REGenableMED

A Social Science Analysis of Regenerative Medicine

Regenerative medicine in the United Kingdom

Reimbursement

Policy Briefing April 2016

"We have the academic excellence, some significant infrastructure, a growing community… what we don't have is a route to reimbursement" (Trade organisation representative)

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Overview

- Securing reimbursement has been identified as a major challenge in the field of Regenerative Medicine (RM).
- Manufacturers of RM therapies with marketing authorisations have struggled to obtain national reimbursement in the EU.
- There remains considerable variability in Health Technology Assessment (HTA) uptake within the EU, despite initiatives to improve harmonisation.
- Commentators questioned the suitability of existing HTA methodologies which led NICE to undertake a review of the technology appraisal of an RM therapy. There is a need to extend this analysis to a wider range of RM technologies.
- Priority should be given to gathering information on Clinical Commissioning Groups' positions on RM in service contracts and further support for co-ordination between the MHRA, NICE's the Office for Market Access and NHS England.
- Within the UK and across Europe there is a need to co-ordinate evidence derived from post-licensing schemes

Background

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

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

Reimbursement – general background

In the National Health Service (within England and Wales – there are separate processes for Scotland and N. Ireland) new healthcare therapies may be reimbursed in accordance with decisions at a local level via specific NHS Foundation Trusts and regional Clinical Commissioning Groups, or at a national level via a NICE Technology Appraisal recommendation (or for rare indications, a NICE Highly Specialised Technologies Evaluation). In addition, specialized commissioning exists outside of NICE through routes such as NHS England's commissioning of 'specialised services'.

Securing reimbursement has been identified as a significant hurdle for manufacturers within the field of RM, and as a potential hindrance to the field as a whole. RM therapies with current marketing authorization have struggled to obtain reimbursement arrangements throughout the EU: This has led to some scrutiny of existing methods used to inform commissioning decision-making at a national level: Within the UK, the Regenerative Medicine Expert Group (RMEG) report questioned the suitability of existing health technology assessment (HTA) methodologies used by NICE, suggesting that such methods may unfairly disadvantage highly novel therapies such as RM. There may be insufficient data for calculating cost and clinical effectiveness for such therapies, and some may have –at least initially – very high upfront costs. In response, an 'exploratory study of the appraisal of exemplar regenerative medicines products' focused on an emerging RM technology (CAR-T cell immunotherapy) was carried out by the Centre for Health Economics at York to assess the suitability of existing HTA

[i] Advanced Therapy Medicinal Products, including gene therapy medicinal products, somatic cell therapy medicinal products, combined products incorporating a medical device and tissue engineered products to restore or regenerate functionality

methodologies. The report[ii] published March 29 2016 concluded that the 'Technology Appraisals framework is applicable to regenerative medicines and cell therapy technologies' (p.15). This conclusion is especially important given the huge growth of research and commercial interest in CAR-T Cell therapies, especially for cancer. At the same time, the report acknowledges that there are still uncertainties and risk surrounding the area and there is a need for further methodological work to quantify uncertainty. The report also concludes that 'innovative payment methods, such as the lifetime leasing, may have a key role to play in managing and sharing the financial risk'. It is also important to note that an important consideration for reimbursement is budget impact and affordability which was outside the NICE report which was mainly taking the HTA rather than the actual payer perspective.

Other potential ways for navigating the reimbursement hurdle have also been suggested. These include establishing a specific fund for regenerative medicine (similar to the Cancer Drug Fund, where, unique in Europe, draft recommendations on the use of medicines can be given *before* they are licensed), and risk-sharing agreements in which various parties (providers, patients and/or manufacturers) share the initial costs. The move towards risk-sharing and 'managed entry' agreements is gathering pace as is the parallel process of adaptive licensing to bring new therapies more quickly to the clinic (such as the Early Access to Medicines scheme, and similar initiatives associated with 'accelerated access'[iii]). These schemes are very different from HTA procedures and vary considerably across Europe[iv]

More generally, there has been some discussion of moving towards a method of HTA assessment that could recognise the wider social value of a therapy ('value-based pricing' or 'value-based assessment'), which some commentators believe may be more appropriate for assessing RM therapies. However, wider societal considerations, if they were to be implemented, would not be selectively applied to a specific therapeutic category only (like RM) but across the spectrum; furthermore such approaches need refinement as in their current form they have been criticised for discriminating subpopulations on the basis of working age; therefore plans for their implementation have been halted across various countries including the UK. Some RM therapies have become available outside the NHS through private clinics, reflecting different criteria for assessment based on the formularies found in private health plans.

General European reimbursement climate

Reimbursement decision-making varies significantly among EU Member States. The degree to which HTA is used in decision-making, HTA methodologies, and the level at which commissioning decisions are made (i.e. regional or national) has been highly variable, creating a challenging and uncertain environment for RM manufacturers. ChondroCelect, for example, is reimbursed at a national level in Spain, Netherlands and Belgium, but has struggled elsewhere, particularly the UK (See below). For over 20 years there have been attempts to improve HTA harmonisation, and in 2004 the EU Commission and Council of Ministers declared HTA as a 'political priority'. The EU has actively engaged in HTA issues via various governance and research initiatives (such as AdHopHTA (2012- 2015)[v]; Advance_HTA (2013- 2015)[vi]; INTEGRATE HTA (2013- 2015);[vii] MedTechHTA (2013- 2015)[viii]; and SEED (2013-2015)[ix]. The emphasis is on limiting the gap between market authorisation and HTA, mainly by increasing early parallel dialogue and scientific advice between regulators and HTA bodies. Another trend is a movement towards "progressive HTA", which ranges from early awareness at the R&D stage, to a comprehensive HTA at the clinical stage, via 'Mini- HTA' and 'Rapid HTA', which may then result in investment and disinvestment.

[ii] https://www.nice.org.uk/news/press-and-media/nice-publishes-report-on-approaches-to-assessing-innovative-regenerative-medicines

[iii]https://www.gov.uk/government/organisations/accelerated-access-review

[iv]http://www.sciencedirect.com/science/article/pii/S0277953614007266

[v] http://www.adhophta.eu/

[vivi] http://www.advance-hta.eu/

[vii] http://www.integrate-hta.eu/

[viii] http://www.medtechta.eu/wps/wcm/connect/Site/MedtecHTA/Home

[ix] http://www.eunethta.eu/seed

In 2013 the EU HTA Network was established to develop a co-operative approach in the field. It has notably adopted an overall 'strategy for EU Cooperation on HTA'[x], which entails promoting the use of HTA in decision-making, improving harmonisation in HTA methodology across EU Member States, and reducing duplication. It receives technical support from EUnetHTA (European Network for HTA), a collaboration of stakeholders (including national HTA agencies) which provides a forum for sharing project details and which has produced several tools, especially a specific methodological framework (HTA Core Model) for producing and sharing HTA information. At this stage, the model has been used to undertake 13 'joint assessments' of therapies (non-RM), however medical device industry associations (Eucomed, EDMA, COCIR) have argued that Member States' response to such assessments (and other harmonising initiatives) has been too slow.[xi] The degree of coordination and harmonisation among Member States remains limited.

Such variability is highlighted by the way in which England and France are attempting to make ready their reimbursement regimes for RM. While England has a strong background in conducting economic analyses of therapies (via NICE's technology appraisals), it has moved more recently to supporting innovation and evaluation more generally via 'progressive value assessment' and 'productive risk sharing', whereas France, which has a strong background in assessment based on perceived public health impact, is moving in the opposite direction and adopting assessments based on more stringent economic analyses.[xii]

NICE guidance on ACI

The use of autologous chondrocyte implantation (ACI) for articular cartilage defects of the knee represents one of the more advanced developments within RM: two ACI products - MACI (Vericel) and ChondroCelect (Sobi/Tigenix) - have received EU marketing authorisation via the ATMP's regulatory framework, and ACI is one of the few RM therapy areas to have been subject to formal HTA. This serves as a useful illustration of the potential challenges entailed in securing reimbursement within the field of RM.

As stated above, SOBi/Tigenix have secured national reimbursement for their product, ChondroCelect, in Spain, Belgium and the Netherlands, but have struggled to do so in other member states. In the UK, three ACI products (MACI, ACI and 'the OsCell method', the latter developed at the Robert Jones and Agnus Hunt Orthopaedic Hospital) were subject to a formal technology appraisal as part of a review of NICE's earlier (2005) guidance in which ACI was not recommended except in the context of ongoing or new clinical studies. The new draft guidance on ACI was released for public consultation in March 2015, and stated that, based on the findings of the technology appraisal, ACI is recommended only in research (clinical trials and observational studies to measure long-term benefits), and not as a standard of care. The justification for the recommendation is that the evidence of clinical effectiveness was inconclusive: presented studies and reviews were heterogeneous and of mixed quality, some were poor due to small sample sizes and lack of adequate durations of follow-up. The assessment group also noted that the evidence had been limited by the changing nature of ACI technology over the last decade. Evidence of cost effectiveness was also hampered by uncertainties in long-term data.

The British Association for Surgery of the Knee (BASK) has expressed its disappointment in the recommendation and has encouraged patients who have undergone ACI to submit their comments of support to NICE.[xiii]

ACI is, however, available to UK patients via other means. More than one large insurance scheme, such as Bupa's, provides coverage for ChondroCelect, which is administered at several private hospitals. It has also been commissioned at a regional level by two Primary Care Trusts (now Clinical Commissioning Groups).

Emerging reimbursement expertise

While the RM industry may still be described as relatively immature, emerging patterns in enterprise activity are becoming apparent.

[x] (October 2014)

[xi] ec.europa.eu/health/technology_assessment/docs/ev_20151029_co09_en.pdf

[xii] Mahalatchimy, A. (in review) Reimbursement of Cell-based Regenerative Therapy in the UK and France. *Medical Law Review*

[xiii] http://public.baskonline.com/NewsArticle.aspx?tabId=7&n=55

Innogen/REGenableMED have characterised at least nine emerging business models within the field, broadly defined according to translational stages.[xiv] Amongst these are several business models which indicate that some enterprises and agencies are positioning themselves as having specific expertise in dealing with activities leading up to reimbursement issues. One such model is a 'Translational Services' model, a good example of which is the Cell and Gene Therapy Catapult (CGTC), which works with and consults for other agencies on navigating various aspects of the RM development process. Some well-resourced companies such as Organogenesis in the USA are deploying what could be called a 'fully-integrated' business model in which all aspects of translation are managed 'in-house', including reimbursement negotiation. Other agencies such as Videregen are adopting what can be described as an 'early market access' model by focusing on technologies for orphan designations and thus making use of adaptive regulatory channels (such as the Hospital Exemptions and Specials schemes) and specialised commissioning schemes for rare indications. These business model patterns indicate that the 'challenge of reimbursement' is having structuring effects on the RM field, and that an infrastructure of reimbursement expertise is emerging within the UK.

Emerging issues that REGenableMED is exploring

Several aspects of reimbursement are currently being explored by REGenableMED.

- An in-depth comparative legal analysis of the English and French reimbursement regimes as they relate to RM
- An analysis of the diverging ways in which reimbursement challenges are being framed amongst stakeholders in the public domain and how this may effect innovation pathways
- An exploration of flexible payment approaches and a clearer analysis of the possible payers that may be needed within the sector.

[xiv] Draft paper: 'Regenerative Medicine Business Models; Towards an Indicative Model and Typologies in the UK' The Innogen Institute, STIS, University of Edinburgh.

Conclusion: priorities for policy

In light of the issues highlighted above, the following *priorities for policy* include:

- Following the publication of the NICE report, extend the evidence base to a wider range of RM technologies beyond CAR T-Cell therapy
- Collect information on CCGs' positions on RM in service contracts
- Give further support to increasing the dialogue and co-ordination between the MHRA, the NICE Office for Market Access and NHS England
- Increase the role of intermediary organisations such as KTNs and AHSNs in developing reimbursement infrastructures.
- Support coordinated study of effectiveness of 'adaptive pathways' schemes applied to RM products
- Look at other countries experiences on how to take into account the wider value of RM technologies
- To consider how the Europe-wide EUnetHTA could take advantage of the long experience of HTA in the UK. Because of its expertise , the UK could take the lead or drive European cooperation here, especially since, after 2020, the EU Health programme cannot be used to fund EUnetHTA except for particular research challenges
- Finally, within the UK and across Europe there is a need to co-ordinate and avoid duplication in post-licensing (or conditional licensing) evidence generation schemes (such as the EU's IMI Get Real project).

REGenableMED Advisory Group:
Jacqueline Barry, Cell and Gene Therapy Catapult
Carol Bewick, Fight For Sight
Angela Blake, Pfizer
Edmund Jessop, NHS England
Panos Kefalas, Cell Therapy Catapult
Fiona Marley, NHS England
Kath Mackay, Innovate UK
Robert McNabb, Cardiff University
Magda Papadaki, Innovate UK
Bernie Stocks, NHS England
Mike Sullivan, Innovate UK
Ahmed Syed, NHS England

Further Information on the REGenableMED project:

www.york.ac.uk/satsu/regenablemed/

email/correspondence:

andrew.webster@york.ac.uk