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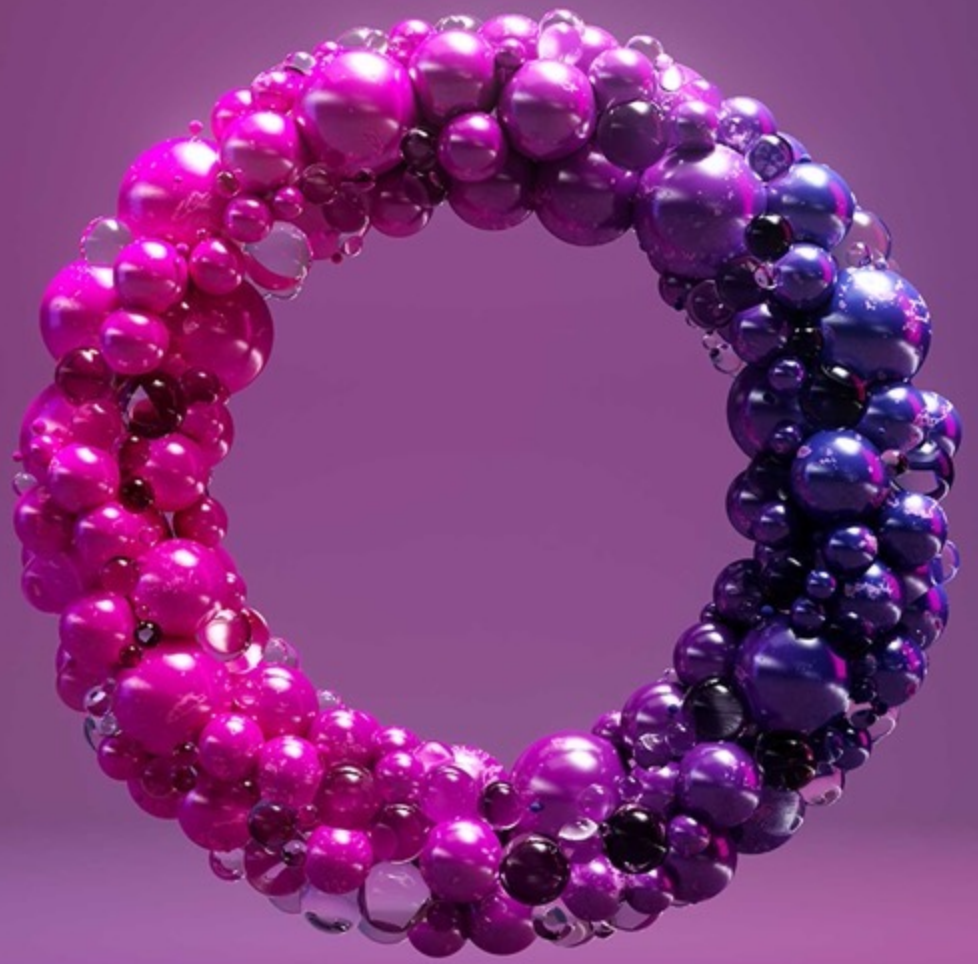
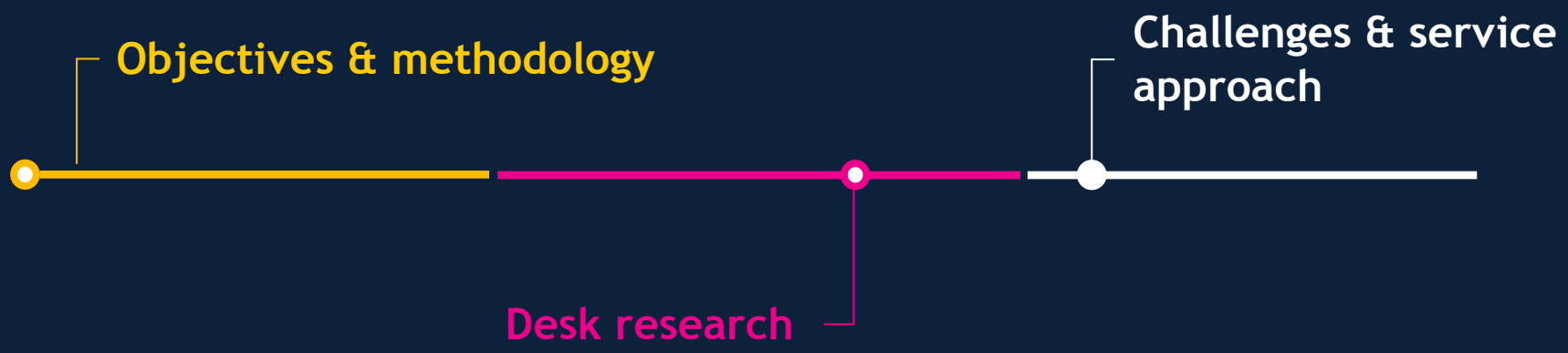
European Haemophilia Consortium



Gene Therapy Landscape
Prepared for EHC
June 2022

Contents



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Landscape assessment for gene therapy services in EU

OPEN Health have conducted desk research on gene therapy services in the EU to understand the how the service is currently set up, run, funded and how they may change in the future

Core project objectives:

- Secondary research on the service for gene therapy within 4 markets to provide an understanding of:
  - Organisational setup
  - Service setup
  - Future of gene therapies given the evolving evidence generation
  - Optimal evidence generation for long term follow-up
  - Gene therapy legislation
  - Funding of gene therapies

Scope: UK, Czech Republic, Italy & Sweden




1

United Kingdom 

The service for gene therapies

- Care for patients with congenital blood disorders is provided by a network of specialist centres including 28 large comprehensive care centres (CCC) and 40 smaller haemophilia treatment centres (HTC) in the UK[1]
- Gene therapy is accessed via clinical trials which are conducted at a number of sites[2,3]

Specialist facilities

- **Guy's & St Thomas' Advanced Therapies Accelerator (ATA) Facility**[5] – opened in 2021 to bring together in one location the infrastructure required for clinical grade manufacturing of gene and cell therapy products and the enterprise to support development of therapies through early phase clinical trials and commercialisation
- A DHSC-funded **clinical biotechnology centre at NHS Blood and Transplant Base in North Bristol**[6] opened in 2021 specialising in production of plasmid DNA and viral vectors for early phase clinical trials and experimental gene therapy medicines for rare and other genetic diseases

There are 3 national gene therapy hubs:[4]

- University of Sheffield*
- King's College London
- NHS Blood and Transplant Bristol

The Hubs works in coordination with each other sharing technical resources, which will have the potential to innovate gene therapy research

The ATTC network provide Institutional readiness guidance for the implementation of new advanced therapy services in a clinical setting[9]

The Cell and Gene Therapy Catapult

"The Cell and Gene Therapy Catapult is part of a network of world-leading centres designed to transform the UK's capability for innovation in specific areas and help drive future economic growth"[7]

The CT catapult coordinates a network of advanced treatment therapy centres which are working with the NHS and industry to accelerate the adoption of advanced therapies. The centres are based in Manchester, Midlands and Wales and a Northern Alliance led by Newcastle hospitals[8]

Click here to view information

ATTC: Advanced Therapy Treatment Centres; CT catapult: Cell and Gene Therapy Catapult; DHSC: department of health and social care; NHS: National Health Service; UKHCDO: United Kingdom Haemophilia Centre Doctors' Organisation. *Not known to conduct haemophilia gene therapy trials at present. References shown in slide notes.

The service for gene therapies

What's required to set up a centre to deliver gene therapy?

- The Advanced Therapy Treatment Centre Network coordinated by the Cell and Gene Therapy Catapult provides a number of resources for operational delivery to help accelerate patient access to advanced therapies[1]
- An Advanced Therapies NHS Readiness Toolkit exists providing a number of resources including practical advice for centres implementing gene therapies detailing GMSC and governance requirements and optimal preparation locations[2]
    - First step is ensuring you comply with governance and legislation. Pharmacy is the first port of call when an organisation wants to introduce a gene therapy trial – see legislation slide for additional detail and this document[2]
        - A risk assessment and evaluation by a GMSC is the preferred organisational governance route – details on risk assessment and committee recommendations can be found in the guidance document
        - SOPs must be put in place
        - A notification needs to be made to the HSE
    - Once governance approval has been granted there is additional guidance on operational set up for a centre

Clear guidance for setting up a gene therapy centre is provided by the advanced treatment therapy centre network and we recommend EHC read this documentation in full[1]

EHC: European Hemophilia consortium; GMSC: Genetic Modification Safety Committee; HSE: Health and Safety Executive; NHS: National Health Service. References shown in slide notes.

Clinical preparation

If thaw or manipulation is required either for in vivo or ex vivo then the following are included in the clinical preparation SOPs:

- Roles and responsibilities should be clearly documented
- Pharmacy approved clinical area worksheet in line with the SmPC/Protocol should be issued
- PPE appropriate to the containment level should be available
- Any preparation should be undertaken by trained and competent staff and be in line with an SOP detailing whether additional labelling is required

Operational set-up

In Vivo Gene Therapy[3]

- Receipt and storage – operators should wear appropriate protective clothing; appropriate waste management risk assessment should be in place in case of product damage; correct storage at an appropriate temperature is required
- Additional detail for in vivo therapy can be found here

Ex Vivo Gene Therapy[4]

- Pharmacies must have the appropriate location to receive, thaw and issue where stability allows or to receive and issue prior to thaw in the clinical area – additional guidance is provided including steps for more complex preparation.
- Additional detail for ex vivo therapy can be found here

Evolving evidence generation for gene therapies

Data collection

Haemtrack is a secure therapy recording system connecting patients and clinicians through the haemtrack phone apps and website. It enables patients to record all therapies as they occur so clinicians can see up to date therapy information, including use to ***support data collection in clinical trials***. Haemtrack is being developed to include functionality for Care Networks to have shared access to. The specific data collected by Haemtrack is not currently available to the public.[1]

National haemophilia database collects, holds, processes and analyses confidential data for both research (non-invasive/non-interventional) and non-research purposes (direct care, planning and commissioning)[2]

Evolution of data collection

According to the APPG haemophilia report 2020, the national haemophilia database, if appropriately funded, could work with people with bleeding disorders and the haemophilia society to design methods of capturing and recording outcomes. The report suggests that data on the burden of treatment should become more prominent within the commissioning processes to enable additional weights of treatments when they are commissioned[3]

Some of the information collected by the NHD covers information required for the WFH GTR core data set[5]:

- Demographics & Diagnosis ✓
- Medical/Clinical History ✓
- Gene Therapy Infusion Details ✓
- Safety Data ✓
- Efficacy Data*
- Patient Reported Outcome Measures
- Mortality ✓

All centres administering gene therapy for haemophilia will be invited to participate in the WFH GTR

Types of evidence

The National haemophilia database dataset 2020 outlines the information collected for all bleeding disorders including quarterly treatment data. There is a section for gene therapy, collecting basic information including the product administered, dosage and outcome[4]

The EMA produced a guideline in 2009 on follow-up of patients administered with gene therapy medicinal products[6]

APPG: All party parliamentary group; EMA: European Medicines Agency; NHD: National haemophilia database; UK: United Kingdom; WFH GTR: world federation of haemophilia gene therapy registry. *Limited field provided by NHD investigating "outcome", but not in-depth efficacy outcomes. References shown in slide notes.

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Legislation impacting gene therapies

- According to directive 2001/18/EC, gene therapy medicinal products will be classified as GMO in most cases (whether delivered by in vivo or ex vivo methods). EU legislation defines classification based on the use of the GMO i.e. contained or deliberate release – most studies in the UK are considered contained use (Directive 2009/41/EC) i.e. specific measures are used to limit their contact with the environment (physical, chemical, biological barriers)[1]

- Gene therapy clinical trials must apply for ethical approval from the Gene Therapy Advisory Committee – this is a national research ethics committee (REC) for gene therapy according to the regulation 14 of the medicines for human use (clinical trials regulations) 2004[2]
- All gene therapy and cell therapy applications for Clinical Trials Authorisation will be assessed by the MHRA and, where appropriate will now be submitted to the **MHRA Clinical Trials Expert Advisory Group** for review[2]

The UK's "compliance culture" including the MHRA's involvement in regulation is a major factor in enabling the success of cell and gene therapy products[3]

When setting up a centre to implement a gene therapy clinical trial a number of legislations should be consulted as outlined in this guidance document[4]

- There are 4 classes of containment activity that need to take place according to the GMO contained use regulations 2014, from class 1 activity (of no or negligible risk) to class 4 activity (of high risk). Most activities involving gene therapies are currently clinical trials and class 1 or 2 (low risk)
- Organisations must have a defined organisational governance process in place: a risk assessment and evaluation by GMSC is the preferred governance route *(see institutional readiness guidance on earlier slide)*

EU: European Union; GMO: Genetically modified organism; MHRA: medicines and healthcare products regulatory agency; UK: United Kingdom. References shown in slide notes.

Funding for gene therapies and the future

Funding

The England Rare Disease Action Plan 2022 outlines the national priorities for improving the lives of those affected by rare diseases including various funding sources:[1]

- £18 million in partnership with LifeArc to develop a network of cutting-edge "gene therapy innovation hubs"
- An additional £340 million of funding has been announced for the innovative medicines fund to provide early access to promising new medicine including cutting edge gene therapy
- Through innovate UK, the government also funds the Cell and Gene Therapy Catapult

The Cell and Gene Therapy Catapult established by Innovate UK provides clinical trial, technical, manufacturing, regulatory, and market access expertise to advanced therapy developers and the wider supply chain.[2]
The catapult:

- aims to build an £10 billion industry
- has invested £125 million in a development facility in London with 120 staff, and in a large scale manufacturing centre in Stevenage
- works with 200 commercial and academic partners from 24 countries

Commissioning

A recent report by the haemophilia society suggests a new payment model/ commissioning approach needs to be considered for procurement of gene therapies in the UK:[3]

- Current haemophilia treatments (SHL coagulation factor products) undergo a commissioning and tender process but this model will be hard to transfer to gene therapies that do not have a mechanism to compare different types of treatment
- There are challenges in terms of both evaluation and payment models for commissioning of gene therapies
- New models might include risk sharing agreements, outcomes based payments and payment instalments spread over a period of time to ensure timely access to gene therapies

UK: United Kingdom. References shown in slide notes.

2

Sweden 

The service for gene therapies

- Care for patients with congenital blood disorders is provided by 3 CCC's within Sweden, however, they are also able to access all centres in the Nordic region which includes an additional 2 in Denmark and 1 in Norway, Finland and Iceland[1].
- Gene therapy is accessed via clinical trials which are conducted at a number of sites.

Gene therapy clinical trial locations and R&D centres include:[2]

- Chalmers University of Technology, Gothenburg
- KTH Royal Institute of Technology, Stockholm
- *Lund University, Lund
- Umeå University, Umeå
- *Uppsala University, Uppsala
- *University of Gothenburg, Gothenburg
- *Karolinska Institute, Solna
- Karolinska University Hospital, Solna
- Centre for Advanced Medicinal Products (CAMP)

There are 3 EAHAD certified centres:[3]

- Skåne University Hospital
- Sahlgrenska University Hospital
- Karolinska University Hospital

When products are not funded nationally or in a home region in Sweden, patients have previously received access to treatment via cross-border initiatives and in other local regions[4]

** Universities that are classified as the nations top affiliations, based on the highest number of researchers present. These universities have researchers that involved previously in ATMP research, lecturing and studies.[5]*

Other specialist facilities

ATMP Sweden

- **ATMP Sweden** is a national network for activities within medicines based on genes, cells and tissue engineering (classified as Advanced Therapy Medicinal Products, ATMPs)
- **ATMP Sweden** has a total of 48 partners including pharmaceutical companies such as AstraZeneca, Pfizer and Sanofi
- **ATMP Sweden** has a total of 14 facilities for manufacture and process development of ATMPs

CCC: Comprehensive Care Centre; EAHAD: European Association for Haemophilia and Allied Disorder; ATMP: Advanced Therapeutic Medicinal Products. References shown in slide notes.

Evolving evidence generation

The EMA produced a guideline on follow-up of patients administered with gene therapy medicinal products

Data collection

The TLV, is a government agency that determines whether a pharmaceutical product, medical device or dental care procedure should be subsidised by the state. TLV collect patient data from all regions health care register, which allows the data to be utilised for follow-ups at a national level. However, the regions are not legally obliged to provide TLV with their data.[1]

EU data collection

ATMP Sweden runs two conferences a year, one based in Sweden and a virtual "world tour" conference. The aim of these conferences is to strengthen the Swedish and international ATMP network[6]

The 3 Swedish EAHAD certified centres participate in using the EUHASS, an adverse event surveillance scheme. The EUHASS reports events when they occur or every 3 months, it covers patients with Haemophilia A and B of all severities and vWD type 1,2 and severe type 3.[3]

Some of the information collected by the EUHASS covers information required for the WFH GTR core data set[4,3]:

- Demographics & Diagnosis ✓
- Medical/Clinical History
- Gene Therapy Infusion Details ✓
- Safety Data ✓
- Efficacy Data ✓
- Patient Reported Outcome Measures
- Mortality ✓

All centres administering gene therapy for haemophilia will be invited to participate in the WFH GTR

Data analysis

Sweden has developed a programme nationally, that is centred in managing the introduction of new therapies, this programme will increase the level that new medicines are monitored at. This will allow data collection that can be used to analyse cost-effectiveness as well as the possibility of outcomes-based contracting within new therapies.[5]

EUHASS: European Haemophilia Safety Surveillance; GTR: Gene Therapy Register; HAL: Haemophilia Activity List; PWH: Persons with Haemophilia; NHD: National Haemophilia Database; TLV: Dental and Pharmaceutical Benefits Agency; vWD: von Willebrand's Disease; WFH: World Federation of Hemophilia. References shown in slide notes.

Legislation impacting gene therapies

- According to directive 2001/18/EC, gene therapy medicinal products will be classified as GMO in most cases (whether delivered by in vivo or ex vivo methods)[1]
- EU legislation defines classification based on the use of the GMO I.e. contained or deliberate release:[1]
  - Contained use (Directive 2009/41/EC) "…any activity for which specific containment measures are used to limit their contact with, and to provide a high level of safety for, the general population and the environment…"
  - Deliberate release (Directive 2001/18/EC) "…any intentional introduction into the environment…for which no specific containment measures are used..."
- Swedish legislation regulating medicinal products include[2]:
  - The Medicinal Products Act (SFS 2015:315)
  - The Decree on Medicinal Products (SFS 2015:458)

- Directive 2004/726/EC is responsible for the guidelines for gene therapy in Sweden, it states that biological medicinal products that are produced using recombinant DNA-technique, transformed cells or hybridoma and monoclonal antibodies, must be authorised by the centralised EU system[3]
- Gene therapies that have been proposed for clinical trials have to be authorised by the Swedish Medical Products Agency (Swedish MPA) as of July 2021. Additionally they must undergo ethical review by the Swedish Ethical Review Authority before they can start[3]
- SWElife outlines a regulatory guide for ATMPs which also includes guidelines specifically for gene therapies including quality, pre-clinical guidance and also clinical guidance[4]

EU: European Union; GMO: Genetically modified organism; MHRA: medicines and healthcare products regulatory agency; UK: United Kingdom. References shown in slide notes.

Funding for gene therapies and the future

Funding

Sweden 8-year $36.6 million government initiative to position country as a leader in biologics[1]:

- $5.5 million will be spent between 2018 and 2023 in partnership with regenerative medicine firm Vinnova to establish a CAMP cell and gene therapy research centre.
- The CAMP research centre will work with Sweden's universities and research institutes to be recognised as a centre for R&D, innovation and clinical practice.
- Vinnova has also awarded an additional 1 million between 2020 – 2022 to ATMP development in Sweden.

Sweden is currently investigating the possibility of establishing a Centre for Commercialisation of Regenerative Medicine (CCRM)[2]:

- ATMP Sweden has developed a report that investigates the current CCRM's in place in Europe, looking into CGTC (UK), CCRM (Canada), Fraunhofer IZT (Germany) and BioInnovation Institute (Denmark).
- The study concludes that the model could see full scale operation in 2030 and bridge the gaps in ATMP with the additional infrastructure.

Commissioning

Challenges in gene therapy budget and commissioning:[3]

- Pharmaceutical budgets for gene therapies are held by regions, therefore, as ATMP eligible patients may not be evenly distributed funding challenges could occur in specific regions.
- A Rare Impact study for the Swedish region suggest that to create equal conditions for gene therapies across all regions of Sweden, a special state contribution scheme could be implemented in order to support use of new pharmaceutical areas like ATMPs.

ATMP: Advanced Therapy Medicinal Products; CAMP: Center for Advanced Medical Products; CCRM: Centre for Commercialisation of Regenerative Medicine. References shown in slide notes.

3

Italy 

The service for gene therapies

- Care for patients with congenital blood disorders is provided by 7 European CCC's within Italy, and 4 European HTC's. With a network of 54 AICE accredited HTC's throughout Italy to treat haemophilic syndromes[1,4,5]

Gene therapy clinical trial locations include:[2, 3]

- San Raffaelle Institute, Milano Phase II cryopreserved clinical trial and phase III late juvenile trial
- Centre for Outcomes Research and Clinical Epidemiology, Pescara

There are 11 EAHAD certified CCC/HTC centres:[4]

- Careggi University Hospital, Florence
- University Hospital of Parma, Parma
- Giannina Gaslini Childrens Institute, Genova
- Haemophili and Thrombosis Centre, Milan and Venice
- Centro Emofilia, Rome, Pavia, Padova, Cantanzaro, Reggio Calabria

Other specialist facilities:[5]

- The 54 country wide HTCs are run by the **AICE**
- **AICE** promotes a unified approach to treatment, developing shared therapeutic strategies by conducting collaborative clinical research
- **AICE** work with the **ISS** to manage and update the national registry of congenital coagulotherapies

AICE: Italian Association of Haemophilia Centres; CCC: Comprehensive Care Centre; EAHAD: European association for Haemophilia and Allied Disorder; HTC: Haemophilia Treatment Centre; ISS: National Institute of Health. References shown in slide notes.

Evidence generation for gene therapies

The EMA produced a guideline in 2009 on follow-up of patients administered with gene therapy medicinal products

Data collection

Since 2005 Italy has used the NRCC, a registry for congenital coagulopathies with information provided by the 54 HTC's run by AICE. This registry collects data for patients with Haemophilia A/B, von Willebrand's disease and other coagulation disorders[1]

Some of the information collected by the NRCC covers information required for the WFH GTR core data set[3]:

- Demographics & Diagnosis ✓
- Medical/Clinical History
- Gene Therapy Infusion Details ✓
- Safety Data
- Efficacy Data*
- Patient Reported Outcome Measures
- Mortality

All centres administering gene therapy for haemophilia will be invited to participate in the WFH GTR

The data from the NRCC has been analysed to compare efficacy and adverse events of new and old therapies and proven to demonstrate patient compliance for haemophilia therapies. This demonstrates that the large data sets can ultimately provide learnings through data analyses regarding congenital coagulopathies[4]

In Italy, regions will also collect their own data; In the Emilia Romagna region of Italy, a web based clinical record was created to allow the 8 HTCs of that region to share to a regional data base, and this took place over 12 years from 2003-2015, the region has since stopped collecting data although the reasons for why are unknown.[2]

AICE: Italian Association of Haemophilia Centres; HTC: Haemophilia Treatment Centre; NRCC: National Registry for Congenital Coagulopathies; WFH GTR: world federation of haemophilia gene therapy registry World; References shown in slide notes.

Legislation impacting gene therapies

- All ATMPs, including gene therapies, fall under the mandatory scope of the centralised procedure
- The EMA is responsible for the scientific evaluation of their marketing authorisation applications in the EU, which are granted by the European Commission
- However, national competent authorities are responsible for their pricing and reimbursement at member state level
- AIFA has implemented several innovative schemes for the reimbursement of ATMPs, for example, making reimbursement conditional on their efficacy (through "payment at result")

- According to directive 2001/18/EC, gene therapy medicinal products will be classified as GMO in most cases (whether delivered by in vivo or ex vivo methods)[1]
- EU legislation defines classification based on the use of the GMO I.e. contained or deliberate release:[1]
  - Contained use (Directive 2009/41/EC) "…any activity for which specific containment measures are used to limit their contact with, and to provide a high level of safety for, the general population and the environment…"
  - Deliberate release (Directive 2001/18/EC) "…any intentional introduction into the environment…for which no specific containment measures are used..."

- EC Regulation 1394/2007 is the regulatory legislation for ATMPs, amending the previous EC Directive 2001/83, which relates to medicinal products for human use, and the EC Regulation 726/2004 which establishes the authorization and surveillance of medicinal products for human and veterinary use, and established the EMA.[2]

EU: European Union; EMA: European Medicines Agency; GMO: Genetically modified organism; References shown in slide notes.

Funding for gene therapies and the future

Funding

A specialist fund has been created for innovative drugs within Italy, which consists of 2 budgets:[1]

- €500m towards innovative drugs that are within the field of oncology
- €500m towards all non-oncology innovative drugs, with congenital coagulopathy drugs falling within is this budget, however, this budget is largely used up by existing Hepatitis C drugs.
- The funding from this initiative is only applicable to these drugs for the first 3 years after their launch, providing long term challenges to manufacturers if their drug is not initially profitable.

A recent budget law has been passed in Italy that has had an impact on not only the general SSN budget but also the innovative funds budget as well[2]

- The new law impacts the budget over the next 3 years (2022-2024), will see the SSN budget increase every year by €2 billion, which could see an increase in drug reimbursement from this budget change
- The innovative drug fund will also increase by €100 million in 2022 and up to €300 million compared to the previous year in 2024. Therefore, the budget for innovative drugs could increase by a total of €600 million by 2024.

Reimbursement

Routes and challenges in gene therapy reimbursement:[1,3]

- ATMPs can apply for innovative status and if successful can gain quicker reimbursement by the SSN. Additionally, if innovative status is not gained for the drug, AIFA will ask the company producing the drug to give economic case for the drug to be reimbursed to the pricing committee.
- A challenge to the reimbursement model for Italy is that regional formulary committee's and regional HTA agencies assess the ATMP at a regional level even after the national reimbursement has been agreed, leading to a possibility for pricing to vary across the nation and ATMP availability varying in HTC's around Italy.

AIFA: Italian Medicines Agency; ATMP: Advanced Therapeutic Medicinal Product; HTA: Health Technology Assessment; HTC; Haemophilia Treatment Centre; NHS: National Health Service; SSN: Servizio sanitario nazionale. References shown in slide notes.

4

Czech Republic 

The service for gene therapies

European public assessment reports of gene therapy in other disease areas give an indication of the practical steps required to deliver gene therapy once an eligible patient has been identified at an equipped centre

- Care for patients with congenital blood disorders is provided by a network of haemophilia centres, centralised by the Czech National Haemophilia Program. The CNHP declaration as of 24 January 2012 states the requirements for CCC and HTC centres[1]
- Treatment of haemophilia disorders with gene therapy is currently uncommon but there are a number of learnings from centres administering gene therapy in other disease areas
- There are 6 EAHAD certified haemophilia centres in Czech Republic, 3 x HTCs and 3 x CCCs (including one paediatric specific CCC: Department of Paediatric Haematology, University Hospital Brno) which are known to deliver CAR-T gene therapy[2]

Institute of Haematology and Blood Transfusion[3]

- Largest haematology centre nationwide with clinic and laboratories featuring top-class equipment and collaboration with international research teams – it is advised to review the organisation structure to understand the infrastructure set up to deliver gene therapy
- IHBT treats patients through clinical studies – strict entry criteria and supervision over clinical evaluation is performed by a clinical study contractor and an inspecting authority (e.g. a local ethics committee, a multi-centric ethics committee or state institute for drug control)

Centre set up examples from other disease areas

- The Blood and Cancer Research Facility in Czech Republic is equipped to facilitate future clinical trials including: a biobank to collect and store biological samples; a cell sorting laboratory; heamatopoietic cell lab for processing at all stages from removal to transplant for ex vivo use; animal facility to enable in vivo experimental validation[4]
- Masaryk University is involved in the European Consortium for communicating gene and cell based information (EUROGCT) and has infrastructure for research that is part of the European Strategic Forum on research infrastructures projects and benefits from government funding for research infrastructure (see funding slide)[5,6]
- The RARE IMPACT study suggests Czech Republic could work with Austria through a cross-border scheme utilising the first EU cross border health care centre which opened in October 2021 allowing access to a multi-professional team of therapeutic experts – the current system in Austria considers cell and gene therapies hospital products so this could be hugely beneficial to gene therapy access in Czech Republic[7,8]

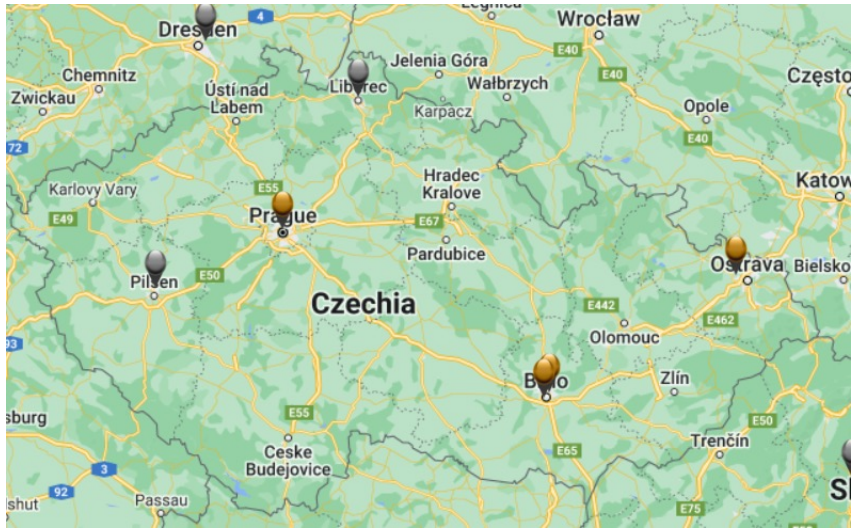
CAR-T: Chimeric Antigen Receptor T-cells; CCC: comprehensive care centre; CNHP: Czech National Haemophilia Program; EAHAD: European Association for haemophilia and allied disorders; EU: European Union; IHBT: Institute of haematology and blood transfusion. References in slide notes.

The service for gene therapies

- There are 6 EAHAD certified haemophilia centres in Czech Republic

CCC Centres:

- **Department of Clinical Haematology, University Hospital Brno Jihlavská 20 ,/**
- Centre for Thrombosis and Hemostasis
  Institute of Haematology and Blood Transfusion,U Nemocnice 1,
- CCC Department of Paediatric Haematology, University Hospital Brno Cernopolni 9 ,



HTCs

- **HTC: University Hospital Plzen - Institute of Clinical Biochemistry and Haematology – Department of Haematology Fakultni nemocnice Plzen, Alej Svobody 80,**
- **HTC: Hemophilia Treatment Centre Liberec**
  Dept of Clinical Haematology, Regional Hospital LiberecBaarova 15, building T
- **HTC Ostrava**
  Hematooncology Clinic, University Hospital in Ostrava, 17.,

CCC: Comprehensive Care Centre; EAHAD : European association for Haemophilia and Allied Disorder; HTC: Haemophilia Treatment Centre.
References in slide notes.

- EHCCC (European Haemophilia Comprehensive Care Centre) - EHTC (European Haemophilia Treatment Centre)

Evolving evidence generation for gene therapies

Current Data Collection

Presently there is a CNHP registry - this is a registry of haemorrhagic conditions within the Czech National Haemophilia Programme created to keep records on patients with inherited haemorrhagic conditions including severity and usage of medicinal products[1]

Information collected by the CNHP registry that is relevant to the WFH GTR core data set include[3,4*]:

- Demographics & Diagnosis ✓
- Medical/Clinical History ✓
- Gene Therapy Infusion Details
- Safety Data ✓
- Efficacy Data ✓
- Patient Reported Outcome Measures
- Mortality ✓

All centres administering gene therapy for haemophilia will be invited to participate in the WFH GTR

Feeding into the WFHGTR

Can we use learnings from CAR-T therapy data collection?

To ensure that there is complete and accurate data, EBMT invites centres that treat patients with commercial CAR T-cell therapies to participate in a data collection initiative to support Post Authorisation Safety (PAS) studies mandated by the European Medicines Agency (EMA). Centres that participate will be financially compensated.

Data collection is based on standard registry forms and procedures and there are lead study coordinators and lead investigators assigned by the EBMT for each country – in the Czech republic this is an individual from the institute of haematology and blood transfusion[2]

The primary objective of the WFH GTR is to determine the long-term safety of factor VIII and factor IX gene therapies in haemophilia. All HTCs that will be administrating gene therapy for haemophilia will be invited to participate. The secondary objectives of the WFH GTR are to determine the long-term efficacy and the durability of factor VIII and factor IX gene therapies in patients with haemophilia, assessed as bleeding rate and plasma factor activity level; and to assess the long-term quality of life, assessed by the EQ-5D-5L and the PROBE, post gene-therapy infusion. There is currently a funding program designed to provide funds to support data collection activities for centres in **low and lower-middle income countries.**[4]

CAR-T: Chimeric Antigen Receptor T-cells; CNHP: Czech National Haemophilia Program; EBMT: European Society for Blood and Marrow Transplantation. EQ-5D-5L: EuroQol quality of life 5-dimensional questionnaire; HTC: Haemophilia treatment centre; PROBE: patient reports outcomes burden and experiences; WFH GTR: world federation for haemophilia gene therapy registry. *criteria from WFH GTR compared to information collected in CNHP registry annual report 2021. References in slide notes.

Legislation impacting gene therapies

- According to the Czech legislation on medicinal products, applicants for authorization to conduct a clinical trial/study involving products containing GMOs are required to obtain an authorisation for the use of GMOs as specified by the Act No. 78/2004[1]

- The Czech Act No. 78/2004, covers the contained and deliberate release of GMOs and placing on the market of such products including import and export
- The administrative process is longer for deliberate release GMOs (under EU directive 2001/18/EC, Part B), than in the case of contained use (under EU Directive 2009/41/EC)

- The Czech ministry of health receives notifications and regulates the use of GMOs
- The Czech commission for the use of GMOs and genetic products (CzC GMO) is an expert committee which deals with environment risk assessment of GMOs
- The Czech environmental inspectorate (CEI) cooperates with other state supervision bodies

General requirements set by Czech act on GMOs[1]

- The notifier of the GMO use must be a person established in the EU – a separate notification must submitted by each institution participating in the trial or study
- Prior to notification a biosafety officer must be appointed, responsible for risk assessment
- The notifier and biosafety officer may be one person across sites

EU: European Union; GMO: genetically modified organism. References in slide notes.

Funding for gene therapies and the future

Funding

The roadmap of large research infrastructures in the Czech Republic details the strategy of large research infrastructures funding from 2016-2022 with a future roadmap scheduled for 2023[1]

- It is based on the ESFRI Roadmap and includes the large research infrastructures approved for public funding by the government of Czech republic
- Operations costs are funded directly by MEYS (ministry of education, youth and sport) and the investment costs are covered using European structural and investment funds via the operational research programme research development and education

Czech National Node to the European Clinical Research Infrastructure Network (CZECRIN) is a large infrastructure for clinically orientated biomedical research included within the roadmap which is[2]:

- Focused on investigator initiated clinical trials
- Working in collaboration with Masaryk University and St Anne's University Hospital in Brno and a network of clinical trial centres developed with a focus on the development of innovative personalised somatic cell therapy for oncology, paediatric medicines and rare diseases as its main priorities
- This includes the development of new ATMPs

Reimbursement & Access[3]

- Public expenditure on orphan drugs as a proportion of all pharmaceutical expenditure in the Czech Republic is 2.25% compared with 3.84% and 6.5% in Austria and Belgium respectively
- Hospital budgets are initially responsible for paying for ATMPs as healthcare providers have limited budgets for reimbursement - a state contribution to the hospital drug procurement budgets for ATMPs could address this
- There is no clear pathway or exemption in the assessment process for ATMPs in Czech Republic - direct negotiations between manufacturers and insurers are required to secure patient access, requiring BI and CEA
- For highly innovative products they may obtain reimbursement for up to 3 years. Prior to launch there is a compassionate use program and also managed entry agreements

ATMP: advanced therapeutic medicinal product; BI: budget impact; CEA: cost effectiveness analysis; ESFRI: Roadmap of European Strategy Forum on Research Infrastructures. References in slide notes.

5

Key insights

Potential challenges for access to gene therapies

Topic	Challenge
HTA review	The national assessment is determined by cost-effectiveness which is a major challenge for gene therapies given this type of evidence is not available as usually based on small sample size, single arm trial, surrogate endpoints and lack of natural history AIFA/CZ review does not incorporate value associated with long term cost offsets but rather focuses on budget impact so decision to adopt a new treatment is largely due to short-term budget impact Innovative status can be difficult to achieve due to the evidence requirements e.g. randomised controlled trials Early access opportunities exist for gene therapies but they are under an individual basis so may not be practical for wider access
Access	Proximity to a treatment centre could present a geographic barrier or disparity in care from centre to centre including disparities in dosing, access to multidisciplinary care, access to physiotherapy, mental health support etc. Therapy may require novel surgical or non-surgical administration devices or protocols Cross-border treatments are a legal right but can result in administrative hurdles. Additionally, hospitals are not reimbursed for treatments conducted outside of the patient's own region, which could be a disincentive Delay in patient access at regional level due to lack of DRG code/criteria for reimbursement • Capacity constraints, laboratory issues or registry setup delays which hinder uptake
Funding	Limited experience with innovative payment options and the current structure is incentivising long term treatments over one-off treatment options – lack of experience with annuity payments or gene therapy payment models Budgets held by regions even though assessment conducted nationally which is a challenge given eligible patients may be unequally distributed across centres
Data	• Databases do not account for outcomes outside of clinical care indicators e.g. bleed rates or other outcomes perceived as important by patients • Outcome data collected not always publicly available which hampers transparency and ability to gather learnings

Insights for gene therapy centres[1]

- Identify eligible patient
- Pre-treatment
  - Pre-treatment assessment: Clinical assessment & laboratory assessments
  - Prepare the patient and their family: 1) Administer any pre treatments e.g. for infectious disease management, allergic reaction management myeloablative conditioning; 2) Discuss required vaccination delays, the need to be vigilant for side effects and what to do in that scenario & advice on viral shedding (if relevant)
  - Prepare the treatment for administration by pharmacist
- Treatment administration
  - Administer the treatment with one caregiver in room; treatment team may be pharmacist, consultant, anaesthetist, ICU nurse, transport team, gene therapy dosing nurse
  - Typical equipment: Bed, chair, drip stand, two biohazard bins, spill kit, anaphylaxis kit, call bells, observation machine, toilet facilities, computer/phone, cannulation and resuscitation trolley
- Post treatment monitoring through inpatient and outpatients assessments
  - Typical post-treatment interventions
- Protective procedures
  - Handling, accidental exposure, spills & disposal, vector shedding
- Formal training
  - Country-specific guidelines on safe handling of hazardous drugs to minimize the risk of exposure should be followed and personnel handling hazardous drugs must be appropriately trained before, specific to each stakeholder type (e.g. pharmacists and nurses) and that it covers topics such as the molecular biological principles behind gene therapy, decontamination, and local requirements and regulations
- Facilities and equipment
  - Each institution to develops their own procedures and evaluates gene therapy products individually. The risk group and biosafety level of each viral vector should be taken into consideration, along with the potential risk associated with the transgene

Summary of key gaps

The following points were not identified through grey literature searching. It is recommendable to conduct stakeholder interviews in order to address these topics:

1. How the centres communicate with one another
   - Do they share resources and overlap patients
   - Is the lab equipped for gene therapy and are the necessary resources available. Are the centres ready in terms of services and function?
2. The financial impact on the hub and spoke model e.g. further funding/competition for centres that provide gene therapies