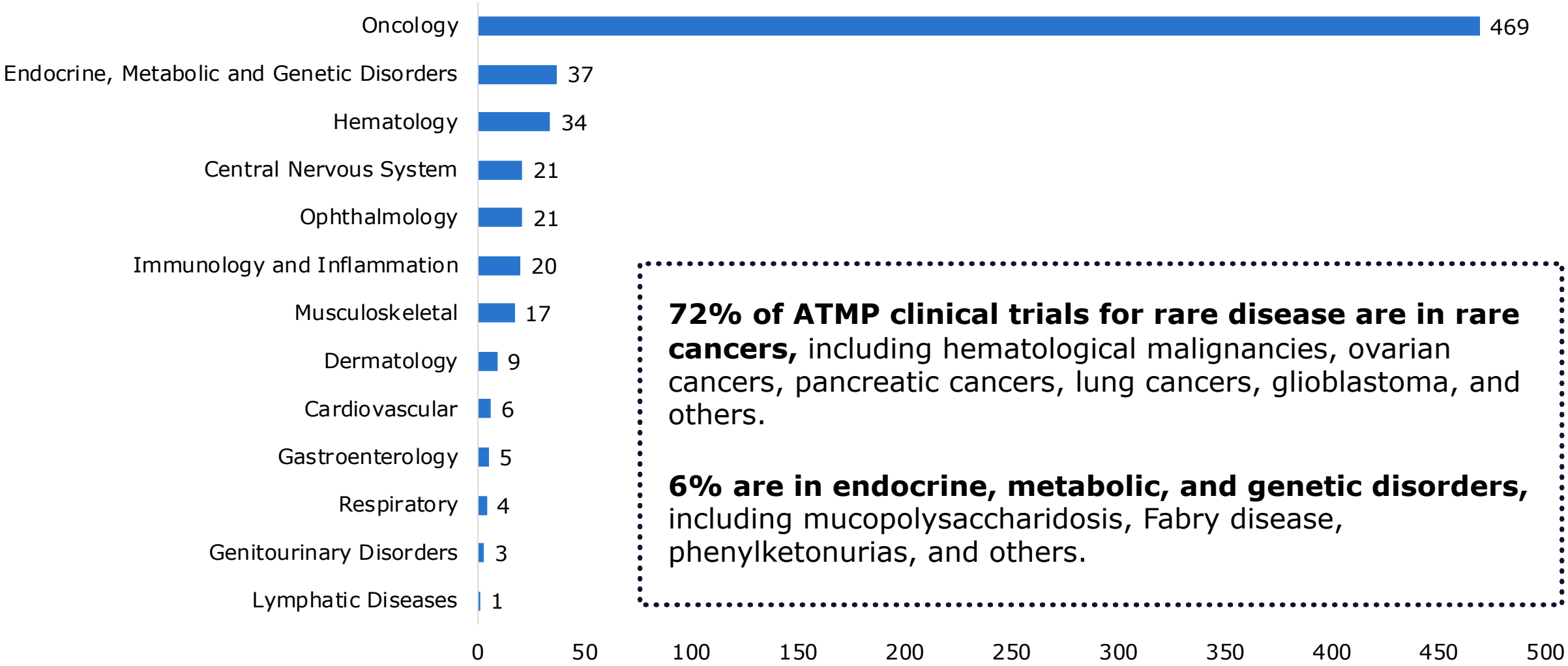


Phase 3: 42
across all tech types
in rare disease

Gene Therapy: 24
Gene-Modified & Cell-Based IO: 9
Cell Therapy: 7
Tissue Engineering: 2

Source data provided by: informa

Clinical Trials for Rare Disease by Indication



72% of ATMP clinical trials for rare disease are in rare cancers, including hematological malignancies, ovarian cancers, pancreatic cancers, lung cancers, glioblastoma, and others.

6% are in endocrine, metabolic, and genetic disorders, including mucopolysaccharidosis, Fabry disease, phenylketonurias, and others.

Relevance of Cross-Border Healthcare to ATMPs

- Complex or rare diseases and conditions require highly specialised treatment and a concentration of knowledge and resources, not available in all countries.
- Ultra rare diseases affect only a few patients per year in Europe.
- ATMPs most often need to be administered by trained/certified healthcare providers or in highly specialised centers, not necessarily available in all countries.
- Many ATMPs are autologous, requiring specific logistic requirements and may be better addressed if administered only in a limited number of specialised centres.

Getting Ready for ATMPs in Europe

- Brings together the views of a number of European policy makers and experts
- Recommendations:
  1. Better adapt HTA frameworks to ATMPs
  2. Favor wide application of conditional reimbursement schemes
  3. Develop pan-European initiatives (RWE, early dialogues, cross-border treatment)
  4. Favor wider application of innovative access and funding arrangements

Report released on July19, 2019 and available at https://alliancerm.org/publications-presentations/
See also ARM recommendations on cross-border and regional access to ATMPs in Europe released on 27 Jan 2020

What is the legal framework for cross-border healthcare in Europe?

Two possible routes exist for accessing and getting reimbursement for healthcare abroad

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EU/EEA citizen have the right to access medical diagnosis, medical treatment or prescription in any other EU/EEA country or Switzerland

Social Security Regulations

- (EC) N° 883/2004 on the coordination of social security systems, and
- (EC) N°987/2009 laying down the procedure for implementing Regulation (EC) No 883/2004 on the coordination of social security systems

Cross-Border Healthcare Directive

- Directive 2011/24/EU on patients' rights in cross-border healthcare

Two different situations exist, under both frameworks:

- Unplanned medical treatment: sudden illness or injury whilst abroad
- Planned medical treatment: healthcare is the reason for stay abroad (e.g. specialised treatment)

Summary of the Current EU Provisions for PLANNED Treatments Abroad - Differences

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	Social Security Regulations 883/04 and 987/09	Directive 2011/24/EU on patients' rights in cross-border healthcare:
General principles	• **Direct assistance** - The health services are **paid directly as if the patient is insured by social security system of that country.**	• **Indirect assistance** - **The patient have to pay** for treatments and then to **request a refund** in home country with proofs of payment. Refund will be based as if the treatment was provided in home country
Country variability	• Regulation => **same process/ requirements/conditions in all the EU Countries**	• Directive => **may result in different national implementations with additional specific national rules**
Need for prior authorisation	• **Yes,** prior authorisation from home country required (**S2 Form**). Cannot be refused if treatment in the home country cannot take place within a time limit medically justifiable.	• **No**, for a wide range of treatments. **Prior authorisation should be an exception, not the rule**
Costs covered & Tariffs	• **Form S2 covers treatment costs (i.e. drugs) + clinical costs (i.e. DRG if hospitalised/clinical services). Based on tariffs in treatment country** • Logistics (i.e., travel & lodging) are not covered and are managed case by case by the insurance, social assistance, etc.	• **Costs covered are based on home country tariffs** (=> country to country variations). • Travel and lodging typically not covered. • Not covered: Long term care, organ transplantation, public vaccination programmes
Eligible HC providers	• Covers **only public or private contracted with the National Health System healthcare providers** in the EU.	• Covers **all healthcare providers** in the EU, public or private

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Country variability	•	•
Need for prior authorisation	•	•
Costs covered & Tariffs	• are managed case by case by the insurance, social assistance, etc.	• public vaccination programmes
Eligible HC providers	• Covers **only public or private contracted with the National Health System healthcare providers** in the EU.	• Covers **all healthcare providers** in the EU, public or private

Cross-border treatment under the Regulations is the only practical option, but difficulties exist

The requirement of upfront payment by patients makes cross-border treatment with ATMPs under the Directive highly unlikely/impossible.

Summary of the Current EU Provisions for PLANNED Treatments Abroad - Commonalities

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- The National Contact Point can advise on both the legal paths, since these 2 EU regulatory provisions may have specific applications in the State where the patient is insured and they can be supplemented
- National health authorities may not refuse to reimburse costs:
  - if the patient is entitled to this treatment in his/her home country
  - The treatment cannot be provided on its territory within a time limit which is medically justifiable

NOTE - Rare diseases: patients may be offered the possibility under the Social Security Regulation to seek treatment in another EU/EEA country even for diagnosis and treatments which are not available in the patient's home country. **As long as the treatment concerned is covered in the country of treatment prior authorization may be granted.**

Reference: https://ec.europa.eu/health/sites/health/files/cross_border_care/docs/2019_ncptoolbox_manualpatients_en.pdf

Is it working for ATMP treatment abroad?

Payer's perspectives on providing reimbursement for ATMP treatment abroad

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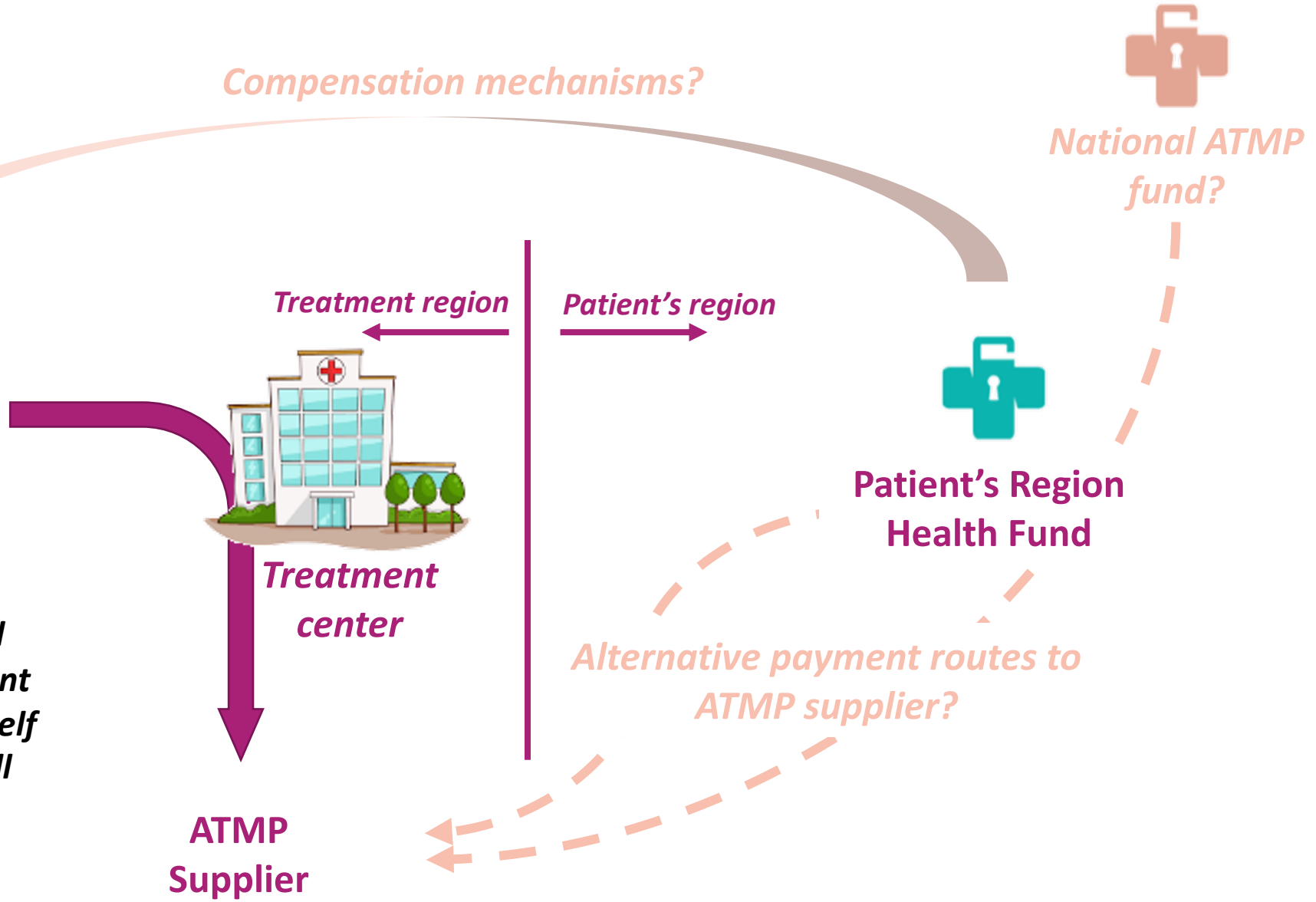
Major concerns & difficulties from payers on authorising S2 forms for ATMP treatment abroad:

- Biopharma companies could abuse the system to circumvent/avoid P&R procedures in some countries
- Payers from the patient's home country do not know the details and do not benefit from the managed entry agreement that may be in place in the treatment country
- Legal limitations when the ATMP is not included in the basket of care in the home country (despite being in the basket of treatment country)

In practice, relatively few patients have benefited from reimbursement of ATMP treatment provided abroad and payers are reluctant to use such system on a routine basis

Why do similar difficulties exist in some regionalized countries?

Cross-region funding challenges in regionalized funding models when few ATMP treatment centers



Alternative funding mechanisms needed to avoid that the Regional Health Fund of the ATMP treatment center or the Treatment center itself bears the cost for patients from all regions

What are the proposed solutions?

ARM proposed recommendations

1. **To create a one-stop shop coordination body at EU/EEA level** that will act as a broker between the different stakeholders to facilitate cross-border patient treatment and funding:
   - To assess whether cross-border treatment is justified: based on specific reasons such as the rarity of the condition, logistic issues, training & other specific requirements for healthcare providers, lack of other treatments providing similar benefit (based on pan-EU assessment of the therapeutic benefit), etc.
   - To centralize and speed up approval of S2 forms*, by signing agreements between MAH, payers and treatment centers detailing the potential market entry agreement and compensation mechanisms valid in the treatment center
   - To reduce financial uncertainty for treatment centers (no payment delays)
   - To agree on conditions to compensate for the additional travel & accommodations for patients

*As required for planned cross-border healthcare under the Social Security Regulations (EC) 883/2004 and 987/2009

ARM proposed recommendations

2. **In countries with regional funding or with multiple payers/insurers**:
   - **To create a one-stop shop (possibly leveraging National Contact Points)**
     - to compensate regional funding authorities in the region of treatment for the costs of patients coming from other regions or
     - to anticipate potential difficulties when patients change from payer/insurer over time
   - To reduce financial uncertainty for treatment centers (no payment delays)
   - Potentially, to leverage or expand existing national funds (e.g. the innovation fund in Italy or the cancer fund in the UK).

ARM proposed recommendations

3. **More effective coordination of HTA activities:**
    - To align EMA and HTA post-launch evidence requirements across the different EU countries
    - To have a single clinical assessment with mandatory adoption by EU countries as foreseen in the original EC proposed HTA Regulation on health technology assessment and amending Directive 2011/24/EU (COM(2018) 51 final)

ARM proposed recommendations

4. Additional measures:

- Improve opportunities for cross-countries collaboration to deliver faster and broader access by removing duplicative processes at national level and adopting policy principles to enhance cross-country collaboration.
- Exclude cross-border treatments from claw-back or other pay-back mechanisms potentially in place in the treatment country (such pay-back mechanisms are typically based on the pharma expenses/sales in the country for their 'national' patients)

Conclusion

- Cross-border treatment will become more important and common with ATMP market adoption
- Legal instruments for cross-border healthcare exist but processes need to be adapted, such as by creating a new coordination body
- Cross-regional treatment in regionalized countries or reimbursement in countries with multiple payers/insurers causes similar difficulties and need to be addressed
- ARM proposed a series of recommendations and is willing to foster discussion with all stakeholders to see whether and how these could be implemented

Thank You!

Market access report recommendations available here

Recommendations on cross-border and regional access to ATMPs in Europe: see here

Visit **www.alliancerm.org** to access additional resources, including:

- Slides from this and other ARM presentations
- Quarterly sector data reports
- Upcoming near-term clinical trial milestones & data readouts
- Our weekly sector newsletter, a robust round-up of business, clinical, scientific, and policy news in the sector
- Commentary from experts in the field