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.[2] NICE is also in the process of appraising a cell therapy for treating asymptomatic or minimally symptomatic metastatic hormone-relapsed prostate cancer.[3] 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).

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

3 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.[4] Clinical commissioning policies for specialist services are developed by Clinical Reference Groups (CRGs),[5] 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,[6,7] 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.

4 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.

5 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

6 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

7 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.

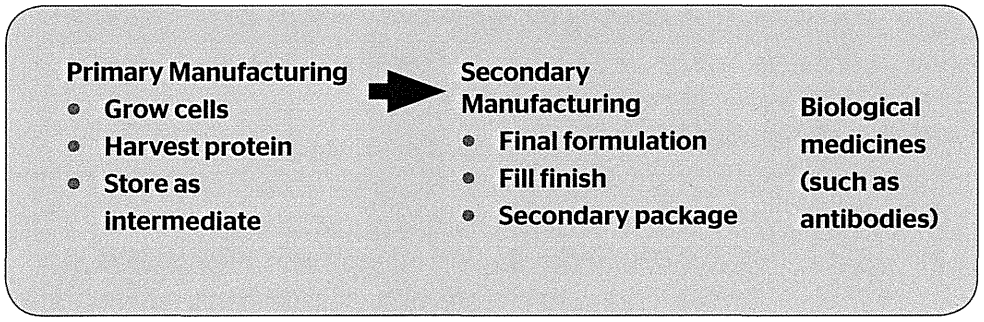
The Expert Group recommends that the Department for Business, Innovation and Skills and the Department of Health engage with NHS England and other relevant partners, including the Cell Therapy Catapult, to further develop the concept of Cell Therapy Centres of Excellence and how they should be identified,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

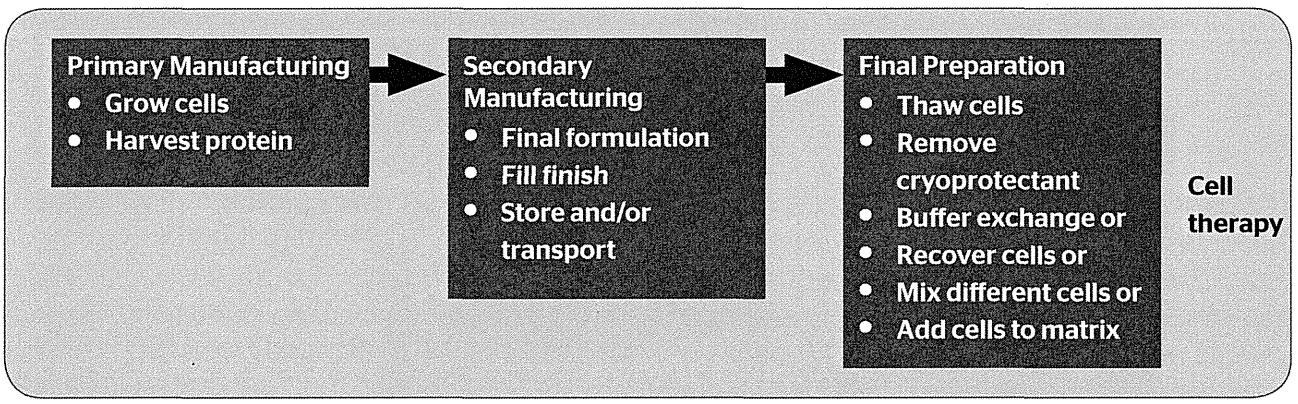
6.3 Manufacturing

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[8]





8 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,[9] 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

9 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

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

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

CHAIR	Professor Sir Michael Rawlins
Air Marshal Paul Evans	Ministry of Defence
Aisling Burnand	Association of Medical Research Charities
Alan Clamp	Human Tissue Authority
Carole Longson	National Institute for Health and Care Excellence
Charles ffrench-Constant	University of Edinburgh
Chris Mason	UK BioIndustry Association/University College London
David Williams	Loughborough University
Fiona Watt	King's College London
Huw Williams	NHS Blood and Transplant
Ian Hudson	Medicines and Healthcare Products Regulatory Agency
James Palmer	NHS England
Janet Wisely	Health Research Authority
Keith Thompson	Cell Therapy Catapult
Marc Turner	Scottish National Blood Transfusion Service
Michael Hunt	ReNeuron
Nick Rijke	Multiple Sclerosis Society
Peter Thompson	Human Fertilisation and Embryology Authority
Robin Ali	University College London/Academy of Medical Sciences
Robin Buckle	Medical Research Council
Ruth McKernan	Pfizer
Stephen Field	Welsh Blood Service
Steve Bates	UK BioIndustry Association
Yvonne Wilding	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 Peffer, 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

Regulation and licensing sub-group

Keith Thompson, Chair	**Cell Therapy Catapult**
Robin Ali	University College London
Steve Hall	Pfizer
Aidan Courtney	Roslin Cells
Chris Mason	University College London
David Williams	Loughborough University
Nick Medcalf	Loughborough University
Amit Chandra	Loughborough University
Imogen Swann	Human Tissue Authority
Amy Thomas	Human Tissue Authority
Ian Rees	Medicines and Medical Healthcare products Regulatory Agency
Joan Kirkbride	Health Research Authority
Sue Bourne	Health Research Authority
Glyn Stacey	National Institute for Biological Standards and Control
Anthea Mould	National Institute for Health Research
Mark Lowdell	University College London
Michael Hunt	ReNeuron
Natalie Mount	Cell Therapy Catapult
Jacqueline Barry	Cell Therapy Catapult
Paul Kemp	Intercytex
Nick Jones	Human Fertilisation and Embryology Authority
Robin Buckle	Medical Research Council
Marc Turner	Scottish National Blood Transfusion Service
Andy Baker	University of Glasgow
Belinda Cole	GSK
Joyce Tait	University of Edinburgh

Evaluation and commissioning sub-group

Nick Crabb, Co-Chair	**National Institute for Health and Care Excellence**
Ahmed Syed, Co-Chair	**NHS England**
Michael Hunt/Richard Moulson	ReNeuron
Fiona Watt	King's College London
Steve Kelly/Angela Blake	Pfizer
Greg Amatt	Chiesi Ltd
Siobhán Connor	Bupa
Philip Newsome	University of Birmingham
Alex Faulkner	University of Sussex
Andrew Webster	University of York
Anke Friedetzky/Holger Muller	Cell Medica
Matthew Durdy	Cell Therapy Catapult

Panos Kefalas	Cell Therapy Catapult
Andrew Stevens	University of Birmingham
Peter Bennett	Department of Health
Mike Ringe	Association of the British Pharmaceutical Industry
Paul Catchpole	Association of the British Pharmaceutical Industry
Nick Rijke	Multiple Sclerosis Society
Matthew Taylor	York Health Economics Consortium/University of York

Delivery sub-group

Chris Mason, Co-Chair	**University College London**
Stephen Ward, Co-Chair	**Cell Therapy Catapult**
Marc Turner	Scottish National Blood Transfusion Service
Emily Culme-Seymour	London Regenerative Medicine Network
Graham Lord	Guy's and St Thomas' NHS Foundation Trust and King's College London
Celia Moss	Birmingham Children's Hospital
Mark Bacon	Spinal Research
Paul Eldridge	The Walton Centre NHS Foundation Trust
Paul Johnson	University of Oxford
Anthony Mathur	Queen Mary University of London
Tony Pagliuca	King's College London and representing NHS England's Regenerative Medicine Cross-CRG
Paola Bonfanti	University College London
Charles ffrench-Constant	University of Edinburgh
Robert Hawkins	University of Manchester
Colin Pavelin	Health Education England and Department of Health
Huw Williams	NHS Blood and Transplant
John Smyth	NHS Blood and Transplant
Daniel Hollyman	NHS Blood and Transplant
Catherine McKenzie	Guy's and St Thomas' NHS Foundation Trust and representing the Royal Pharmaceutical Society
Mehdi Tavakoli	Health Technology Knowledge Transfer Network
Francisco Figueiredo	Newcastle University
Ian Pitfield	GSK
Paul Johnson	University of Oxford
Anne Black	Newcastle upon Tyne Hospitals NHS Foundation Trust