



Regenerative medicine in the United Kingdom

Clinical Delivery Policy Briefing February 2017

“Clinical delivery...what are the logistical challenges with getting [an RM product] from your manufacturing centre, with all the paperwork, into your hospital? It’s not going to sit in a pharmacy... you have living cells that [might] need to be back into a patient within a 15 hour therapy window... How does the clinician at the end of the day know that the product is quality controlled? How do they know that it’s been transported appropriately?... How do [we] bring all this together to [deliver to] the patient?” - Innovation network representative.

Overview

- Implementing RM therapies within the healthcare system will pose a range of challenges over and above the usual institutional challenges of launching new health technologies or clinical services
- RM products are sensitive and the shelf life for some products will be short. Novel logistics and administrative arrangements will be needed to receive, store, approve and administer them.
- Some RM products will be partially or fully manufactured at or near the clinic. This requires specialist technical (including GMP) and regulatory expertise, and high-cost bioprocessing systems.
- Some proposed risk-sharing commissioning systems will require coordinated data infrastructures between clinical sites.
- Initiatives in the UK have proposed the establishment of a network of Cell and Gene Therapy Treatment Centres. Resources will be concentrated around these, enabling the development and testing of supply-chain, delivery and organisational systems.
- Existing arrangements in the UK and elsewhere, such as Haematological Services, current risk sharing arrangements, and the establishment of a national proton beam therapy service, provide important precedents for the formation of specialist RM treatment centres.

The aims of the project are:

1. To provide an overview of the current RM landscape in the UK, and also in the EU and US.
2. To explore how actors navigate logistical, legal, regulatory and reimbursement challenges.
3. To identify the challenges associated with the upscaling, and the delivery and dissemination of RM products in clinical settings.
4. To identify and explore the roles various stakeholders play in enabling the development and potential adoption of RM.
5. Identify common business models and their relationship to regulatory, social and political factors.
6. To predict how RM is likely to evolve, and provide recommendations aimed at supporting responsible research and innovation within RM

Introduction: Regenerative Medicine

Regenerative medicine (RM) involves using cells, tissues, or genetic material to treat and manage disease. It represents a significant departure from conventional, drug or device based therapies, and it has been identified as having the potential to deliver major clinical and economic opportunities. In several countries including the UK, RM has been identified as an important element of their industrial strategy, and government-supported initiatives have been launched to facilitate the emergence of an RM industry.

A diverse range of RM products and procedures are currently under development, involving a range of tissue types, such as adult stem cells, human embryonic stem cells and induced pluripotent stem cells. Some therapies entail using the patient's own cells or tissues (autologous), while others entail the use of material that has been expanded from an original donor (allogeneic). Generally, most RM technologies are early in the development pipeline (most RM clinical trials are in Phases I & II), but more advanced developments include T-Cell immunotherapies for leukaemia, gene therapies for severe combined immunodeficiency, the use of mesenchymal stem cells for autoimmune conditions, and limbal stem cell transplantation for blindness caused by limbal stem cell deficiency.

Project background

REGenableMed (2014-2017) is an ESRC-funded social science project examining the ways in which institutions and agencies are interacting and 'readying' themselves for regenerative medicine (RM), focusing mainly on the UK. It identifies the various institutional, legal, social and political factors that enable and hinder the development of new RM/stem cell therapies.

The complexity of developing such therapies from tissues, cells and genes presents a range of interconnected challenges relating to regulation, manufacturing, reimbursement and commissioning, and – the focus of this briefing – the adoption and delivery of RM therapies within healthcare systems. The readiness of organisations and institutions to implement RM products (i.e. their *institutional readiness*) is a key area of concern for RM advocates.ⁱ This briefing anticipates the key tensions associated with the clinical delivery of RM, and it provides some considerations for policy making to *improve the institutional readiness* for emerging RM therapies.

The challenge of clinical delivery

The introduction of novel therapeutic, diagnostic or administrative technologies into busy, resource-constrained healthcare systems is a challenging process. Successful introduction requires a solid business case, institutional and managerial support, active championing by frontline staff, time for training and reflective evaluation, and often, the implementation of supporting technologies.ⁱⁱ The introduction of RM technologies and techniques – which some commentators have suggested will constitute one of the greatest changes to the delivery of medicine in recent times^v - poses significant challenges above and beyond these issues.

First, the live tissues and cells that form the basis of many RM products are highly sensitive, and the shelf life for some products may be as little as a few hours. Specialised, costly infrastructures are needed for transporting products (in compliance with specific regulatory requirements) and for preparing products prior to administering. It is likely that many products, for example, will arrive at the clinic cryopreserved in vapour phase nitrogen, for which many hospital pharmacies are currently ill equipped. Similarly, hospital pharmacists (who are responsible for all medicines once they arrive at a hospital) will generally be unfamiliar with the handling of tissues and cell-based products and associated quality assurance protocols.

Second, the production of many RM products will entail new manufacturing and logistical arrangements. In addition to serving as the site of procurement of starting materials (cells and tissues) and the delivery of final product to the patient, the hospital may also become the

site of partial or full manufacturing of the product. This is particularly the case with autologous products derived from patient-derived materials. Consequently, sites within the hospital will become subject to national and European-level regulatory mechanisms that govern procurement, manufacturing and delivery of RM products. Adherence to these mechanisms requires costly expertise and infrastructure, such as a Good Manufacturing Practice (GMP)-licensed clean room for the production of Advanced Therapy Medicinal Products.

Third, on-site manufacturing will require expensive bioprocessing equipment such as cell separation and expansion systems, systems for viral transfection, and associated quality assurance systems. Many current bioprocessing systems tend to be labour intensive and require highly trained technicians, and emerging closed (automated) systems are high cost and require significant up-front expenditure.

Fourth, the production and delivery of many RM products will also require hospitals to act as a procurement service for a third party, such as a specialist commercial RM manufacturer. Contract arrangements for such services can be complex, requiring legal expertise and considerable time to compose, and it is unclear how quality assurance responsibilities and liabilities should be distributed among parties. Systems for ensuring traceability of human tissues (a regulatory requirement) are also needed.

And fifth, many emerging RM therapies are likely to be nationally commissioned by NHS England (NHSE) after appraisal by Clinical Reference Groups. Some high cost RM therapies, however, may be funded via risk-sharing reimbursement mechanisms. These would require careful, detailed measurement of social and clinical benefits. This would require investment in coordinated infrastructures for data gathering at clinical and other sites.

Finally, while these challenges will characterise all treatment centres, emerging RM therapies are diverse and will present varying levels of disruption. Some promising RM products will have important homologies with existing therapies, while the delivery of other, more novel therapies will require a coordinated inter-organisational response. The *institutional readiness* for emerging therapies will differ substantially.

Generally, such challenges relate to an incommensurability between existing healthcare delivery mechanisms which have emerged to support drug and device-based therapies, and the particular requirements of tissue, cell or gene-based RM products. The fact that RM therapies and bioprocesses for manufacturing RM products are, for the most part, still in the early stages of clinical research adds a layer of complexity: it is still not clear precisely what technologies, protocols, standards and skills will be required at sites of clinical delivery.

The UK Context: Proposed Cell & Gene Therapy Treatment Centres

Several reports aimed at identifying means of facilitating the emergence of RM in the UK have proposed the establishment of specialist cell and gene therapy delivery centres.ⁱⁱⁱ The proposed centres will consolidate resources at several co-ordinated clinical sites that are already pioneering the development and trialling of RM therapies, and which, then, have nascent RM manufacturing and delivery expertise. Examples of potential sites include hospitals in Edinburgh, Newcastle and London (University College Hospital and Guy's and St Thomas' Hospitals), all of which have made strategic investments in RM, and have access to GMP facilities with expertise in cell, tissue and gene-based product development. In particular, these centres would build upon the considerable expertise and infrastructure of haematological services and NHS Blood and Transplant (NHSBT), which have thus far provided an important springboard for innovation in RM.^{iv} It is envisaged that such centres of excellence would continue to pioneer the development and trialling of RM therapies, and in the process, would develop streamlined, coordinated systems and skill-sets for at-scale clinical delivery. Importantly, the consolidation of resources around such centres, and supporting coordination between them, would, it is suggested, facilitate the formation of standards for ensuring quality, safety and potency of RM products.

More recently the Advanced Therapies Manufacturing Taskforce has suggested that the UK government devote 30 million pounds, to be administered by Innovate UK, for the development of a national network of Cell and Gene Therapy Treatment Centres.^v These would be based at existing hospitals, and grants would

be awarded competitively perhaps initially to three institutions. The centres would represent a partnership between the NHS and industry, the former providing patient access, clinical expertise, and expertise in tissue and blood handling and transportation, and the latter providing the investment and manufacturing expertise. It is argued that the formation of such a network of centres would provide a sense of stability in the emerging RM industry, thus facilitating innovation within the UK: it would enable the consolidation of supply chains and data-collection infrastructure, and the development and testing of business models.

Lessons from elsewhere

Existing clinical services provide a useful precedent for proposed RM treatment centres, and for advancing the *institutional readiness* for RM more generally. Many emerging RM products have their origins in haematological services and are similar to existing haematological treatments such as Haematopoietic Stem Cell Transplantation (HSCT). Consequently, these services, along with the NHSBT and the Scottish equivalent (SNBTS), represent a vital reservoir of infrastructure for the emerging RM field. Clinicians and technicians within these services have considerable experience in procuring cells and tissues from donors, transporting this material, administering cell and tissue-based treatments, and preparing the patient. This means that they are familiar with the technical, administrative and importantly the regulatory aspects of this work. Because of this, commenters have suggested that these services represent a vital starting component of any proposed cell and gene therapy treatment centres. A useful example is the HSCT stem cell laboratory at the Royal Free Hospital in London. It is part of the Centre for Cell, Gene & Tissue Therapeutics, which includes a partnership with the hospital's Pharmacy Department. This means that all cryopreserved ATMPs are received by HSCT laboratory staff, rather than through the pharmacy.^{vi}

The implementation of risk-sharing reimbursement arrangements for the delivery of high-cost RMs can be informed by existing arrangements in the EU. In Scotland, some high-cost cancer medications are provided via an agreement in which the drug manufacturer is reimbursed only for those individual patients who

met certain clinical milestones. Similarly in Italy, dozens of high-cost treatments are provided under such systems, including the recently approved gene therapy Strimvelis for the very rare disease ADA-SCID (Severe Combined Immunodeficiency due to Adenosine Deaminase deficiency), developed by GSK in partnership with the San Raffaele Telethon Institute for Gene Therapy in Milan. These arrangements have required carefully coordinated data collection infrastructures including integrated electronic patient records. Italy has legislated to standardise the use of data registries that will support such arrangements.

Some RM therapies will represent highly disruptive innovations, entailing new patient pathways and requiring substantial new infrastructures and organisational forms. The current establishment of a national proton beam therapy programme in the UK provides a useful precedent. The programme has required a considerable capital investment from the Government and Trusts involved, as well as coordinated action from various agencies within the healthcare system. It involves the construction of bespoke facilities to house the technology, new training programmes for staff and information for patients, and appropriate commissioning mechanisms. The future implementation of some RM therapies, particularly those that differ markedly from existing treatments, will require similar levels of coordination across healthcare agencies.

Conclusion: priorities for policy

- **Policy should be informed by social science literature exploring the adoption of technologies, ideas and practices within healthcare settings (see notes ii & iv)**
- **It is necessary to comprehensively explore existing risk-sharing commissioning systems and the data-gathering infrastructures that support them. The standardisation of data registries may be an important step.**
- **A range of stakeholders, including the NHS Foundation Trusts, NHSE, NICE, Clinical Reference Groups, Clinical Commissioning Groups, patient advocacy groups and industry need to be engaged in development of proposed RM treatment centres. In particular, haematological services, NHSBT**

and SNBT have a wealth of important knowledge.

- **The formation of new RM services can be informed by similar precedents in other areas of medicine. A good example is the UK's National Proton Beam Therapy Service.**
- **The geographical distribution of proposed treatment centres should take into account patient concerns over ease of access.**
- **The centres will need to consider the diversity of emerging RM products. They should also reflect diverse disease areas such that any specific demands can be properly explored and so provide lessons for prospective centres elsewhere.**
- **Most importantly, how far such centres move flexibly to accommodate autologous and allogeneic clinical *and* business models will be central to any longer term prospects of 'scale-up' across the NHS.**
- **Clinical delivery challenges should be taken into account within future evaluation and revision of the relevant regulations, such as in the current evaluation of the European Directives on blood and tissues and cells (mainly Directive 2002/98/EC on blood and Directive 2004/23/EC on tissues and cells.**

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ⁱ *Institutional readiness* is an analytical term developed with the REGenableMED project. It refers to the capacity and willingness of key pre-existing organisations and inter-organisational structures to adopt, respond to and utilise novel technologies.

ⁱⁱ May, C. and Finch, T. (2009). Implementing, Embedding and Integrating Practices: An Outline of Normalization Process Theory. *Sociology* 43(3): 535-554.

ⁱⁱⁱ See: Regenerative Medicine Expert Group: *Building on our own Potential: A UK Pathway for Regenerative Medicine* (2015). Available at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/415919/build-on-potential.pdf; Advanced Therapies Manufacturing Taskforce report, November 2017, <http://www.bioindustry.org>

^{iv} Gardner, J., Higham, R., Faulkner, A. and Webster, A. (2017). Promissory Identities: Sociotechnical Representations & Innovation in Regenerative Medicine. *Social Science & Medicine* early access online.

^v *Advanced Therapies Manufacturing Action Plan: Retaining and Attracting Advanced Therapies Manufacture in the UK*. (2017). From the 'Medicine Manufacturing Industry Partnership'. <http://www.abpi.org.uk/our-work/mmip/Documents/Advanced-Therapies-Manufacturing-Taskforce-report.pdf>

^{vi} Lowdell, M. and Thomas, A. (2017). The Expanding Role of the Clinical Haematologists in the New World of Advanced Therapy Medicine Products. *British Journal of Haematology* 176: 9-15.