The Role of Pharmacy for delivery of Advanced Therapy Medicinal Products in NHS Scotland

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Ruaridh Buchan, Scottish Pharmacy Clinical Leadership Fellow

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Foreword – Ruaridh Buchan

Over the last year, I have explored the role of pharmacy to support safe and effective delivery of advanced therapy medicinal products (ATMPs) for patients in Scotland. I have listened to clinicians with experience delivering these products from across the UK and observed various models of delivery that have been successfully implemented. I also had the opportunity to hear the stories of patients whose lives had been changed following treatment with ATMPs.

A common theme to these conversations was a sense of excitement and optimism about the potentially life changing benefits that ATMPs offer our patients. I believe that ATMPs will change the way that some diseases are managed, however consideration regarding how pharmacy in Scotland needs to adapt to support a multidisciplinary approach to widespread adoption is required.

This paper outlines what I have learned and describes how pharmacy in Scotland can adapt to realise the benefits of these products for our patients.

ATMPS and their potential benefits for our patients

Advanced Therapeutic Medicinal Products (ATMPs) are a revolutionary type of medicine which allow the patient's genes, cells or tissues to be engineered restore the function of the body and reverse the effects of disease. We can use these therapies as living drugs to regenerate damaged tissues or even target certain cancers by modulating the immune response. ATMPs have the potential to change the way currently manage degenerative diseases such as cancer, diabetes and heart disease.

There are three classes of ATMP. These three types are defined by the European Medicines Agency

- Gene Therapy: *contains or consists of genes, to prevent, treat, diagnoses, or cure disease*
- Somatic cell therapy: *contains or consists of cells or tissues that have either been substantially manipulated or are not intended to be used for the same essential function in the recipient and donor*
- Tissue engineered products: *contain or consist of cells or tissues administered with a view to regenerating, repairing or replacing human tissue* [1].

Each class has unique challenges in terms of medicines governance, toxicities, and operational considerations for preparation. These challenges also vary within the class on an individual product basis.

Whilst cell-based therapies such as bone marrow transplant have been around for years, the novelty of advanced therapies is that the cells that are isolated can be purified or altered and the consequence of that is that their function changes meaning that they become more effective for the treatment of a range of diseases including genetic conditions.

Importantly for pharmacy, through engineering the cells they also become medicines, meaning that pharmacy then become responsible for their safe and effective use within our hospitals. Cell based therapies are regulated by the Human Tissue Authority (HTA) under Directive 2004/23/EC and associated EU directives which have been transposed in the UK as the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended). ATMPs on the other hand are regulated by the Medicines and Healthcare Regulatory Agency (MHRA) under Directive 2001/83/EC (amended by the ATMP regulation to 1394/2007) on the community code relating to medicinal products for human used which has been transposed in the UK as the Human Medicines Regulations 2012 (SI 2019/1916) [2].

Figure 1: Types of Advanced Therapy Medicinal Product

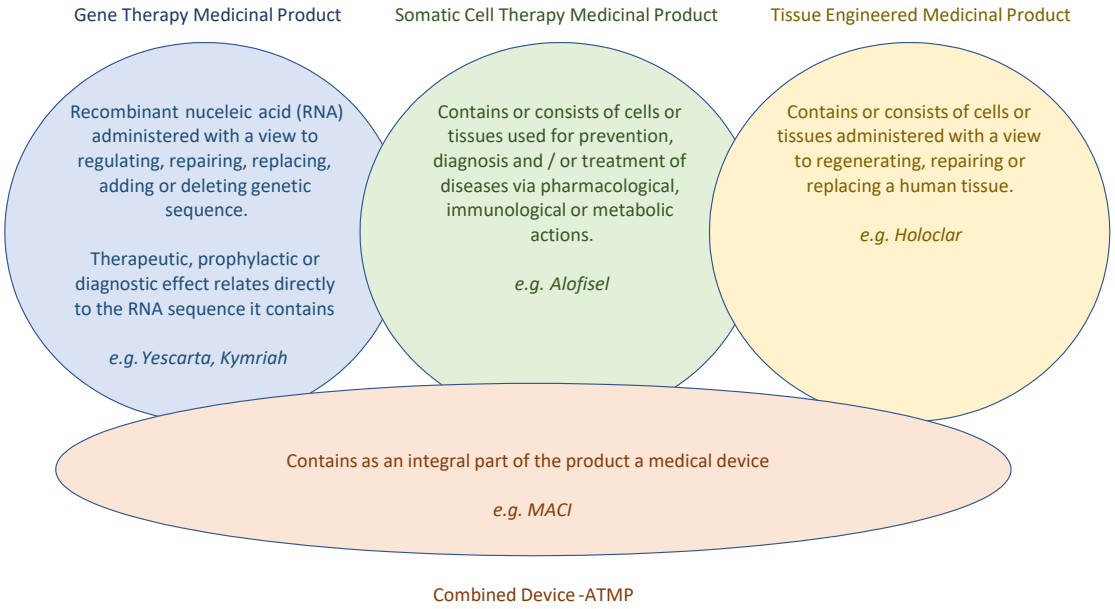


Figure 2: Case Study - Macrophage Cell Therapy for Liver Cirrhosis Clinical Trial (MATCH)

Researchers in Edinburgh have recently completed a phase 1 clinical trial which found that treatment of liver cirrhosis – where long term damage produces scarring – using macrophages had no significant adverse effects. During the trial, white cells were taken from patients. These were manufactured into autologous macrophages, which were then re-injected into the same patient. At present the only successful treatment for end-stage liver cirrhosis is an organ transplant, so this is a vital step forward in finding an alternative therapy. The next stage of the trial will measure whether the therapy helps the liver to reduce scarring and stimulate repair.

"Liver cirrhosis is a major healthcare issue in the UK and is one of the top five killers. The results from this first safety trial are encouraging and we can now progress to testing how effective it is in a larger group of people. If this was found to be effective it would offer a new way to tackle this important condition."

— Professor Stuart Forbes
Chair of Transplantation and Regenerative Medicine, MRC Centre for Regenerative Medicine at the University of Edinburgh

What does the future look like for ATMPs?

The Cell and Gene Therapy Catapult forecast, pro-rata for Scotland, predicts that by 2021 delivery of ATMPs will be required for 250 patients increasing to 1000 patients by 2028. At the time of writing the Scottish Medicines Consortium (SMC) has assessed 6 ATMPs (5 gene therapies and one somatic cell therapy) and a further 1 gene therapy is currently under consideration [3].

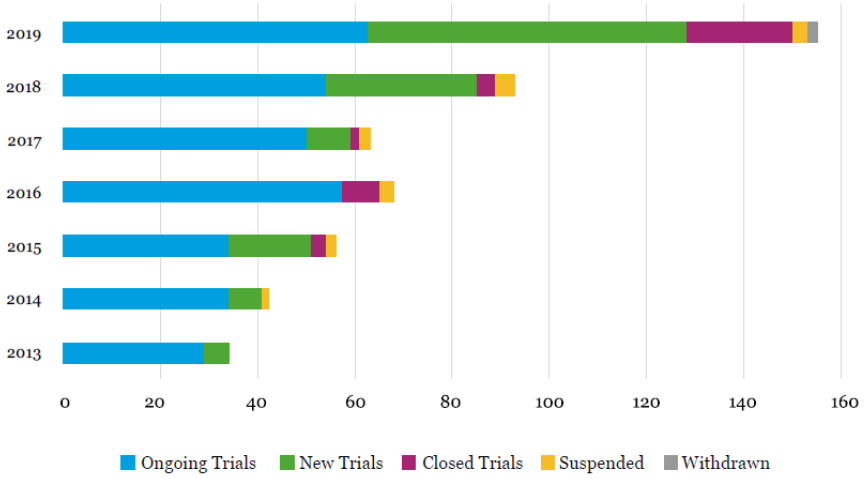
As ATMPs are a relatively new technology, they are currently delivered more often through clinical trials than as licensed medicines through embedded care. They are often for orphan indications meaning they move from phase II studies through to NHS availability faster than traditional medicines. Clinical trials are therefore a useful indicator of the future of embedded clinical care involving ATMPs. Data shows a year on year increase in the number of clinical trials involving ATMPs for various indications; however oncology is the most common indication. Gene therapies are the most common class of ATMP being researched [3].

The Advanced Therapy Treatment Centre (ATTC) network is a UK system of ATTCs operating within the NHS framework. The ATTC network aims to address the challenges associated with ATMP delivery by the establishment of national processes and procedures and through supporting collaboration between the NHS, industry, and academia to address the unique and complex challenges of bringing ATMPs to patients. The Northern Alliance Advanced Therapies Treatment Centre (NA-ATTC) comprises NHS Lothian, NHS Greater Glasgow and Clyde, The Newcastle upon Tyne Hospitals NHS Foundation Trust and Leeds Teaching Hospitals Trust as well as academic and industry partners. In the immediate future, it is anticipated that ATMPs will be delivered within ATTCs that are working towards being institutionally ready to delivery ATMPs.

Figure 3: Introduction to the Northern Alliance Advanced Therapies Treatment Centre (NA-ATTC)
In this video, Michael Whitaker, chair of NA-ATTC's Steering Board, explains the remit and vision of the NA-ATTC for accelerating patient access to Advanced Therapy Medicinal Products.

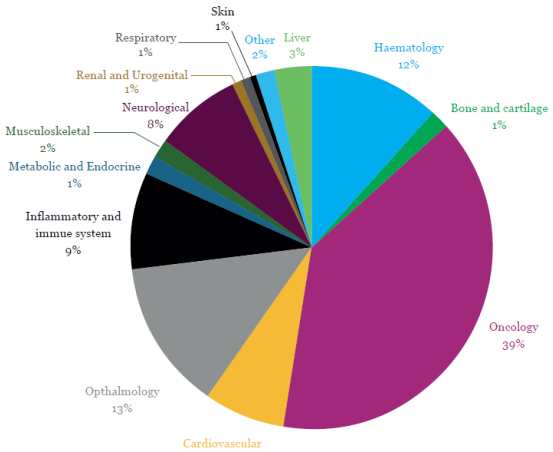
Figure 4: Number of ongoing, new and completed Advanced Therapy Medicinal Product (ATMP) clinical trials in the UK from 2013 – 2019

The Cell and Gene Therapy Catapult ATMP clinical trial database shows a year on year increase in the number of ATMP clinical trials with 127 ATMP clinical trials ongoing in the UK in 2019 compared to 85 reported in 2018.

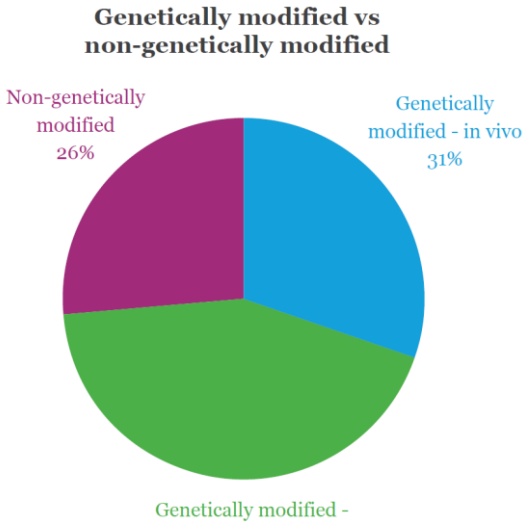


The distribution of therapeutic indications is widespread, however oncology is the dominant indication.

Figure 3. Distribution of UK ATMP clinical trials according to therapeutic area in 2019



Gene modified product trials account for 74% of all ongoing clinical trials in the UK.



Source: Cell and Gene Therapy Catapult – Clinical Trials Database 2019.
Available at https://ct.catapult.org.uk/sites/default/files/publication/Clinical%20Trials%20Commentary_for%20publication_150120.pdf

Why are ATMPs important for pharmacy?

As well as having a legal responsibility to ensure safe and effective use of medicines, pharmacy professionals are experts in medicines and this skill set means the pharmacy workforce should be central to the safe and effective delivery of ATMPs within our hospitals. Directors of pharmacy who are routinely appointed by their hospital board to be the named individual responsible for safe and secure handling of medicines are therefore responsible for safe and effective use of ATMPs within their organisation [4, 5].

Given the complex nature of ATMPs, they are currently always delivered in the hospital setting where specialist expertise and infrastructure exists. Hospital pharmacies must provide appropriate clinical pharmaceutical care pre-admission, during the episode of care and post admission for all patients that receive ATMPs. There must be appropriate medicines governance and systems for efficient supply of novel ATMPs. Finally, there must be strong local and national leadership which enables hospital teams to provide personalised high quality care for patients that are treated using these innovative medicines.

The increase in ATMP clinical trials is an important consideration for hospital pharmacy clinical trials services. Hospital pharmacy infrastructure required to deliver investigational ATMPs overlaps infrastructure that is required to deliver marketed ATMPs. Through investing in infrastructure to deliver ATMPs as part of research, the wider pharmacy service benefits as the knowledge and experience gained is transferrable to routine clinical care.

Although ATMPs will be delivered in the hospital setting, community pharmacy services and pharmacy teams that are integrated into GP practices play an important role in provision of pharmaceutical care for patients that are treated using these innovative medicines. This includes, but is not limited to, providing or signposting patient education and recognising the signs of and managing toxicity or referring for management as appropriate.

Figure 5: Case Study - CAR-T Patient and Product Flow Chart
The role pharmacy in the delivery of these medicines is well illustrated by using the example of Chimeric Receptor T-cell (CAR-T) therapies, an in-vivo (viral based) gene therapy.

The role can be broadly categorised into three roles;

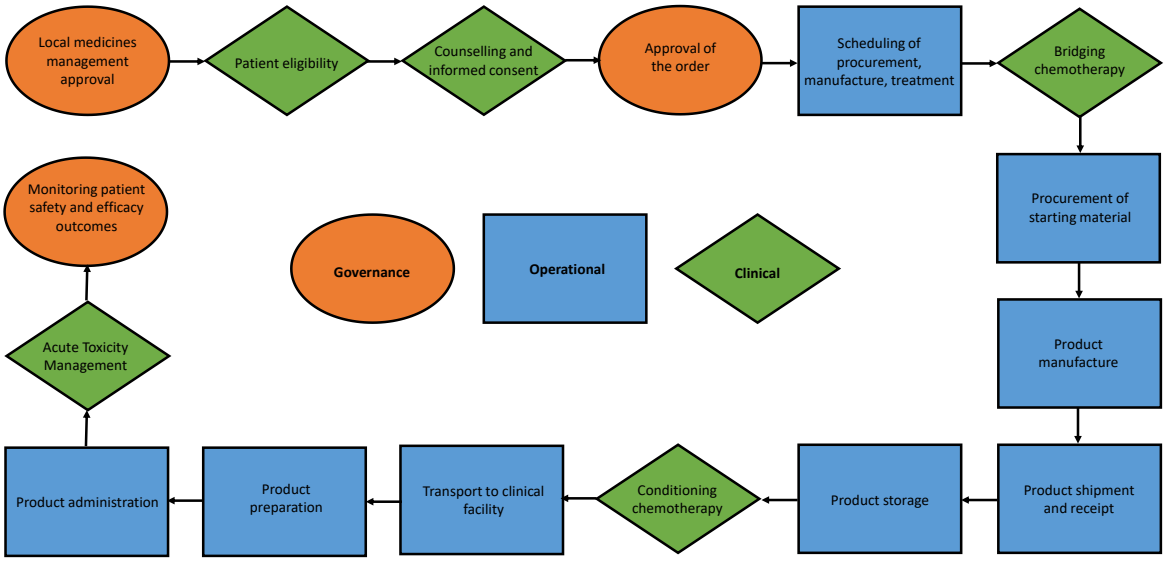
- Clinical governance
- Operational delivery of ATMPs
- Clinical pharmaceutical care of patients prescribed ATMPs

During CAR-T therapy, T-cells are removed from the patient's blood, genetically modified, and re-infused into the patient. The new CAR-T cell then attacks and kills the patient's cancer cells. The journeys of both the patient and the CAR-T cell product are very complex and require a multidisciplinary team to provide safe and timely treatment.

The pharmacist's role involves creating policies and procedures for all aspects of the service, order of the product, managing finance and organizing bridging or lymphodepletion therapy. The CAR-T products that are currently licensed must be stored at ultra-cold temperatures (<150 degrees Celsius) in vapour phase liquid nitrogen and pharmacists must oversee their storage, dispensing and administration. Pharmacy departments must work with cellular therapy units where they do not have these cyro-storage facilities in-house, whilst maintaining appropriate pharmacy oversight.

Clinical pharmaceutical care to monitor the patient after the infusion is key for ensuring patient safety because CAR-T is associated with unusual and potentially fatal toxicities including early toxicities such as cytokine release syndrome and late toxicities such as cytopenia.

Pharmacists that are responsible for CAR-T delivery should ensure training is provided to the wider hospital pharmacy team including on-call, critical care and neurology specialists, as well as medical and nursing staff, and pharmacists from other hospitals who may refer patients for CAR-T therapy or see patients who have received the treatments.



What are the challenges for pharmacy?

ATMPs are different to traditional biopharmaceutical and small molecule medicines meaning that pharmacy must adopt new ways of working to ensure successful adoption of these disruptive therapies.

ATMPs are described as a 'disruptive technology' because they will potentially replace several traditional pharmaceuticals or medical procedures. The literature around adoption of disruptive technologies suggests that an institutional approach to implementation is necessary. This method should include adaption of organisational practices, process and skills, as well as alignment of the institutions values and the professional interests of its healthcare leaders. Pharmacy services are key to achieving institutional readiness to deliver ATMPs and therefore must adapt, however, it is important to recognise that active engagement from the multidisciplinary team (including front line clinicians, hospital managers and administrators) to address the complex challenges associated with this innovative technology is essential [6, 7, 8].

Delivery of ATMPs often carries substantial risks, both to the patient in terms of potential for immediate and delayed toxicities, but also to the organisation in terms of health and safety (e.g. potential for gene shedding) and financial risk as a result of them often being high cost. Therefore, robust medicines' governance is required at various levels encompassing both national and local requirements. As part of their overall responsibilities for medicines governance, pharmacists should oversee local governance arrangements to ensure that ATMPs are of appropriate quality for their intended use.

ATMPs are associated with complex supply chains as well as demanding storage and traceability requirements. Hospital pharmacies are a vital part of the supply chain and will be responsible for the storage, handling, preparation, and logistics delivery within the hospital. ATMPs, especially those which are cryopreserved or with a very short shelf life, may require specialist handling and expertise that is not be immediately available within pharmacy departments. Specialist aseptic preparation of some gene therapy products requires either dedicated and appropriate aseptic isolators, or capacity to use appropriate aseptic isolators on a sessional basis. Currently in Scotland, such facilities exist only in NHS Greater Glasgow and Clyde and NHS Forth Valley; the latter is not currently used for preparing gene therapy.

The role of clinical pharmacy centres around clinical pharmacy verification of prescriptions for ATMPs and concomitant medicines, linking with referral centres where required and toxicity management of the treatment. Where ATMPs are prepared at ward level, or delivered directly to clinical areas, ward-based pharmacists may be best placed to complete required quality checks prior to administration. As a result, patients that receive ATMPs often require enhanced pharmaceutical care which has implications in terms of workforce planning.

Existing reimbursement practices do not easily accommodate the potential outstanding value and risk profile that the potentially curative and disease modifying ATMPs can deliver. These therapies may result in a long period of patient benefit from a single treatment. This contrasts with traditional pharmaceuticals that are administered and paid for in small instalments over the course of a patient's life. The Scottish Medicines Consortium considers that existing health technology assessment methodology is appropriate for assessment of ATMPs. However, the combination of high upfront cost and uncertainty surrounding long-term benefits with single treatment therapies presents a particular challenge for SMC decision making. There is a need to collect longer term post launch outcomes data to establish real world performance of ATMPs and ultimately satisfy regulatory and reimbursement requirements.

The adoption of ATMPs, and subsequent sustainable delivery and growth, will require new knowledge, skills, and competencies for pharmacy professionals of all experience levels and across all sectors.

Figure 6: Institutional Readiness to of NHS Institutions to Deliver ATMPs
Institutional readiness (IR) has been suggested as a means of assessing the capacity of an institution to adopt new technologies. The Northern Alliance Advanced Therapy Treatment Centre (NA-ATTC) completed an exercise to map IR for ATMPs across the NA-ATTCs four clinical sites across three time points.

The exercise identified trends in terms of areas where sites are institutionally ready or IR improved, e.g. IR was evidenced in sites that were established centres for delivery of marketed CAR-T products and sites that have experience delivering clinical trials for these products. It also identified gaps, e.g. aseptic capacity to prepare gene therapy medicinal products was identified as a barrier to delivering this class of product on sites where there were no dedicated aseptic facilities for preparing gene therapy medicinal products.

As a result of this exercise, a validated IR assessment tool has been developed, which can be used by sites looking to adopt new ATMPs or improve IR for delivering ATMPs.

The IR assessment tool as well as other guidance and standardised templates is available in the Advanced Therapies NHS Readiness Toolkit which has been developed by the Advanced Therapy Treatment Centre (ATTC) network. The toolkit was launched to support the accelerated clinical adoption of advanced therapies and reduce the burden on NHS institutions as they plan to delivery these novel therapies to patients at scale.

The readiness toolkit provides resources that support clinical and financial governance, regulatory and commissioning requirements, business cases and contracts, risk management, implementation planning, logistics, pharmacy, clinical administration, cross-specialty working, and service evaluation and outcomes. This initiative is supported by the three ATTC centres; Innovate Manchester Advanced Therapy Centre Hub (iMATCH), Midlands and Wales Advanced Therapy Treatment Centre (MW-ATTC) and Northern Alliance Advanced Therapies Treatment Centre (NA-ATTC)) operating within the NHS framework and coordinated by the Cell and Gene Therapy Catapult (CGT Catapult).

The toolkit can be found at.
https://www.theattcnetwork.co.uk/advanced-therapies-nhs-readiness-toolkit

How can pharmacy overcome challenges surrounding ATMP delivery?

The Pan-UK Pharmacy Working Group (PWG) for ATMPs was established to act as an expert and informed body to support the pharmacies to facilitate ATMP delivery. The group consists of pharmacists from across the UK that specialise in various aspects of pharmaceutical delivery of ATMPs. The group aims to share and promote good practice, identify and resolve pharmacy issues to maximise the effectiveness and development of services for hospitals to administer advanced therapies. It has and will continue to develop guidance on governance and institutional readiness to support hospital pharmacies to deliver ATMPs safely and effectively. This guidance covers aspects of medicines governance, operation delivery of ATMPs and clinical pharmaceutical care of patients that are prescribed ATMPs [9].

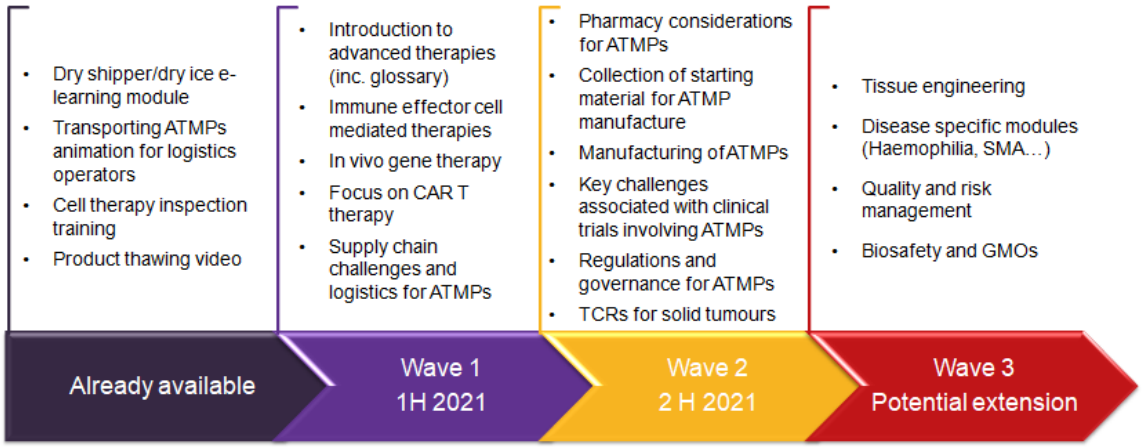
Some hospitals have decided that ATMP governance is within the remit of existing medicines management groups and systems, whereas others have set up bespoke committees to evaluate ATMPs. There are certain aspects of delivery that require special governance considerations. Handling of gene therapy products is governed by the Health and Safety Executive Genetically Modified Organism (GMO) – Contained Use Legislation, which requires risk assessment by a multi-disciplinary GMO safety committee [10]. ATMPs are unique medicines in that tissues or cells are often used as the starting material which is manipulated during manufacture of the final product. Institutions wishing to collect blood or tissue for use in the manufacture of ATMPs must hold a Human Tissue Authority (HTA) Human Application (HA) license. This is usually, held by the cellular therapy unit, but it is important that pharmacy have awareness [2].

If dedicated staff and facilities for preparation of ATMPs exists outside of pharmacy (e.g. a stem cell laboratory) then they may be the most appropriate to handle the products with pharmacy oversight and approval. In some cases ATMPs will need to be delivered directly to the end user in a clinic or within an operating theatre and may not pass through Pharmacy. Systems to allow pharmacy oversight of this practice will be required.

Hospital pharmacies should endeavour to provide pharmaceutical care which meets the Royal Pharmaceutical Societies Professional Standards for Hospital Pharmacy Services. It is imperative that clinical pharmacists engage with the multidisciplinary team around patient selection, patients that receive ATMPs are prioritised during their episode of care, and where applicable, clinical pharmacists provide guidance to the referring clinical team.

Some ATMPs that are currently available, e.g., chimeric antigen receptor T cell (CAR-T) products are associated with potentially serious side effects, and pharmacy professionals must have the knowledge and skills required to manage these. To address education requirements for pharmacy professionals, NHS Education for Scotland is collaborating with the Cell and Gene Therapy Catapult (GCTC) to deliver an eLearning education package, the aim of which to prepare the workforce for introduction of ATMPs into research and standard of care.

Figure 7: Cell and Gene Therapy Catapult Advanced Therapy Medicinal Product (ATMP) Education
The CGTC and ATTC network is developing a range of resources to support healthcare professionals to work with ATMPs at clinical delivery sites. The resources will include a repository of modules hosted on the e-Learning for Healthcare platform. NHS Education for Scotland has contributed to the building of these resources and they will be freely available for all NHS Scotland staff. Modules have been prioritised, developed, and delivered based on educational need. The diagram below outlines the modules that are planned and the expected timescale for their delivery.



Source: CGTC slide deck. ATMP Education and Training Initiatives. Ian Hollingsworth. 10/02/2021

Summary and Recommendations

ATMPs are an exciting development in medicine that offer the potential of cure where there is currently an unmet patient need. Horizon scanning indicates an exponential rise in the number of ATMPs that will be available for patients across multiple indications over the next 10 years. Importantly, they are classified as medicines, so it is essential that pharmacy professionals understand their role in the successful adoption of ATMPs.

Recommendation 1: *As ATMPs are medicines it should be recognised that they are subject to the same requirements as for other medicinal products and the directors of pharmacy are responsible for their governance and management.*

ATMPs are often classified as a disruptive technology and successful adoption requires an institutional approach. The ATTC network has been successful in achieving its aim of addressing many of the challenges associated with delivering ATMPs through shared learning and has led to an improvement in institutional readiness to deliver ATMPs in NHS Lothian and NHS Greater Glasgow and Clyde.

Recommendation 2: *A national approach supporting adoption and delivery should be considered. I recommend that ATMPs are delivered within established ATTCs, however given anticipated growth in the number of ATMPs being delivered, learning from the ATTCs should be rolled out to other boards.*

The ATTC network has been successful in developing national guidance which addresses some of the key challenges associated with ATMP adoption. Continued engagement with the ATTC network is important to ensure that Scottish Boards can contribute to and benefit from shared best practice and national guidance. The ATMP field is evolving quickly and it is important that Scottish pharmacy services are aware of developments and consider the implications.

Recommendation 3: *Pharmacists and Pharmacy Technicians should continue to engage with the ATTC network and should contribute to national work led by the NA-ATTC and the pan-UK pharmacy Working Group for ATMPs.*

The NA-ATTC has undertaken a gap analysis of institutional readiness of its four clinical sites including NHS Lothian and NHS Greater Glasgow and Clyde to deliver ATMP. This work has highlighted institutional readiness both at individual board level and nationally [1].

The report outlines the following national recommendations which have implications for pharmacy services in NHS Scotland:

- Continued engagement with the NA-ATTC and UK ATTC network
- Further work is required to improve capacity and infrastructure for handling ATMPs within pharmacy departments and to formalise relationships between pharmacy departments and cell therapy units / SNBTS for handling ATMPs.
- Investment in pharmacy infrastructure to support ATMP clinical trials and ensuring that lessons learned through delivering clinical trials informs embedded clinical service design.
- Horizon scanning to identify ATMPs that are in early development. Through early identification, the challenges around delivery of the product can be addressed, ensuring timely patient access to ATMPs when they become commercially available.
- Horizon scanning should be used to inform national planning for specialist pathways through engaging the broader clinical community, especially for rare conditions.
- Continued workforce education to upskill pharmacy professionals and ensure that those involved in delivery of ATMPs are informed of recent developments.

- Work is required to achieve consensus from industry and NHS Scotland stakeholders for patient outcome data and manageable systems for its collection. This is particularly pertinent for licensed ATMPs in the post-marketing period.

Recommendation 4: *Boards and research partners should consider recommendations as outlined in the feedback provided by the NA-ATTC and implement an action plan accordingly. Recommendations should also be considered as part of a national approach to ATMP adoption [1].*

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