Cell and Gene Forum Working Group 7 Report

THE FUTURE OF ADVANCED THERAPY MEDICINAL PRODUCT CLINICAL TRIALS IN IRELAND

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Cell and Gene Forum Working Group 7 (Clinical Trials) Brief

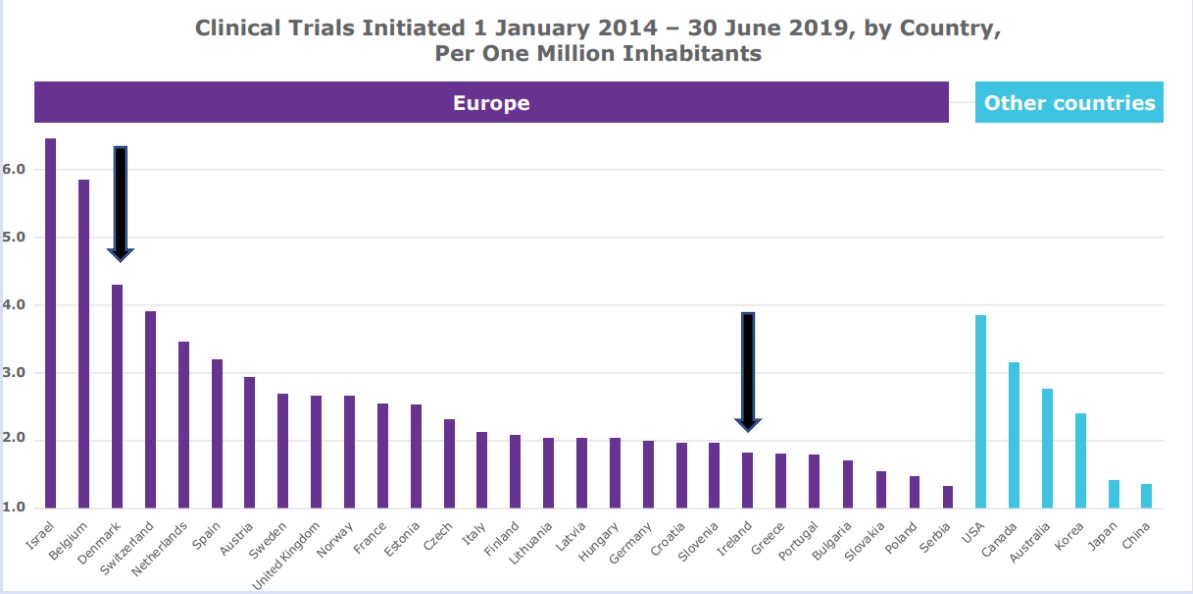
1. Background

Rare diseases are not rare collectively. Across Europe some 30 million people are estimated to fall into this category.[i] Most rare diseases lack effective drug treatments.[ii] Across 7,000 rare disease variants approximately only 340 have a treatment option available.[iii] This challenge has resulted in a drug development pipeline increasingly focused on such conditions.

Advanced Therapy Medicinal Products (ATMPs) include gene therapies, somatic cell therapy and tissue engineered products.[iv] ATMPs are predominantly developed to treat rare diseases. While ATMPs have evolved over four decades, proof of the value proposition they offer is only being recently realised. There are now several commercially viable ATMPs having been authorised, launched and approved for reimbursement.

The international context for drug development, and within that development of ATMPs, is striking. IQVIA Institute's most recent report on global R&D trends states that the number of drug products in development is 68% greater than in 2016.[v] Clinical trial activity is 19% greater than the pre-pandemic level in 2019. Amidst these increases is the precision medicine revolution in oncology, with 40% of these products being next-generation therapeutics including cell and gene therapies. Notably, the R&D spending of the largest pharmaceutical companies increased by 44% compared to 2016. This is the international landscape in which Ireland must ensure it is an active contributor and beneficiary.

Involvement in ATMP clinical trials has obvious advantages. For example, it facilitates access to novel treatments and their early adoption. International comparisons in terms of ATMP clinical trials initiated per million inhabitants show that Ireland is lagging behind. The figure below compares Ireland with Denmark, a similarly sized economy.[vi]



1.1. Problem Statement

At present Ireland lacks an appropriate **infrastructure** to perform clinical studies of ATMPs at scale and there is currently no health and research **policy** specifically aimed at developing the Irish ATMP sector.

1.2. Why?

ATMPs clinical studies have specific considerations when compared to those for small molecule drugs including environmental impact, drug handling, dosing, administration, adverse effect profile and advanced molecular diagnostic services.

1.3. The International Experience

Clinical studies of ATMPs require special research facilities with new skills and expertise. Therefore, specialist research centres have been developed internationally. While Europe has lagged behind the USA in the area of ATMP research, the UK has improved its research capability in the ATMP area with a number of initiatives. These include the Advanced Therapy Treatment Centre (ATTC) Network, the Cell and Gene Therapy Catapult manufacturing centre and an ecosystem involving the NHS, NICE, the MHRA, universities and biopharmaceutical industry. The Cell and Gene Therapy Catapult provides a high-level overview of the cell and gene therapy eco-system. It reports there are more than ninety companies developing ATMPs and 127 ongoing clinical trials of ATMPs in the UK in 2020. This represents 12% of such trials globally. They report a doubling of Phase III trials for ATMPs from 2018 to 2020, indicating significant progress in the drug development process.

1.4. The Beginning in Ireland

Re-organisation of an Irish cell and gene therapy ecosystem accompanied by significant investment and a coherent strategy would greatly increase Ireland's profile in terms of ATMP R&D. To this end the National Institute for Bioprocessing Research and Training (NIBRT) has organised seven working groups of the Cell and Gene Forum to foster collaboration of key stakeholders towards the development of such an ecosystem. This endeavour will require high level support.

1.5. Key Objectives for WG7

- To examine the current Irish context of cell and gene therapies to make recommendations to the Forum related to ATMP clinical trials.

- To influence government policy to support resource allocation to attract ATMP studies to Ireland.
- To enable access for Irish patients to innovative therapeutics, as might be expected for an advanced healthcare system.

2. WG7 Interactive Sessions

To progress the objectives of WG7, five interactive sessions were organised in late 2021 to inform the groups thinking. These involved brief 30 presentations from key opinion leaders followed by a Q&A. The sessions aimed to:

- Highlight developments in the Irish regulatory environment pertaining to ATMPs.
- Ascertain the requirements of industry partners when appraising sites for clinical trial involvement.
- Identify gaps in Irish cell and gene therapy ecosystem by learning of the state of play in the UK/international centres.
- Understand how the ecosystem and it outputs might be measured and reported
- Hear of the current clinical context of ATMP utilization in Ireland

2.1. Session 1 – Health Products Regulatory Agency

Key points:

- The legal and regulatory framework for ATMP trials is well described, for example, in the Guidelines on Good Clinical Practice specific to ATMPs (Eudralex Volume 10, C(2019) 7140)
- While there are differences for ATMPs trials compared to those for other drug therapies, there are also commonalities. Areas of notable

difference include drug quality assessment, trial design, environmental impact, shedding studies as well as more complex logistics, storage and handling requirements.

- The Regulator is a resource for those planning and performing ATMP trials, particularly those that are academic. Within the HPRA there is expertise to advise and guide ATMP studies and a willingness to do so. Nine ATMP trials have been authorised by the HPRA thus far.

2.2. Session 2 – Requirements of Industry Partners

Key points:

- Genomics will guide ATMP trials. Therefore appropriate infrastructure is required to facilitate patient selection. This include:
    - biobanks for rare diseases,
    - integration of companion diagnostics into clinical care to allow patient selection and monitoring,
    - capacity in terms of next generation sequencing to create enriched trial cohorts.
- Ireland needs to integrate its patient cohorts into international registries. This will flag Ireland as a study location when treatments for these disease specific cohorts are in planning.
- Specialist trial units with the expertise of performing ATMPs trials are required. Fatal outcomes have occurred during early phase ATMP trials. Paramount in the due diligence process of industry partners is their confidence in trial units to mitigate risks for patients.
- Variation in patient response is an ongoing issue. Biomarkers to measure this variation are required as standard. The biomarkers should be

provided by trial units in line with study designs and used by clinical services when typing cohorts.

- In order to attract industry supported clinical trials, the regulatory environment must be streamlined and responsive. Progress in this area is noted in terms of the recent establishment of the National Office for Research Ethics Committees.

2.3. Session 3 & 4 – The UK Experience

Key points:

- A cell and gene therapy strategy should set out clear priorities in the first instance and then identify gaps to be addressed to progress implementation.
- A strategy to develop the cell and gene therapy ecosystem should have ATMP clinical trials as a necessary component to foster indigenous ATMP development.
- Building capabilities to perform ATMP trials can be a rapid process, if and when strategy, resources, supports and processes are aligned. The ATTC network was established in the UK in 2018 and a five-fold increase in ATMP trials followed over the next 18 months.
- A cell and gene therapy ecosystem requires collaboration with industry, academia and healthcare organisations to perform ATMP trials.
- Sharing learning among the cell and gene therapy community is necessary to accelerate capability building. The nascent ATMP community in the UK did so via the ATTC Knowledge Hub.

- Supporting clinical adoption of ATMPs is necessary to attract ATMP trial activity. The ATTC provided tools such as the NHS readiness toolkit and pharmacy guidance for healthcare organisations delivering ATMPs.
- Education is essential to ensure the development of a critical mass of ATMP services and trials. Frequent webinars, meetings and guidance documents underpinned the ATTCs educational offering across a wide range of clinical and practical topics e.g. clinical adoption, patient experience, pharmacy, regulation, logistics, product ordering, analysis, reimbursement.
- The progress of the cell and gene therapy ecosystem must be measured and reported. This includes identifying new collaborations (national/international, commercial/academia), reporting ATMP projects, measuring academic output, highlighting training events and tracking ATMP trials as they progress towards product authorisation.
- The UK ATTC network is open to collaboration with Irish centres. Preliminary discussions have occurred with a Northern Irish centre. Closer alignment of ATMP ready centres on the island of Ireland would strengthen the possibility of collaboration.

2.4. Session 5 – The Clinical Context

Key points:

- The possibility of providing curative treatments to patients, who were heretofore resigned to the fatal course of their condition, has created a sense of enthusiasm and excitement for clinicians.
- At present the use of ATMPs is concentrated at a small number of sites and a small number of specialist services within these sites.

- These services are still at an early stage and adequate resources are necessary for further development.
- A component of the service development will be the access of patients to clinical trials and therefore their early access to the most cutting-edge therapies.

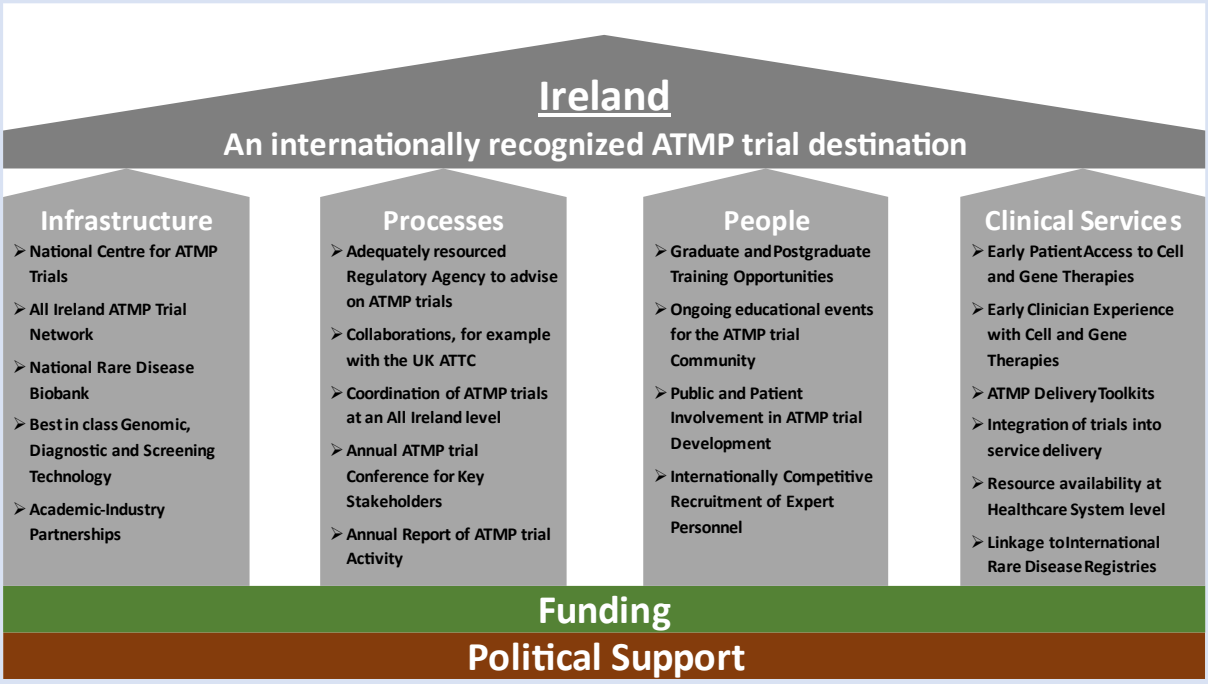
3. Assessment and Conclusions

In terms of ATMP development, Ireland has failed to capitalise on its acknowledged manufacturing capabilities, biomedical leadership across cognate disciplines and highly educated workforce. Ireland must become a significant player in the ATMP space to maintain its reputation as a country with significant scientific prowess and a thriving pharmaceutical industry. At present Ireland lacks an appropriate infrastructure to perform clinical studies of ATMPs at scale.

Importantly, Ireland is without a health and research policy specifically aimed at developing the Irish ATMP sector. Many of the necessary pieces are in place, such as small firms and campus companies in the ATMP sector, a strong biopharmaceutical industry sector and the National Institute for Bioprocessing Research and Training (NIBRT) working with the support of Enterprise Ireland. A greater focus on integrating these components with the health services and publicly funded clinical trials facilities should now be considered to put Ireland on the ATMP research map.

To progress Ireland's cell and gene therapy ambitions, a strategy to attract ATMP trials must focus on addressing the gaps in the Irish cell and gene therapy ecosystem. It is clear that significant gaps exist in terms of infrastructure, people, processes and clinical services. All efforts to rebrand Ireland as an ATMP trial

location must be underpinned by political support and funding. An illustration of the key requirements and recommendations is included below.



Recommendations – WG7 meeting March 2022

- Broaden WG7 to juxtapose ATMP clinical service delivery with clinical trial delivery as co-dependent sectors of the cell and gene ecosystem
    - Overlapping facilities, expertise, patients
    - CHI, HSE (acute services, pharmacy), NCCP, NCPE
- Create a roadmap for ATMP adoption and integration into clinical care and research
- Create a business case and human case for ATMP infrastructure and resources
- Create an All-Ireland Advanced Therapy Centre Network
- Link this network to a UK network and within the ATTC

- Foster political and governmental interest in developing a cell and gene ecosystem

Actions

For WG7

- WG7 to evolve into a group to develop an All-Ireland ATMP Clinical Network – review Spanish and Australian examples
- Create a roadmap for ATMP adoption and integration into clinical care and research – how are the aspirations in the House/Church representation realised

For Cell and Gene Forum

- Create a business case and human case for ATMP infrastructure and resources
- Foster political and governmental interest in developing a cell and gene ecosystem

References

[i] Schieppati A, Henter JI, Daina E, Aperia A. Why rare diseases are an important medical and social issue. The Lancet. 2008 14;371:2039-41.
[ii] Tambuyzer, E., Vandendriessche, B., Austin, C.P. et al. Therapies for rare diseases: therapeutic modalities, progress and challenges ahead. Nat Rev Drug Discov 2020 19, 93–111.
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[iv] European Commission (2009). Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products.
[v] Global Trends in R&D 2022 – Overview through 2021, IQVIA Institute Report Feb 2022
[vi] Clinical Trials in Europe: Recent Trends in ATMP Development by Alliance for Regenerative Medicine, available at https://alliancerm.org