

# **Building on our own potential: a UK pathway for regenerative medicine**

A report from the Regenerative  
Medicine Expert Group





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# 1. Foreword

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In its report on regenerative medicine, the House of Lords Science and Technology Committee described “advanced therapies” as *“methods to replace or regenerate human cells, tissues or organs in order to restore or establish normal function. This includes cell therapies, tissue engineering, gene therapy and biomedical engineering techniques, as well as more traditional treatments involving pharmaceuticals, biologics and devices.”* Since living cell-based therapies have their own unique challenges with respect to translation and commercialisation, this report principally focuses on cell therapies, and in particular their role in regenerative medicine.

Regenerative medicine involves the use of some of the most advanced therapeutic technologies of the 21st century. The rapid pace of the supporting science is likely to see its application across ever increasing fields of clinical practice. The UK has already made a substantial investment in regenerative medicine through support by the Research Councils, by the National Institute for Health Research and particularly the NIHR, Biomedical Research Centres (BRCs) and Units (BRUs).

As with many other emerging technologies in the life sciences sector the UK has the opportunity to be the global leader in this area with an academic, clinical and industrial infrastructure to make it happen. Moreover, the NHS is an obvious partner in cultivating an environment that supports early development, adoption and spread of these new technologies.

Our report has the primary purpose of providing advice on what more needs to be done to bring this about. This will involve ensuring proportionate and streamlined regulation; an approach to product development that maximises the expertise in the academic, commercial and healthcare delivery sectors reflecting the shared objectives of all stakeholders; and a model for delivery to patients that builds upon the excellent work

that is already taking place in the UK. The members of the Expert Group hope its report describes a direction of travel that will place the UK at the forefront in the application of this exciting science.

I would like to thank the members of both the Group itself, and of the three sub-groups, for all their many contributions. I would especially wish to express my appreciation to the chairs of the sub-groups including Mr Keith Thompson (Regulation and Licensing sub-group), Dr Nick Crabb and Ahmed Syed (Evaluation and Commissioning sub-group) and Professor Chris Mason (Delivery sub-group) for all their work. Finally I wish to place on record the Expert Group’s thanks to the officials in the Department of Health, and in other government departments, for their excellent support as well as their timely and expert contributions.



**Sir Michael Rawlins**

Chair, Regenerative Medicine Expert Group

December 2014



## 2. Introduction

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In July 2013, the House of Lords Science and Technology Committee published a report of their inquiry into regenerative medicine. This called for a regenerative medicine expert working group to be established to develop an NHS regenerative medicine delivery readiness strategy and action plan, and report back to the Secretary of State for Health by December 2014. In their joint response to the report, on behalf of the Government, the Department of Health and Department for Business, Innovation and Skills agreed to this recommendation and the Regenerative Medicine Expert Group (the Expert Group) was convened, with a membership from across the UK, including representatives from each of the four countries. The Regenerative Medicine Expert Group was given the remit to monitor progress on the Government's response to the House of Lords inquiry; and to develop, in partnership with other stakeholders, a strategy for regenerative medicine in the NHS and provide an action plan.

This report is the culmination of the work carried out by the Expert Group. It provides an update on the progress that is being made to support the growth of regenerative medicine in the UK, for the benefit of NHS patients and the economy, and advice on what more needs to be done. The report, as is set out, follows the development pathway of a product from clinical trials, to commissioning through to routine use in the NHS.

The term 'regenerative medicine' refers to methods that replace or regenerate human cells, tissues or organs in order to restore or establish normal function. The term includes cell-based therapies, tissue engineering and gene therapy. In reality, the term can also be applied to established therapies, such as haematopoietic stem cell transplantation to treat life-threatening blood disorders, through to emerging new technologies that, for example, use cells to repair or replace damaged or lost tissue.

There is rapid progress being made across a wide spectrum of cell-based therapies, and whilst the report principally focuses on their use in regenerative medicine, the opportunity to realise the potential of cell therapy across the whole breadth of medicine should be seized.

Regenerative medicine is going to be important in future medicine – delivering step changes in the way we treat disease and making a significant economic contribution.

Economic benefit is an area where regenerative medicine could deliver. If we get the environment right, an emerging innovation ecosystem could support the growth of a healthy and robust regenerative medicine industry in the UK. Investment is happening. The UK Cell Therapy Manufacturing Centre, which will be based at Stevenage Bioscience Catalyst – an open innovation campus – will manufacture late phase clinical trial and commercial supply of advanced therapeutic medicinal products including cell and gene therapies. It will also incentivise the private sector to invest in UK-based firms and is anticipated to generate £1.2 billion of private sector revenue by 2020.

Benefits to the UK economy, however, will need to be won in an international market. That is why we need to be able to compete, and be open to partnership, at a national, European and international level. Latest figures from UK Trade and Investment show that, in 2012, annual revenue from regenerative medicine products surpassed the \$1 billion mark. The global regenerative medicine market is predicted to grow significantly.

The report takes a UK-wide view, unless otherwise specified, but accepts that different approaches may be needed for the adoption of regenerative medicine in healthcare that reflect the delivery systems in each country of the UK.

The Expert Group's evidence gathering and analysis were mainly delivered by three sub-groups dealing with: a) regulation and licensing; b) evaluation and commissioning; and c) delivery. The members and Terms of Reference of the Expert Group and members of each of its sub-groups are in the annexes to the report.



### 3. Executive Summary

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As is the case in most life sciences, the UK is well placed to consolidate and build upon its position as a world leader in regenerative medicine. We have the industrial base, the academic excellence and the clinical know-how that is necessary. We also know what success looks like, from the advances in the treatment of leukaemia, to building new tracheas and restoring eyesight after corneal damage. These great success stories show what can be achieved through the collaborative efforts of impassioned individuals. Much of this work is underpinned by the NHS. Its unique position as a single national healthcare provider, our ability to access patient data and an established logistics system are benefits that should not be undervalued.

Cell therapy developers from the academic community, and from industry, indicated to the Expert Group that the current system of multiple, and sometimes overlapping, regulatory advice should be streamlined. We therefore welcome the announcement by the four regulators in the field (the Health Research Authority (HRA), the Human Tissue Authority (HTA), the Human Fertilisation and Embryology Authority (HFEA) and the Medicines and Healthcare products Regulatory Agency (MHRA)) that the MHRA's Innovation Office will be the portal for a 'one-stop shop' service to provide a single point of access for all regulatory queries concerning regenerative medicines.

However, regenerative medicine operates in a global environment. Many countries, especially the United States and Japan, are keen players in the field and we need to ensure that we compete as well as collaborate. Within the European Union the European Medicines Agency (EMA) in most cases provides a single portal to the European market. Here, the international standing of the MHRA helps the UK retain its influence and also provides an avenue for international companies to gain a foothold in European markets, preferably with

the UK as their European home. That is why the report calls for the MHRA to press for an EU-wide consensus on the following points:

- The removal of any disparity in categorisation across the Member States for products which straddle the boundary between cellular therapies regulated under the EU Tissues and Cells Directive and those regulated as medicines under the Advanced Therapy Medicinal Products (ATMP) Regulations (somatic cell therapies, tissue engineered products, gene therapy products and combination products). This should include consideration of a European classification scheme coordinated by the EMA's Committee for Advanced Therapies (CAT) and subsequently adopted by all Member States.
- Changing the definition for the application of the Hospital Exemption Scheme from 'non-routine' to 'meeting an unmet clinical need where no authorised products are available'; and that use of an unlicensed product should be disallowed if there is a licensed product available and it meets the clinical needs of patients.
- Broadening the scope of the quality and non-clinical data certification scheme, when the ATMP Regulations are reviewed, to all types of applicants.
- A review of the cost structure both for scientific advice and to assist with the affordability of ongoing regulatory fees.
- The development of a risk-based model for point of care devices and/or relatively simple preparation steps, and a guideline for comparability assessment detailing quality control and validation requirements and suggesting solutions utilising practical case studies.

More needs to be done on standardisation of approach and reducing the regulatory burden wherever possible. This is especially important for clinical trials where further efforts are needed to make approvals, funding and recruitment more effective. The Expert Group proposes that regulators build on current initiatives and give further consideration to the following:

- Advice about the classification and associated requirements for trials involving gene modification should be made available to researchers through participation of the Department for Environment, Food and Rural Affairs (Defra) and the Health and Safety Executive (HSE) in the regulatory 'one-stop shop' for regenerative medicine.
- An evaluation of the 'one-stop shop' service after its first year that is informed by the experiences of its users, and the findings used to make necessary improvements.
- The possibility of incorporating applications needed for clinical research involving gene therapy products, genetically modified micro-organisms and genetically modified organisms (GMOs) into the HRA's existing Integrated Research Application System (IRAS) should be explored.
- Defra should examine best practice in applying GMO legislation in other EU countries to ensure that UK requirements are comparable and proportionate.

The report is clear throughout that every effort should be made to build on what is already in place. However, further steps are needed to ensure that standardisation of processes, and streamlined regulation, are guiding principles in advancing regenerative medicine. This is why the Expert Group advises that, given there is already a network of appropriately regulated centres with Tissues and Cells licences or Blood Establishment Authorisations, the UK should press for a consistent approach, throughout the EU, to allow the use of centres with either Tissues and Cells licences or Blood Establishment Authorisations for the

procurement and mandatory testing of blood components as starting materials for ATMP development.

There are difficulties for researchers in relation to the issue of 'excess treatment costs' which can be a barrier to carrying out clinical trials. The Expert Group strongly recommends that the funding for excess treatment costs for cell therapy trials, is reviewed by NHS England and the NIHR as well as by their equivalents in the other UK regions; and that a mechanism is found to ensure that meeting of these costs is not a barrier to clinical trials or the early adoption of technologies.

In order for NHS patients to benefit from regenerative medicines, robust and effective product evaluation has to be made to inform commissioning decisions. National Institute for Health and Care Excellence (NICE) guidance is essential in speeding up the adoption and spread of high value regenerative medicines in healthcare. However, applying the Institute's appraisal methodology, based on cost utility analysis, to products whose true value may not be known for many years can be challenging, due to the inherent uncertainty of estimating long-term benefit from evidence derived from short-term studies.

The Expert Group was therefore pleased to learn that NICE has agreed to undertake 'mock' technology appraisals on regenerative medicine products. We encourage the Institute to consider the findings from these studies with a view to assessing whether changes to its methods and processes are needed.

Evaluation and commissioning, as with all steps of the product development pathway, need to be supported by clear, up-to-date and accessible advice and guidance. NICE already provides scientific advice in many areas and the Expert Group calls on the Institute to develop advice focused on the needs of small and medium sized regenerative medicine companies and explore options for supporting their access to NICE scientific advice.

Initiatives such as this are important if we are to get innovative new therapies to patients in the fastest possible time. Early product evaluation

alone, however, is insufficient to speed up this process. Often, the risks of introducing a new, probably disruptive, therapy can be seen as too great for either the company (especially small and medium sized enterprises (SMEs)), or for the relevant healthcare commissioner. Addressing this issue is extremely important if we truly wish to see the NHS as a natural partner in innovation adoption and spread. The report therefore calls upon government to engage with key stakeholders with a view to developing an innovative business model that supports the early adoption of regenerative medicines. The Expert Group recognises that this will be difficult, in a time of budgetary constraints, and understands that imaginative solutions will be required.

To support these efforts, it will be necessary for commissioners and clinicians to have access to quality information, knowledge and advice. All four countries of the UK need to take account of this when developing services to deliver regenerative medicine. For example, NHS England has established a working group on regenerative medicine and the Expert Group calls for this to evolve into a formal 'Clinical Reference Group (CRG) for regenerative medicine' as new products are identified for consideration by NHS England. The CRG should include clinicians covering a wide range of specialties and experience in regenerative medicine (e.g. oncologists, cardiologists, ophthalmologists, orthopaedic surgeons and haematologists) in order to provide specific expertise, insight and advice on regenerative medicine products. Other UK countries should make comparable arrangements for their own healthcare systems.

The final, and arguably the most important, part of the journey, is embedding regenerative medicine in the NHS. In the initial phase, the use of regenerative medicines will be carried out in a few recognised Centres of Excellence located in leading hospitals. These are likely to have established relationships with Academic Health Science Networks and NIHR Biomedical Research Centres and Units. Coordination and collaboration in the use of regenerative medicines should be led by the centres

themselves, who should be champions as well as practitioners.

The Expert Group believes that the establishment of Centres of Excellence is essential if we are to build a concentrated, critical mass of knowledge, skills and therapeutic know-how that will be the foundations on which regenerative medicine can be established. The report recommends that the Department for Business, Innovation and Skills and the Department of Health, together with NHS England, engage with relevant partners to further develop the concept of Cell Therapy Centres of Excellence, and determine how they should be identified and the options for a collaborative development framework. This should include their role in improving the UK cell therapy clinical trials infrastructure as well as the delivery of treatments to NHS patients.

As already mentioned, the whole system delivery model of the NHS brings great benefits. The relevant UK blood service authorities already have cell processing, storage and delivery facilities and expertise alongside other, more local, delivery systems. A logistics system will need to be designed to respond to the specific requirements of regenerative medicine, from harvesting and processing of cells through to near application preparation.

Building on existing networks to address the needs of regenerative medicine should provide access to systems already in place and that are likely to be compliant with all necessary quality standards. The report therefore calls for the UK blood and tissue services in partnership with the Cell Therapy Catapult and other stakeholders, including industry, to undertake analyses of existing infrastructure to assess the options for the delivery of a cell therapy procurement, manipulation, storage and distribution network that supports the development of Centres of Excellence in cell therapy and its application. This should build on existing arrangements including, where possible, the global infrastructure provided by specialist carriers and be informed by the outputs from the Cell Therapy Catapult's Seamless Freight Initiative (a programme designed to aid the tracking and control of

cell therapies on their journey from a donor, through manufacturing and distribution, to an individual patient).

The success or failure of adoption of regenerative medicine in the NHS is also likely to be dependent on the level of education and training of its staff. Work will need to be done, particularly by the Royal Colleges, Health Education England and the healthcare systems across the UK, to ensure that appropriate training is available. To be effective, any education and training will need to encompass raising general awareness when introducing new technologies into healthcare, through in-depth requirements tailored to the needs of individual disciplines. Likewise, in developing the supply pipeline, the need to train scientific staff in translational research and manufacturing will be required. Once again, the UK is in an enviable position, as there is a reservoir of highly trained scientists already in place that could fill this need. The Research Councils and NIHR will also need to play a leading role in this matter.

The collection of validated, standardised robust data on the application of regenerative medicine, the patients who receive it and the products used will be essential in quality assurance and the long-term assessment of efficacy and safety. The report calls for consideration to be given to a central registry of patients treated with cell therapies; and for clinicians to provide follow-up information to capture healthcare outcomes. Furthermore, the Expert Group recommends that the format and use of the Cell Therapy History File, recommended in the HTA/MHRA report on joint working, and which has been further developed as a template by the Cell Therapy Catapult, should be implemented across the UK and promoted for EU-wide adoption.

Finally, to reflect the importance of regenerative medicines for future healthcare and economic growth, the Expert Group strongly recommends the establishment of a Ministerial Group, similar to the Ministerial Medical Technology Strategy Group and Ministerial Industry Strategy Group, for regenerative medicine.

## 4. Development

### 4.1 Introduction

The regulation of regenerative medicines is a vital part of their development. Properly and proportionately carried out, it provides assurances about quality, efficacy and safety as well as giving public confidence that appropriate procedures have been followed. In addition, it offers an endorsement for industry which is a *sine qua non* for opening up access to the market.

Where the cells have only been minimally manipulated and used for homologous treatment they fall under regulation by the EU Tissues and Cells Directive (EUTCD) and are regulated in the UK by the Human Tissue Authority (HTA). Such products are not classified as Advanced Therapy Medicinal Products (ATMPs) and are not regulated as medicines. Consequently, there is no legislative requirement for clinical trials, marketing authorisation, or manufacture in accordance with Good Manufacturing Practice (GMP) for these therapies. Under EUTCD, however, a controlled processing environment (air quality equivalent to GMP) is required, as is a mechanism for evaluating the quality and safety of these cell-based products. Within the UK, this is assessed via authorisation of a Preparation Process Dossier by the HTA.

Cell-based therapies that involve substantial manipulation and/or are used for non-homologous applications are classified as ATMPs. In the UK, the regulation of ATMPs is not the duty of a single body. Procurement and testing of starting materials may be regulated by the Medicines and Healthcare products Regulatory Agency (MHRA) under the EU Blood Directive (EUBD), the HTA (for non-gamete derived tissues and cells), or the Human Fertilisation and Embryology Authority (HFEA) (for human embryonic stem cells). Ethical approval for clinical research is the responsibility of the Health Research Authority

(HRA). Approval for clinical trials of medicines and devices in the UK is the responsibility of the MHRA; and the granting of marketing authorisation is made by the European Commission following a favourable opinion of the Committee for Advanced Therapies (CAT) and the Committee for Medicinal Products for Human Use (CHMP). For this category of medicinal product, in addition to the standard provisions for medicines legislation, there are specific EU ATMP Regulations.

Furthermore, at various points in the process, other agencies may have regulatory oversight, such as Defra (for genetically modified products) as well as the Health and Safety Executive (HSE) on release of products into the environment. Ensuring that the process is as streamlined and simple as possible, with adequate advice and support for developers seeking to take their products through the various stages of clinical development, is crucial.

### 4.2 Clinical trials – the approval process, infrastructure and funding

Clinical trials are authorised by the Competent Authorities of Member States. For the UK, the Competent Authority is the MHRA. Timely delivery of properly designed and powered clinical studies, usually over multiple centres, is key to facilitating the development of the cell therapy field whether undertaken by academia and the NHS or by commercial entities.

The HRA was established to streamline the approvals processes for both ethical review and governance arrangements. A feasibility study has demonstrated that an HRA approval, based on a single application, and consisting of an integrated assessment addressing legal and management aspects of research applications plus the Research Ethics Committee (REC) opinion, was feasible.

Therefore, the previous system of multiple applications will be replaced by a new process that will involve one application to the HRA, and an assessment conducted alongside the REC opinion, to provide an HRA approval. This will provide assurance to sponsors, researchers and any NHS organisations hosting research that the necessary legal and ethical aspects of the study have been fulfilled. The implementation of the process will be supported by mechanisms to ensure that this approval is accepted by others (including clarifying that responsibility for audit and inspection findings relating to the approval rests with the HRA rather than local Trusts). This will eliminate duplication of assessment, requirements for extra documentation or further checking. It will provide a basis for unifying the approval system for health research with other regulators and review bodies. The HRA aims to have the new process in place by December 2015.

To gather feedback on the environment for conducting cell therapy trials, a questionnaire was compiled by a working group of the Regulation and Licensing sub-group. It was sent to 42 organisations (15 industry and 27 academic) who have conducted cell therapy trials in the UK since 2011. A total of 19 responses (7 industry and 12 academic groups) were received commenting on a total of 45 cell therapy trials (23 industry and 22 academic) conducted in the UK over this period. Based on the data collected, in addition to the improvements discussed above, other key areas for action were identified. Difficulties had been encountered with costing templates not specifically designed for cell therapies and a lack of expertise on the ground able to handle cells. It was therefore suggested that specific costing templates and contracts be developed for cell therapy trials; and that there should be centralisation of cell therapy trial expertise and processes for efficient and timely trial start-up and recruitment.

Standardised contracts and costing templates are available for clinical trials generally. In order to maximise their value for regenerative medicine, specific guidance should be available on how to use them; and clauses covering requirements specific to cell therapy (such as

traceability) incorporated. This would improve the speed and ease of conducting studies in the UK and give researchers the ability to anticipate costs that should be included in grant applications. The NIHR Clinical Research Network (CRN) and the HRA are able to support development and use of these templates which are specific to cell therapy trials.

In order to deliver cell therapy clinical trials, it is recommended to explore ways to access the existing infrastructure to further coordinate and bring together individuals with specialist knowledge across the R&D structure for cell therapy trial delivery. This includes cell therapy suites, clinical trial research nurses and trial coordinators with the aim of reducing the cost and burden to the investigators and improving the speed and delivery of clinical translation for these therapies in the UK.

The question of whole pathway funding of clinical trials is also critical. As the development of cellular therapies progresses, the source of funding moves from the Research Councils and becomes eligible for NIHR support, through frameworks such as the NIHR early translational research infrastructure and the Efficiency and Mechanism Evaluation scheme (EME). Under this arrangement, a grant covers the research costs of conducting the study. However, protocols requiring additional overnight hospital stays for patients as well as additional treatments (such as immune-suppressive therapy) should be identified as either NHS Treatment Costs or NHS Support Costs. NHS Treatment Costs may be either in excess of standard treatment costs or in some cases a saving. The responsible commissioner for the service area (most likely to be Specialised Commissioning) should be involved in research planning before ethical approval has been given to define the costs or savings and the funding model to complete the study. Commissioners have to consider the funding of NHS Treatment Costs in the context of consideration of all competing calls on the commissioning resources. The diminishing availability of financial resources for service development is recognised as a potential real barrier to clinical trial progression. A potential

solution may be to direct specific funding allocated to NHS excess treatment costs for cell therapy trials outside of general commissioning.

**The Expert Group recommends that the process for consideration of funding for excess treatment costs for cell therapy trials is reviewed by NHS England, the Department of Health and the NIHR and their equivalents in the other UK countries; and that mechanisms are put in place to ensure that these costs are not a barrier to clinical trials.**

Further work still needs to be done to ensure other aspects of the regulatory approval process of studies specifically related to gene therapy products are also streamlined and effective. These include:

- Clarity on whether gene therapy products, specifically gene modified cells and gene therapy viral vectors, are classed as 'genetically modified organisms (GMOs)'; and whether their use in clinical trials constitutes 'Contained Use' or 'Deliberate Release'.
- Defra should ensure that UK regulations are comparable to those of other Member States and do not inadvertently place UK industry and academia at a disadvantage.

**The Expert Group therefore recommends the following actions:**

- **Advice about the classification and associated requirements for trials involving gene modification should be made available to researchers through the participation of Defra and the HSE in the regulatory 'one-stop shop' for regenerative medicine announced by the regulators in October 2014.**
- **Consolidated guidance on the requirements for cell and gene therapy trials involving GMOs should be produced.**

- **The possibility of incorporating any additional information needed for clinical research involving GMOs into the HRA's existing Integrated Research Application System (IRAS) should be explored.**
- **Defra should examine best practice in applying GMO legislation in other EU countries, so as to ensure that UK requirements are comparable and proportionate.**

### 4.3 Licensing

Medicines legislation requires that a manufacturer's authorisation, with any necessary Competent Authority oversight, is required for the production of any medicinal product. The requirement for such authorisation brings considerable resource implications for both producers and regulators. Whilst it is acknowledged that such oversight is necessary for medium to high risk manufacturing activities, the Expert Group considered that the requirement to hold a manufacturers' authorisation for low risk, and fully closed, operations could be overly burdensome.

As already described, market access is currently regulated by the EU's ATMP Regulations. This was introduced to provide tailored requirements for a novel class of product, and to allow for their safe and effective development. Within medicines legislation, there is a specific exemption for ATMPs which are prepared on a non-routine basis and used within the same Member State in accordance with a medical prescription for an individual patient ('the hospital exemption'). There is also a more general exemption for medicinal products (including ATMPs) which are used as unlicensed medicines ('specials') and which may only be supplied in order to meet the special needs of an individual patient in response to a *bona fide* unsolicited request from the treating physician.

Whilst the objective of the hospital exemption provision was to develop, and make available, products on a non-routine basis, many in industry are concerned that there is no uniform interpretation of the term 'non-routine'. This potentially allows the product prepared under the Hospital Exemption Scheme to continue to be used when a licensed product has reached the market. This has the potential to undermine the case for commercial investment to develop full marketing authorisation with all the data on quality, safety and efficacy that are normally required.

**The Expert Group recommends that unlicensed regenerative medicines should not be supplied under the Hospital Exemption Scheme where an equivalent licensed medicinal product meets the specific needs of a patient. Responsibility for deciding whether an individual patient has a special need which a licensed product cannot meet should be a matter for the clinician responsible for the patient's care.<sup>1</sup>**

Measures have recently been introduced to expedite the availability of novel medicinal products. The so-called 'adaptive licensing' (sometimes called 'staggered approval' or 'progressive licensing') pilot project was launched by the EMA in March 2014. Companies, including those developing ATMPs and who are interested in participating in the pilot, should submit ongoing medicine development programmes for consideration. The process will allow the early authorisation of a medicine, in a restricted patient population, followed by iterative phases of evidence gathering and adaptations of the marketing authorisation, to expand access to broader patient populations. The EMA has indicated that they will work with the various health technology appraisal bodies to ensure that licensing and reimbursement are better aligned and should use all opportunities to seek multi-stakeholder input during development and prospectively plan to use the existing flexibilities in the EU regulatory framework.

**The Expert Group recommends that the developers of regenerative medicines give serious consideration to seeking marketing authorisation through the adaptive licensing pilot scheme where appropriate.**

Within the UK, the Early Access to Medicines Scheme (EAMS) was launched by the MHRA in April 2014. This aims to give patients with life threatening or seriously debilitating conditions access to medicines, including ATMPs, that do not yet have a marketing authorisation and when there is a clear unmet medical need. The scheme is voluntary and the opinion from the MHRA does not replace the normal licensing procedures for medicines.

The quality and non-clinical data certification scheme is another of the measures introduced in the ATMP Regulations. It is designed to provide incentives for small and medium sized enterprises (SMEs) that have been involved in the first stages of the development of ATMPs but may not wish, or lack resources, to conduct clinical trials. Certification that the quality and pre-clinical aspects of the development conform to the relevant regulatory requirements is intended to help SMEs attract funds so as to facilitate the transfer of research activities to organisations with the capacity to further develop and market such medicinal products.

**The Expert Group recommends that the UK, through the MHRA, encourages the EMA to explore options to improve accessibility including the extension of the certification procedure to academic groups and not-for-profit-organisations.**

The Expert Group believes that there is a need to create a more favourable environment for ATMP developers working in an academic or non-for-profit setting and where the majority of clinical translational work is currently conducted. In addition to an extension to the Certification Scheme detailed above, fee reductions for scientific advice, and fee incentives to reduce the financial impact of post-marketing obligations, should be adopted.

<sup>1</sup> MHRA Guidance Note 14 - The supply of unlicensed medicinal products ("specials") 2014



## 4.4 Regulation

In March 2014 the European Commission published a report of its five-year review of the ATMP Regulations. In its conclusions the report recommended revising the requirements for the authorisation of ATMPs, to ensure these are proportionate and adapted to the specific characteristics of autologous products. The scope and extent of any revision to the ATMP Regulation are not yet clear.

**The Expert Group recommends that the UK, through the Competent Authorities, uses this opportunity to press for EU-wide consensus on the following:**

- **The removal of any disparity in categorisation across the Member States for products which straddle the boundary between cellular therapies regulated under the EU Blood Directive (EUBD) and the EU Tissues and Cells Directive (EUTCD) and cellular therapies which are medicinal products and regulated under the ATMP Regulation. Consideration should also be given to European classification coordination by the EMA's Committee for Advanced Therapies (CAT) to be subsequently adopted by all Member States.**
- **Broadening the scope of the quality and non-clinical data certification scheme, when the ATMP Regulations are reviewed, to all types of applicants.**
- **A review of the cost structure both for scientific advice and to assist with the affordability of ongoing regulatory fees.**
- **The development of a risk-based model for point of care devices and/or relatively simple preparation steps and a guideline for comparability assessment detailing quality control and validation requirements and suggesting solutions utilising practical case studies.**

The existing regulatory framework requires developers to establish an acceptable level of product comparability across multiple manufacturing sites. There appears to be a misconception, in the UK, that this requires evidence on comparability at each additional manufacturing site with associated costly clinical qualification studies. This is incorrect. The requirement is for developers and manufacturers to demonstrate, by the provision of data, that the manufacturing process is under appropriate control at each site. The Competent Authority then makes a case-by-case assessment, during the clinical trial and/or Marketing Authorisation assessment process, based on the data provided and the complexity of the manufacturing process as well as the robustness of the characterisation assays and release tests.

**The Expert Group recommends that this issue of product comparability across multiple manufacturing sites be considered by developers, early in the development programme of a regenerative medicine, seeking advice when necessary from the appropriate regulator.**

The Expert Group is aware that blood components as starting materials for ATMPs have been collected under both the EUTCD and the EUBD, with no consistency of approach across EU Member States. Developers in the UK have sought further clarification of this position as in certain circumstances they have been advised by the MHRA that they should procure and test these through blood establishments. In the UK there are only a very small number of licensed blood establishments. These have the primary responsibility of producing blood components for transfusion and limited resources to support the manufacture of ATMPs.

The MHRA and HTA have recently reviewed the legislation in the UK and agreed that blood components as starting materials for ATMPs can be procured through either licensed tissues and cells or blood establishments, given that recipients are afforded comparable levels of protection through either route.

**The Expert Group recommends that extra efforts be made to communicate the current Competent Authority position on blood components as starting materials for ATMPs.**

Because an agreed position does not appear to have been uniformly applied in the EU, the HTA has formally requested the EU Commission to work with the EU's Competent Authorities for both blood and tissues and cells to ensure that a consistent approach is adopted and applied throughout Europe. This should ensure that, in the future, Competent Authorities responsible for blood and/or tissues and cells take a consistent regulatory approach.

**The Expert Group also recommends that, given the existing network of appropriately regulated centres with Tissues and Cells licences broadly aligned with ATMP developers, the UK should press for a consistent approach throughout the EU allowing the use of centres with Tissues and Cells licences to procure and conduct mandatory tests on blood components that are to be used as starting materials for ATMP development.**

## 4.5 Traceability and Cell History File

There is a legal requirement for full traceability for all human starting materials and product contacting materials (media, reagents, plastics etc.) which could potentially affect the quality and/or safety of ATMPs. It is agreed that accurate and timely recording of all information on the manufacture of cell and tissue starting materials, as well as intermediate processing and cell banking of these cells, is necessary to ensure that all relevant information required for regulatory compliance is captured.

A Cell History File, recommended in the HTA/MHRA report on joint working, and which has been further developed as a template by the Cell Therapy Catapult, aims to complement the existing documentary requirements of both the EU Tissues and Cells Directive (2004/23/EC) and the Medicines Directive (2001/83/EC). The Cell History File is an evolving document and captures information at each stage of

manufacture. Although the use of the Cell History File will be optional, the template is designed to help developers of cell therapy products, especially groups without substantial regulatory experience, to meet and maintain regulatory compliance. Additionally, the Cell History File has commercial value as it can provide a complete picture of the source and development of the product.

The Cell Therapy Catapult has agreed to finalise the draft Cell History File and distribute it to interested parties for further comment. Once it has been finalised, the MHRA will take it to the EMA, and the Inspectors Working Group, for comment and hopefully adoption at a European level. Interest has also been expressed in expanding the use of the Cell History File to other jurisdictions such as the USA. The HTA will also be seeking feedback on this issue. It is envisaged that developers of tissue engineered and gene therapy products will also adopt the Cell History File concept and build on it as appropriate.

**The Expert Group recommends that the format and use of the Cell History File is proposed by the MHRA as an EU-wide template.**

Ensuring the quality of raw materials for the development of regenerative medicines is an area where the UK has the opportunity to build on what is already in place. For example, the UK Stem Cell Bank was established to provide a repository of human embryonic, foetal and adult stem cell lines for research. Its role is to provide quality controlled, reliable stocks of cells for researchers. It also prepares stocks of EUTCD-grade cell lines for use as starting materials for the development of cellular therapies. Similarly, the NHS Cord Blood Bank also has over 21,000 haematopoietic stem cell units processed and stored at the Filton site.

**The Expert Group recommends that consideration is given to how potential opportunities provided by the UK Stem Cell Bank and the Cord Blood Bank might be utilised as future base material for the development of allogeneic products.**

## 5. Assessment and adoption in the NHS

### 5.1 Introduction

There is reason to believe that regenerative medicine products will be cost effective, or even cost saving, despite high initial acquisition costs. The National Institute for Health and Care Excellence's (NICE's) technology appraisal methodology is likely to capture the essential features of regenerative medicine, provided there is sufficient clinical data. Under NICE methods and processes the benefit in terms of the increased quality of life gained is multiplied by the years for which the benefits will be enjoyed.

However, NICE has limited experience of appraising regenerative medicines. It previously appraised autologous chondrocyte implantation for cartilage repair and this is currently being updated.<sup>2</sup> NICE is also in the process of appraising a cell therapy for treating asymptomatic or minimally symptomatic metastatic hormone-relapsed prostate cancer.<sup>3</sup> However, it is accepted that there is uncertainty among stakeholders about whether the Institute's methodology is sufficiently flexible to incorporate all the features of regenerative medicine. For example, the initial response to a new cell therapy product could be assessed in phase III trials. However, the impact on long-term healthcare can be conjectured but not demonstrated for several decades. Establishing the certainty of the long-term impact of regenerative medicine interventions will be a great challenge for Health Technology Assessments.

### 5.2 Evaluation

To address this uncertainty, the Expert Group endorses the Institute's proposal to undertake one or two 'mock' technology appraisal studies, on exemplar regenerative

medicine products. Such studies could include T cell therapies where there are a number of products in development. The appraisals will assess, separately, early stage and late stage treatments; and include a range of sensitivity analyses (e.g. clinical effectiveness, dosing schedule and acquisition cost) and other parameters (e.g. discount rates) that might be needed in any potential modifications to the methodology. Given the unusual features of regenerative medicine products, we also recommend that NICE ensures the involvement of independent specialist expertise in appraising regenerative medicines.

**The Expert Group endorses the proposal that NICE should consider the findings from one or more 'mock' technology appraisals and whether changes to its methods and/or processes are required. Any appraisal should include expert advice.**

There are a number of potential barriers to the adoption, by the NHS, of the first regenerative medicine products to reach the market:

- It is likely that there will, initially, be high acquisition costs because of the nature of the starting materials, the complex manufacturing processes and the clinical development pathway.
- There is a lack of a clear pathway, and support infrastructure, for healthcare providers to use these novel, unfamiliar and relatively expensive products.
- There are likely to be uncertainties in estimating long-term clinical effectiveness by extrapolation of data from short-term clinical trials.
- The different approaches required in autologous or allogeneic use and different issues pertaining to base material, e.g. human embryonic stem cells (hESCs).

<sup>2</sup> <https://www.nice.org.uk/guidance/indevelopment/gid-tag446>

<sup>3</sup> <https://www.nice.org.uk/guidance/indevelopment/gid-tag346>

We believe that even following a positive recommendation for use of a product by NICE, healthcare providers may be slow to introduce and use new products and/or design and configure services. This possibility raises additional uncertainties, beyond the evaluation process, particularly for small companies, in forecasting potential reimbursement for these products.

### 5.3 Commissioning

As already discussed, whilst NICE's appraisal methods may be able to capture the features of regenerative medicine, there may be significant challenges in generating the quality of evidence required for robust assessment of their long-term impacts. This is because clinical trials are resource intensive to conduct, and may only be able to measure results in the short to medium term. They may also include relatively small numbers of subjects, particularly for therapies for conditions with low prevalence. In these situations, longer-term effectiveness can only be extrapolated from shorter-term clinical trial data based on professional judgement. Such judgements can be informed if an already established clinical database on similar products exists. However, in the absence of this experience, as is the case currently with the relatively immature nature of the regenerative medicine field, such judgements may be difficult to make.

NICE's current evaluation methods, together with pressures on the NHS's budgets, have reduced confidence, within companies, about the prospects for the acquisition of their products by the service. This is perceived as a major barrier to investment in the translation and clinical testing of prototype products and hence puts the advancement of a UK regenerative medicine industry at considerable risk. Without a business model that can facilitate adequate reimbursement, and without the prospect of earlier adoption in the NHS, UK industry will continue to struggle to bridge this gap. Recent developments at NICE and NHS England, stimulated by both the Expert Group and the UK Early Access to Medicines Scheme, are expected to result in more focus on

managing access to high value technologies, including regenerative medicines and cell therapies.

Mechanisms are needed to mitigate the risk to the NHS of displacing existing healthcare interventions by regenerative medicines where the evidence for clinical effectiveness may be less robust. One way to address this situation could be through wider risk sharing across the system. NICE might recommend the use of promising products by the NHS but with product developers agreeing to a lower initial acquisition cost; and then with subsequent further reimbursement conditional on the clinical outcomes achieved. The current patient access schemes operated by the Department of Health and NICE could thus be used to facilitate risk sharing and potentially be adopted, in conjunction with conditional approval, so that NICE could recommend a treatment subject to the collection of further evidence to demonstrate efficacy and cost effectiveness.

Risk sharing schemes, however, can be difficult to administer and may not provide sufficient commercial incentives to regenerative medicine companies or even be financially viable for SMEs. A more innovative approach, informed by experience in other countries such as Japan, would be to develop a system that provides early reimbursement to companies.

In England, this could support the principles underpinning NHS England's Commissioning through Evaluation (CtE) programme. This programme selects therapies for which evidence is limited, but where there is suggestive evidence of significant clinical benefit. This programme, too, demands the generation of further evidence of effectiveness.

**The Expert Group recommends that an innovative business model is developed between industry, government and the NHS, to support the early adoption of regenerative medicines in the NHS.**

There will be some regenerative medicines that receive marketing authorisation but are not selected for NICE evaluation because, for example, the treatment is only indicated for very small patient populations. In England,

these would be commissioned by NHS England if they fall within the remit of specialised services.<sup>4</sup> Clinical commissioning policies for specialist services are developed by Clinical Reference Groups (CRGs),<sup>5</sup> covering various medical specialties. Currently, there is no CRG for regenerative medicine and, instead, a cross-CRG picks up this area.

**Given the specialist nature of regenerative medicine the Expert Group recommends that NHS England's cross-CRG for regenerative medicine be maintained; and, potentially, further developed into a formal 'CRG for regenerative medicine' as new products are identified for consideration. This CRG should include clinicians covering an appropriate range of specialties and experiences in regenerative medicine in order to provide more specific expertise, insight and advice to other CRGs. The other UK health departments should also consider comparable arrangements.**

## 5.4 Advice and guidance

NICE provides scientific advice to companies, sometimes in conjunction with the MHRA, to help in the design of relevant clinical studies and in the development of economic models to provide evidence for a subsequent technology appraisal. To date, most clients have been major pharmaceutical and biopharmaceutical companies and feedback has been very positive. The cost to companies of such advice is generally in the region of £38,000 – £50,000, which would be prohibitively expensive for some regenerative medicine developers unless subsidised. NICE Scientific Advice has recently developed a 'lighter' and less expensive advice product for SMEs.

NICE also runs seminars on its evaluation processes and how to develop a value proposition. These have also had very good feedback from industry. A bespoke seminar for regenerative medicine could be developed and include both NICE and NHS England evaluation processes and reimbursement. This should include existing guidance materials such as the Cell Therapy Catapult,<sup>6,7</sup> evaluation and a commissioning pathways map for NHS adoption in England. NICE is developing further advice products that may be more suitable for SMEs, and is exploring options to support access to NICE scientific advice. Recent discussions with the Technology Strategy Board (TSB, now Innovate UK) indicate that companies might use funding from some TSB programmes to fund NICE scientific advice.

**The Expert Group recommends that NICE develops a scientific advice product, focused on the needs of SMEs developing regenerative medicines, and explores options for supporting access to this. Additionally NICE and NHS England, together with the Cell Therapy Catapult, should jointly develop and provide a bespoke seminar on evaluation methods and on how best to develop a value proposition for regenerative medicines.**

<sup>4</sup> As regenerative medicine products selected for NICE evaluation would generally include those for larger patient populations which could be commissioned by Clinical Commissioning Groups, those regenerative medicine products that are not selected for NICE evaluation.

<sup>5</sup> NHS England. Clinical Reference Groups for Specialised Services: a Guide for Stakeholders. <http://www.england.nhs.uk/wp-content/uploads/2013/03/crg-stakeholder-guide.pdf>

<sup>6</sup> Cell Therapy Catapult. Overview of Routes to NHS Adoption for Cell Therapies in the United Kingdom. <https://ct.catapult.org.uk/documents/10588/53886/Road+map+to+UK+market+access>

<sup>7</sup> Cell Therapy Catapult. UK Market Access Considerations for the Cell Therapy Industry. <https://ct.catapult.org.uk/documents/10588/75540/pdf/f77f964f-4c51-4fa2-a9df-42eac9a6f8ec>



## 6. Embedding regenerative medicines in mainstream NHS services

### 6.1 Introduction

As already discussed, whilst licensing, evaluation and commissioning are essential for ensuring the availability of new cell therapies, clinical impact and commercial success are also dependent on adoption by the NHS. The highly specialist nature of some of the resources and capabilities required to handle cell therapy products will require workforce development, education and training. Furthermore, plans need to be developed to ensure there is adequate capacity in clinical services such as apheresis units, in-patient beds and Intensive Treatment Units to support clinical trials.

There is also a need to ensure that there are standard operational procedures in place and cell therapy product quality assurance. This is especially so when delivering phase III clinical trials which are likely to be carried out in multiple centres. It will be essential that cell therapy products are delivered in an identical way in each centre.

Finally, the disruptive nature of adopting any emerging technology will need to be assessed and managed. The role of Centres of Excellence in addressing all these issues will be instrumental.

### 6.2 Therapy development and delivery

Already, there are centres emerging with experience in the development of regenerative medicines across a range of products and therapeutic indications.

The consolidation of investment and specialist resources, skills and services – through the establishment and coordination of a group of specialised Cell Therapy Centres of Excellence – would respond more effectively, and prove better value for money, than attempting to disperse the techniques across the NHS as a whole. Models similar to the Centres of

Excellence proposed by the Expert Group exist, or are being actively established, in the United States, Australia and Canada. In these jurisdictions, such Centres aim to evaluate cell therapies through clinical studies to obtain the evidence needed for establishing safe and effective therapies; and then to provide access and delivery of proven therapies to patients.

The Expert Group believes that the identification of Cell Therapy Centres of Excellence in the UK would help to provide the human and physical infrastructure, competencies and resources required to facilitate clinical development and adoption across a range of cell therapy products and clinical specialties.

The development of the proposed Cell Therapy Centres of Excellence needs to be based on the expertise and experience of NHS England, the NIHR including the NIHR Biomedical Research Centres and Units, Academic Health Science Networks, the HRA and existing initiatives such as the clinical research facilities and not-for-profit organisations (such as the Leukaemia & Lymphoma Research Trials Acceleration Programme).

Coordination of the Centres will be crucial in order to drive development and implementation and instil a degree of standardisation of approach. Key issues will include streamlining of clinical trial set-up and execution, a common approach to cell therapy manufacture and provision of a clinical central reference facility and evaluative analytics. The coordinating function should also facilitate and promote collaborative working among UK and internationally based cell therapy researchers, companies and relevant groups to encourage the optimal use of resources. Coordination of the Cell Therapy Centres of Excellence should be led by a coalition of the Centres and key partners and follow an operational model that accommodates both short and longer-term participation in programmes and projects. One of its primary objectives should be that of

inclusion, ensuring equitable opportunity for participation for industry, academia and clinical groups in the development of the Centres and their services.

The established Centres of Excellence for stem cell transplantation (and other types of therapies) could be future models for regenerative medicine. These Centres already work as a coordinated network supporting research, clinical development and treatment of patients. The experiences of these current Centres should be taken into account when considering Cell Therapy Centres of Excellence.

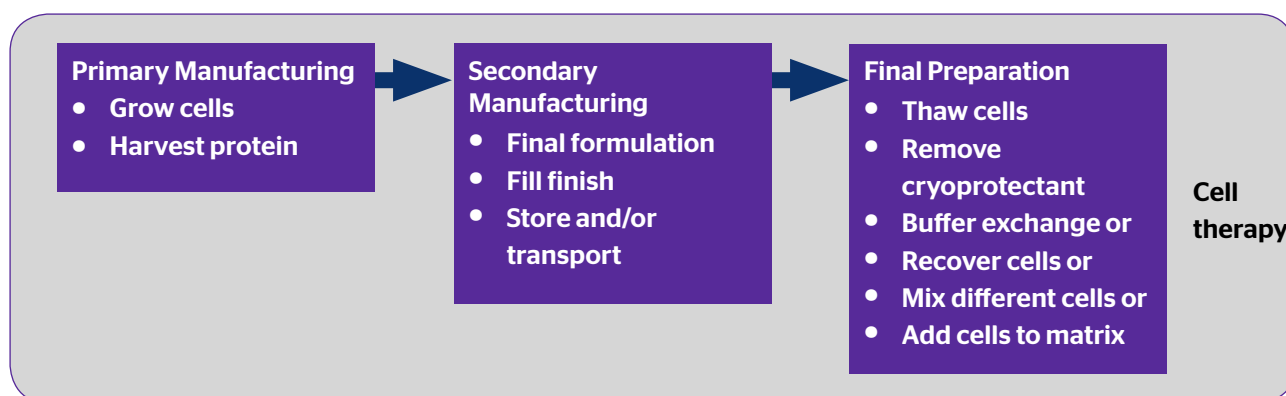
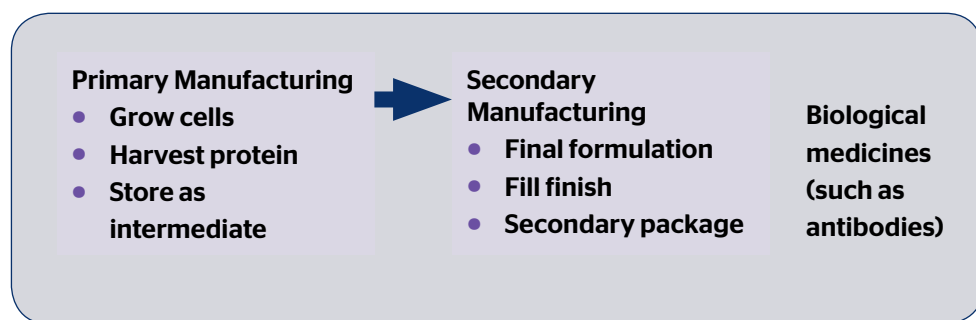
**The Expert Group recommends that the Department for Business, Innovation and Skills and the Department of Health engage with NHS England and other relevant partners, including the Cell Therapy Catapult, to further develop the concept of Cell Therapy Centres of Excellence and how they should be identified, and examine the options for their coordinated, collaborative development.**

### 6.3 Manufacturing

The ‘manufacture’ of regenerative medicines involves the preparation, testing, storage and distribution of blood, tissues and cells. Cell therapy manufacture is unusual because, unlike most other biological medicines, manufacture is in three, rather than two, phases.

For regenerative medicines steps one and two can be completed at geographically centralised facilities, although for autologous procedures this may be done locally. The final preparation step is likely to be conducted at the same site as where the therapy will be administered. Both autologous and allogeneic cell therapy products may require preparatory activities that go beyond reconstitution for administration. These include thawing cells, removing cryoprotectant, allowing cells to recover in a holding medium, or combining different cell types as preparatory steps to administration. As ATMPs are classified as medicines, the legal responsibility for this third manufacturing step falls to Pharmacy Departments where hospitals have on-site GMP-licensed facilities.

#### Manufacturing stages<sup>8</sup>



<sup>8</sup> Excluding the collection of starting materials



The lower risk nature of preparing cell product for administration, particularly when carried out in enclosed and/or automated facilities, and where the products are intended for immediate administration, raises the question of whether reduced GMP requirements and licensing may be appropriate. These issues need to be addressed to enable the embedding of cell therapy in mainstream NHS services.

**The Expert Group recommends that regulators review the requirements placed on final preparation and/or finishing of regenerative medicines when intended for immediate administration and the requirement for low risk manufacture to be carried out in GMP facilities. This should also take into account the role of hospital pharmacies and, in particular, how governance oversight may be most appropriately exercised over existing arrangements for blood banks, haematopoietic stem cell processing and cell therapy manufacturing facilities.**

## 6.4 Procurement, manipulation, storage and distribution

Cells or tissues for manufacture of autologous or allogeneic cell therapies may be procured locally, nationally or internationally. A strong network of tissue establishments currently operates within the UK and provides flexibility to therapy developers.

Products shipped fresh, or requiring a final preparation step, may have a short shelf life prior to use. This necessitates bespoke delivery and supply arrangements. The UK's Blood Services already have large processing, manipulation and storage capacity, as well as a logistics service, that covers the whole of the NHS. NHS Blood and Transplant, for example, has cell processing, manipulation and storage facilities at multiple locations in England.

Cell-based therapies also face a number of critical supply chain challenges. The ability to scale up and scale out manufacturing, across multiple locations, will be essential for any commercialised product. This will require a cost-effective supply chain, delivered through

integrated logistics from the collection of starting materials, through manufacturing, to storage and delivery of the finished product. Whether autologous, allogeneic or matched-allogeneic, the chain of custody needs to be clearly defined and the entire process tracked. A digital backbone that provides an unbroken audit trail, and complete visibility to therapy sponsors, manufacturers and physicians, is essential to effectively manage time and temperature sensitive therapies. UK Blood Services already have a wealth of expertise in this area which could be used to support regenerative medicine.

**The Expert Group recommends that the UK blood and tissue services, in partnership with the Cell Therapy Catapult and other stakeholders, including industry, undertake analyses of existing infrastructure to assess the options for the delivery of a cell therapy procurement, manipulation, storage and distribution network. This should be informed by the outputs from the Cell Therapy Catapult's Seamless Freight Initiative,<sup>9</sup> building upon the existing Blood Service competencies in this area and support the development of Cell Therapy Centres of Excellence.**

## 6.5 NHS staff training and continuing professional development

Health Education England (and its equivalents in the devolved administrations), together with the NHS and the Royal Colleges, are key to ensuring that there is an appropriately trained workforce for the development and use of regenerative medicines. Informal discussions with several Royal Colleges have been positive and, without exception, they agreed that there is a need to address education and training in regenerative medicine.

These, and other conversations, have highlighted to the Expert Group the urgency of planning training and education programmes

<sup>9</sup> This is a programme designed to aid in the tracking and control of cell therapies on their journey from a donor, through manufacturing and distribution, to the patient.

for NHS staff at all levels, from awareness raising to continuing professional development. There is already a template for how this could be achieved with the recent work that has been undertaken on education and training in genomics.

**The Expert Group recommends that an education and training programme for cell therapy should be designed, commissioned and rolled out across the appropriate NHS workforce.**

## 6.6 Patient and product data

Regulation requires full traceability from donor to recipient, and vice versa, to be maintained for a period of no less than 30 years. This requirement refers to all cell therapies, whether for clinical trials, fully licensed products or those supplied under a Specials Licence or Hospital Exemption.

Clinicians will have a key role in providing patient follow-up after treatment with cell therapies. As a consequence of the persistence of cell therapy products there may be a prolonged period in which adverse effects could emerge. Patient follow-up is essential for those treated with cell therapies, to allow for monitoring of efficacy and identify any adverse effects. The information collected as a part of this is also important to inform future cell therapy development.

Bespoke registries provide one important option and NICE, in collaboration with NHS England, is establishing an observational data unit to support data collection as part of the NHS England CtE programme.

**The Expert Group endorses the development of the NICE/NHS England observational data unit and its application to the collection of data on regenerative medicine products. The Expert Group also recommends that the Department of Health ensures that appropriate arrangements are in place for the very long-term follow-up of patients receiving regenerative medicines.**

## 7. Going forward, remaining engaged

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Regenerative medicine, in some disciplines such as treatments for leukaemia and anaemia, is already well established. However, the type of regenerative medicine that the report focuses on is still very much an emerging technology. The UK has many strong areas in academic centres, the NHS and industry; but there is considerable additional regenerative medicine investment in the USA and Japan. Also, Japan has recently introduced a Regenerative Medicine Law, aimed at accelerating the clinical trials process through a form of early conditional licensing.

In the Government response to the House of Lords Science and Technology Committee's Inquiry into Regenerative Medicine, it was envisaged that the Regenerative Medicine Expert Group would continue to monitor the future development of regenerative medicine.

However, to reflect the importance of regenerative medicines for future healthcare and economic growth (it is identified as one of the '8 Great Technologies' in life sciences and supported by the Department of Health, the Department for Business Innovation and Skills, the National Institute for Health Research, Innovate UK and the Research Councils) and to ensure that progress continues to be made, the Expert Group strongly recommends that a cross-sector UK group for regenerative medicine is put in place to monitor the development of regenerative medicine globally and provide a forum to engage with industry and others to ensure that the UK remains competitive in an area of life sciences that has true potential.

**The Expert Group recommends the establishment of a Ministerial Group, similar to the Ministerial Medical Technology Strategy Group and Ministerial Industry Strategy Group, for regenerative medicine.**



# Annex 1 – Recommendations from the Regenerative Medicine Expert Group

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## Development

1. The Expert Group recommends that the process for consideration of funding for excess treatment costs for cell therapy trials is reviewed by NHS England, the Department of Health and the NIHR and their equivalents in the other UK countries; and that mechanisms are put in place to ensure that these costs are not a barrier to clinical trials.
2. The Expert Group recommends the following actions:
  - Advice about the classification and associated requirements for trials involving gene modification should be made available to researchers through the participation of Defra and the HSE in the regulatory ‘one-stop shop’ for regenerative medicine announced by the regulators in October 2014.
  - Consolidated guidance on the requirements for cell and gene therapy trials involving GMOs should be produced.
  - The possibility of incorporating any additional information needed for research involving GMOs into the HRA’s existing Integrated Research Application System (IRAS) should be explored.
  - Defra should examine best practice in applying GMO legislation in other EU countries, so as to ensure that UK requirements are comparable and proportionate.
3. The Expert Group recommends that unlicensed regenerative medicines should not be supplied under the Hospital Exemption Scheme where an equivalent licensed medicinal product meets the specific needs of a patient. Responsibility for deciding whether an individual patient has a special need which a licensed product cannot meet should be a matter for the clinician responsible for the patient’s care.
4. The Expert Group recommends that the developers of regenerative medicines give serious consideration to seeking marketing authorisation through the adaptive licensing pilot scheme where appropriate.
5. The Expert Group recommends that the UK, through the relevant MHRA Competent Authorities, encourages the EMA to explore options to improve accessibility, including the extension of the certification procedure, to academic groups and not-for-profit organisations.
6. The Expert Group recommends that the UK, through the MHRA Competent Authorities, uses this opportunity to press for EU-wide consensus on the following:
  - The removal of any disparity in categorisation across the Member States for products which straddle the boundary between cellular therapies regulated under the EU Blood Directive (EUBD) and the EU Tissues and Cells Directive (EUTCD) and cellular therapies which are medicinal products and regulated under the ATMP Regulation. Consideration should also be given to European classification coordination by the EMA’s Committee for Advanced Therapies (CAT) to be subsequently adopted by all Member States.
  - Broadening the scope of the quality and non-clinical data certification scheme, when the ATMP Regulations are reviewed, to all types of applicants.
  - A review of the cost structure both for scientific advice and to assist with the affordability of ongoing regulatory fees.
  - The development of a risk- based model for point of care devices and/or relatively simple preparation steps and a guideline for comparability assessment detailing quality control and validation

requirements and suggesting solutions utilising practical case studies.

7. The Expert Group recommends that this issue of product comparability across multiple manufacturing sites be considered by developers, early in the development programme of a regenerative medicine, seeking advice when necessary from the appropriate regulator.
8. The Expert Group recommends that extra efforts be made to communicate the current Competent Authority position on blood components as starting materials for ATMPs.
9. The Expert Group also recommends that, given the existing network of appropriately regulated centres with Tissues and Cells licences broadly aligned with ATMP developers, the UK should press for a consistent approach throughout the EU allowing the use of centres with Tissues and Cells licences to procure and conduct mandatory tests on blood components that are to be used as starting materials for ATMP development.
10. The Expert Group recommends that the format and use of the Cell History File is proposed by the MHRA as an EU-wide template.
11. The Expert Group recommends that consideration is given to how potential opportunities provided by the UK Stem Cell Bank and the Cord Blood Bank might be utilised as future base material for the development of allogeneic products.

### **Assessment and adoption in the NHS**

12. The Expert Group endorses the proposal that NICE should consider the findings from one or more 'mock' technology appraisals and whether changes to its methods and/or processes are required. Any appraisal should include expert advice.
13. The Expert Group recommends that an innovative business model is developed between industry, government and the NHS, to support the early adoption of regenerative medicines in the NHS.

14. Given the specialist nature of regenerative medicine the Expert Group recommends that NHS England's cross-CRG for regenerative medicine be maintained; and, potentially, further developed into a formal 'CRG for regenerative medicine' as new products are identified for consideration. This CRG should include clinicians covering an appropriate range of specialties and experiences in regenerative medicine in order to provide more specific expertise, insight and advice to other CRGs. The other UK health departments should also consider comparable arrangements.

15. The Expert Group recommends that NICE develops a scientific advice product, focused on the needs of SMEs developing regenerative medicines, and explores options for supporting access to this. Additionally NICE and NHS England, together with the Cell Therapy Catapult, should jointly develop and provide a bespoke seminar on evaluation methods and on how best to develop a value proposition for regenerative medicines.

### **Embedding regenerative medicines in mainstream NHS services**

16. The Expert Group recommends that the Department for Business, Innovation and Skills and the Department of Health engage with NHS England and other relevant partners, including the Cell Therapy Catapult, to further develop the concept of Cell Therapy Centres of Excellence and how they should be identified, and examine the options for their coordinated, collaborative development.
17. The Expert Group recommends that regulators review the requirements placed on final preparation and/or finishing of regenerative medicines when intended for immediate administration and the requirement for low risk manufacture to be carried out in GMP facilities. This should also take into account the role of hospital pharmacies and, in particular, how governance oversight may be most appropriately exercised over existing arrangements for blood banks, haematopoietic stem cell processing and cell therapy manufacturing facilities.

18. The Expert Group recommends that the UK blood and tissue services, in partnership with the Cell Therapy Catapult and other stakeholders, including industry, undertake analyses of existing infrastructure to assess the options for the delivery of a cell therapy procurement, manipulation, storage and distribution network. This should be informed by the outputs from the Cell Therapy Catapult's Seamless Freight Initiative, building upon the existing Blood Service competencies in this area and support the development of Cell Therapy Centres of Excellence.

19. The Expert Group recommends that an education and training programme for cell therapy should be designed, commissioned and rolled out across the appropriate NHS workforce.

20. The Expert Group endorses the development of the NICE/NHS England observational data unit and its application to the collection of data on regenerative medicine products. The Expert Group also recommends that the Department of Health ensures that appropriate arrangements are in place for the very long-term follow-up of patients receiving regenerative medicines.

### **Going forward, remaining engaged**

21. The Expert Group recommends the establishment of a Ministerial Group, similar to the Ministerial Medical Technology Strategy Group and Ministerial Industry Strategy Group, for regenerative medicine.





# Annex 2 – Membership of the Regenerative Medicine Expert Group and its Terms of Reference

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## **CHAIR**

Air Marshal Paul Evans  
 Aisling Burnand  
 Alan Clamp  
 Carole Longson  
 Charles ffrench-Constant  
 Chris Mason  
 David Williams  
 Fiona Watt  
 Huw Williams  
 Ian Hudson  
 James Palmer  
 Janet Wisely  
 Keith Thompson  
 Marc Turner  
 Michael Hunt  
 Nick Rijke  
 Peter Thompson  
 Robin Ali  
 Robin Buckle  
 Ruth McKernan  
 Stephen Field  
 Steve Bates  
 Yvonne Wilding

## **Professor Sir Michael Rawlins**

Ministry of Defence  
 Association of Medical Research Charities  
 Human Tissue Authority  
 National Institute for Health and Care Excellence  
 University of Edinburgh  
 UK BioIndustry Association/University College London  
 Loughborough University  
 King's College London  
 NHS Blood and Transplant  
 Medicines and Healthcare Products Regulatory Agency  
 NHS England  
 Health Research Authority  
 Cell Therapy Catapult  
 Scottish National Blood Transfusion Service  
 ReNeuron  
 Multiple Sclerosis Society  
 Human Fertilisation and Embryology Authority  
 University College London/Academy of Medical Sciences  
 Medical Research Council  
 Pfizer  
 Welsh Blood Service  
 UK BioIndustry Association  
 Association of the British Pharmaceutical Industry

## **Government observers**

### **Northern Ireland Government**

Jackie Johnston  
 Heather Livingston

### **Scottish Government**

Gareth Brown  
 Robert Girvin

### **UK Government**

Mark Bale, Department of Health  
 Tom Barlow, Department of Health (December 2013 to August 2014)  
 David Griffiths-Johnson, Department for Business, Innovation and Skills  
 Colin Pavelin, Department of Health (from August 2014)

## Welsh Government

Caroline Lewis  
Christopher Pickett  
Andrew Riley  
Jenny Thorne

## Secretariat

Emyr Harries, Department of Health (December 2013 to August 2014)  
Kate Cornford, Department of Health (July to August 2014)  
Melanie Pepper, Department of Health (from August 2014)  
Benjamin Halliday, Department of Health (from September 2014)

## Regenerative Medicine Expert Group - Terms of Reference

1. The Regenerative Medicine Expert Group will consist of key individuals and organisations in the field of regenerative medicine, and in particular those with key expertise in its delivery in the NHS. It will develop an NHS regenerative medicine delivery readiness strategy and action plan. The group will also monitor and report on the effect of regulation on the development of regenerative medicines in the UK, addressing any concerns where possible.
2. To enable this, the Group will:
  - monitor progress on the Government response to the 2013 Regenerative Medicine inquiry;
  - develop, in partnership with other stakeholders, a strategy for regenerative medicine in the NHS;
  - put in place an action plan for delivering the strategy;
  - report by December 2014.
3. The Group will report its findings to other relevant committees, reporting on their impact on services and how they might be introduced into mainstream practice. This would include, for example, the Ministerial Industry Strategy Group (MISG) and the Ministerial Medical Technology Strategy Group (MMTSG).
4. All members of the Group will be appointed for a period of eighteen months (starting from the date of the first meeting). At the end of the eighteen month period, members may be re-appointed for an additional year, upon notification by the RMEG Secretariat.
5. The Group may commission other bodies or individuals to conduct research or provide papers to RMEG for consideration and decision making.

## Annex 3 – Membership of sub-groups

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### Regulation and licensing sub-group

#### Keith Thompson, Chair

Robin Ali  
 Steve Hall  
 Aidan Courtney  
 Chris Mason  
 David Williams  
 Nick Medcalf  
 Amit Chandra  
 Imogen Swann  
 Amy Thomas  
 Ian Rees

Joan Kirkbride  
 Sue Bourne  
 Glyn Stacey  
 Anthea Mould  
 Mark Lowdell  
 Michael Hunt  
 Natalie Mount  
 Jacqueline Barry  
 Paul Kemp  
 Nick Jones  
 Robin Buckle  
 Marc Turner  
 Andy Baker  
 Belinda Cole  
 Joyce Tait

#### Cell Therapy Catapult

University College London  
 Pfizer  
 Roslin Cells  
 University College London  
 Loughborough University  
 Loughborough University  
 Loughborough University  
 Human Tissue Authority  
 Human Tissue Authority  
 Medicines and Medical Healthcare products Regulatory Agency  
 Health Research Authority  
 Health Research Authority  
 National Institute for Biological Standards and Control  
 National Institute for Health Research  
 University College London  
 ReNeuron  
 Cell Therapy Catapult  
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NHS Blood and Transplant  
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Health Technology Knowledge Transfer Network  
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## Annex 4 – Glossary

Term	Definition
AHSN	Academic Health Science Network
Allogeneic	Where donor and recipient are different individuals
ATMP	Advanced Therapy Medicinal Products
Autologous	Where donor and recipient are the same individual
Biological Medicinal Product or Biologic	A product where the active substance is made by or extracted from a biological source rather than synthesised chemically
Biomedical engineering	The application of engineering principles and design concepts to medicine and biology for healthcare purposes (e.g. diagnostic or therapeutic)
Blood establishments	Any agency, body or organisation that is responsible for any aspect of collection and testing of human blood or blood components
BRC	Biological Records Centre
Cell History File	A file documenting the development of a cellular product, and ensuring that consent remains valid at all stages of the process: <a href="https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/326823/Cellular_Therapy.pdf">https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/326823/Cellular_Therapy.pdf</a>
Cell therapies	Therapy in which cells are administered to the body to the benefit of the recipient
Cell Therapy Catapult	The Cell Therapy Catapult is part of a family of Catapults which are not-for-profit, independent centres which connect businesses with the UK's research and academic communities. Each Catapult specialises in a different area of technology but they all offer innovative facilities and expertise to enable businesses and researchers to collaboratively solve key problems and develop new products and services on a commercial scale. The Cell Therapy Catapult was established in 2012 as a Centre of Excellence in innovation, with the core purpose of building a world-leading cell therapy industry in the UK. Supported by Innovate UK, its mission is to drive the growth of the industry by helping cell therapy organisations across the world to translate early stage research into commercially viable and investable therapies
Cell Therapy Catapult's Seamless Freight Initiative	Supply chain initiative for cell therapies

Term	Definition
Combined Advanced Therapy Medicinal Product (Combined ATMP)	Product that incorporates one or more medical devices or one or more active implantable medical devices and either its cellular or tissue part contains viable cells or tissues, or its cellular or tissue part containing non-viable cells or tissues is liable to act upon the human body with action that can be considered as primary to that of the devices referred to
CRG	Clinical Reference Group
Cryoprotectant	Agent used to protect cells, tissues and organs from damage that can occur during cooling and storing at very low temperatures
Defra	Department for Environment, Food and Rural Affairs
EUBD	European Union Blood Directive
EUTCD	European Union Tissue and Cells Directives
Gene therapy	Deliberate manipulation of genetic material into cells for therapeutic purpose
GMO	Genetically modified organism
Haematopoietic stem cell	Stem cell that gives rise to all red and white blood cells and platelets
HRA	Health Research Authority
HSE	Health and Safety Executive
HTA	Human Tissue Authority
MHRA	Medicines and Healthcare products Regulatory Agency
Ministerial Medical Technology Strategy Group	The MMTSG brings together government and the medical technologies and diagnostics industry to promote a strong and profitable UK-based medical technologies and diagnostics sector
NHSBT	NHS Blood and Transplant
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
Regenerative medicine	Process of replacing or regenerating human cells, tissues or organs to restore or establish normal function
Somatic cell therapy	Fully differentiated cell from an adult body or foetus
Tissue engineering	Use of a combination of cells, engineering, materials and methods to manufacture ex vivo living tissues and organs that can be implanted to improve or replace biological functions
Viral vector	Vector derived from a virus and modified by means of molecular biology techniques in a way as to retain some, but not all, of the parental virus genes



