**Are there specific translational challenges in regenerative medicine? Lessons from other fields**

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**Abstract**

***There is concern that translation ‘from bench to bedside’ within regenerative medicine (RM) will fail to materialise, or will be dismally slow, due to various challenges arising from the highly novel and disruptive nature of RM. In this article, we provide a summary of these challenges, and we critically engage with the notion that such challenges are specific to RM. It is important, we argue, not to overstate the exceptional nature of RM, as valuable lessons can be learned from elsewhere in medicine. Using several examples of technology adoption, we suggest that emerging RM products and procedures will have to work hard to find or create an adoption space if translation into the clinic is to be successful.***

**Key words**

Translational medicine; translational challenges; technology adoption; adoption space: regulation; reimbursement; clinical trials, manufacturing.

# Introduction

High expectation surrounds the emerging field of regenerative medicine (RM). It is hoped that RM will provide much-needed treatment options, especially curative treatments, for a range of ailments for which there is currently a high unmet clinical need [1], RM has also been framed as a driver of future economic growth. The UK government, for example, has identified RM as one of ‘eight great technologies’ which will generate significant economic prosperity and in which the UK can become a global leader [2]. Commentators have described regenerative medicine as a potentially disruptive, transformative endeavour [3], as RM therapies will ideally be curative and will replace a number of major pharmaceuticals and medical prostheses” [1].

This optimistic discourse is accompanied by a sense of concern. Aside from ethical concerns regarding some aspects of RM, some suggest advances in the lab will fail to be translated into clinical applications, or that such translation will be dismally slow [4]. Many RM therapies and procedures involve the use of live tissues and cells, which are substantially more complex in terms of their stability and safety than drugs and devices and thus pose a range of challenges for translation [5]. Many of these challenges are well-known to those working within the RM field, and in the UK they have been the subject of much deliberation [6-8] . Some relate to the difficulties of working with, scaling-up and transporting tissues and cells, and others relate to gatekeeping mechanisms within healthcare systems. They derive from having regulatory and commissioning schemes developed to accommodate pharmaceuticals and devices, and which may be poorly-suited to regenerative medicine products [9]. As with many highly innovative projects, then, the perceived ‘novelty’ of RM is both the subject of considerable optimism and a cause for concern. In response, authorities in several countries have launched initiatives aimed at accelerating translation, such as the Californian Institute for Regenerative Medicine (CIRM); the New York Stem Cell Science agency (NYSTEM), and the UK’s Cell Therapy Catapult [10].

In this paper, which focuses principally on the UK in respect to particular policy issues but which has wider empirical applicability across Europe, and in conceptual terms lessons of a more global nature, we critically interrogate the perceived ‘novelty’ and specificity of innovative developments within the field of regenerative medicine. We then compare developments within RM to other areas of medicine where new technologies have been introduced. In what follows we provide a concise overview of the major translational challenges within RM as they have been described in recent reports. Second, we suggest that while some of these may be particular to RM, others have been seen elsewhere, and thus we cannot say that it is the specific ‘novelty’ of RM that either hinders or facilitates translation. We argue that ‘novelty’ is context specific, rather than technically-specific. We use the social science notions of ‘adoption space’ and ‘technology identity’ [11, 12] to make this argument. It is important, we suggest, not to overstate the ‘specific’ nature of RM as important lessons can be learned from elsewhere in medicine. There are and have been other innovations within healthcare that have been perceived as novel according to a number of dimensions, and which have had highly uncertain futures. The degree to which these innovations have been successfully adopted has varied for a number of reasons. By exploring these reasons this paper aims to draw-out some useful lessons for those involved in the translational activities within the field of RM. We suggest, however, that while RM has translational challenges that have been encountered in areas other than RM, developments within the field are characterized by specific challenges arising from the perceived complexity, fragility and manipulation of living tissues and cells, not simply to treat but to cure diseases. There is little by way of precedent in how to manage these challenges.

# Overview of translational challenges in RM

In the UK there has been a concerted effort to create a healthcare system that fosters research and is receptive to innovative ideas. The NIHR Biomedical Research Centres were established to strengthen ties between academia and hospitals, the Academic Health Science Networks have recently been formed to create regional innovation alliances involving clinicians, academics and commercial partners, and NHS England has pledged to foster an environment in which innovation is “integral to the daily work of every member of staff” [13]. Against this backdrop, several initiatives have set about assessing elements of the healthcare system as they relate to regenerative medicine with the intention of identifying potential translational challenges [6-8, 14]. In this section, we provide a summary of the main challenges identified within these reports, particularly those identified in the recent report produced by the Regenerative Medicine Expert Group (RMEG) [6].

***Clinical trials***

The existence of a national health system, the close linkages with world leading academic centres, and the establishment of research infrastructure such as the NIHR Clinical Research Networks, make the UK a potentially attractive place to do clinical trials. There has been criticism, however, that clinical research within the UK is stifled by a “complex and bureaucratic regulatory environment”, in which investigators must navigate a fragmented system with multiple approval processes coordinated by different bodies with overlapping responsibilities [15, 16]. In addition to this criticism of the general clinical trials environment within the UK, particular challenges have been identified regarding regenerative medicine, principally related to the characterisation and manipulation of live tissues and cells for their therapeutic use, notably due to their natural intrinsic variation which poses particular demands in regard to ensuring their long- term stability [17].

This in turn means that complexity of the therapeutic agent create challenges for the determining of safety and efficacy of cell-based therapies [17, 18]. Safety concerns relate to the potential for tumorigenicity, contamination of cells and tissues with infectious agents, immunogenic and autoimmune rejection [19], or, in the case of gene therapies, unwanted integration of genetic material into host genome. Additionally, decisions need to be made about how much variation in cell-behaviour is tolerable, how dose escalations (in terms of numbers of cells and relevant safety measures) are to be defined, and procedures for tracking cell behaviour and movement within the body will all need to be developed [17] Endpoints in some clinical areas may be difficult to determine if patients have a range of morbidities [8], and the therapeutic effect of an intervention in some therapies – such as in some neurological disease areas – may not be discernible for several years [17]. Additionally, randomized double blind clinical trials will not be possible for therapies with small patient cohorts, or for invasive procedures involving tissue engineered products [5].The highly novel nature of some cell-based therapies has led to the view that more adaptive clinical trial designs that permit a range of variables should be explored [20].

The funding of clinical trials has also been identified as a challenge. Research funding will cover research costs, but trial protocols may entail additional treatment costs that may be in excess of standard treatment costs, and which will need to be negotiated with the responsible commissioner (the body responsible for planning and purchasing healthcare goods and services) [6]. This issue is not peculiar to RM, but it is more likely to be problematic for trials of highly innovative therapies with complex protocols which may entail various ‘non-standard’ treatment costs. Procedural difficulties have also been noted. For example, investigators have noted that much of the standard governance documentation relating to clinical trials within the NHS are not well-suited for the trialing of cell-based therapies [6]. Contracts and costing templates do not necessarily accommodate the added complexity of RM clinical trials (such as the stipulation of traceability), and existing expertise on cell therapy clinical trials tends to be dispersed. It could be suggested then that the speed and ease of clinical studies could be improved if there was a degree of centralisation of this expertise and if RM-specific costing and contract documentation were created [6].

***Regulatory challenges***

Within RM, the translational route from basic science to clinical application is covered by a myriad of EU legal instruments. These include mainly directives for the quality and safety of cell and tissue, directives for clinical trials, marketing authorisation regulation (the ATMP framework) and notably, guidelines on GMP [21, 22]. There is, then, an extensive regulatory burden on investigators and clinicians working within the field [5], much of which derives from the complexity of the therapeutic agent, as noted above [4, 17]. This burden is complicated by the apparent variation in how regulatory provisions are implemented within EU countries [23]: some have suggested, for example, that the hospital exemptions and other national schemes, such as Specials in the UK, are used more liberally in some Member States, possibly providing them with a competitive advantage. A lack of clarity regarding certain regulatory requirements has also been highlighted as an issue [21]. The current EU law does not explicitly answer the question of whether the same surgical procedure use of autologous ATMPs which have been substantially manipulated, or the non-homologous same surgical procedure use of tissues and cells, should comply with the medicinal products regulatory frameworks. Although they should be covered as they are not explicitly excluded from these frameworks, it may be unfeasible in [24]. Several well-established surgical procedures use tissue grafts that could meet these criteria but are not regulated as ATMPs, such as coronary artery bypass surgery using peripheral vein tissue, or some spinal fusion procedures. Alternatively, we find point-of-care procedures that are classified as ‘devices’ but which produce ‘regenerative cells’ intra-operatively [25].

The regulatory climate of RM, then, is a cause of some uncertainty and requires particular skills to navigate [4, 5]. Partly in response to this, the Committee for Advanced Therapies has been created at the European Medicines Agency level, and at the UK level the MHRA and HTA have established a one-stop-shop for regulatory advice service for RM. Here, investigators and manufacturers can seek advice regulatory aspects covered by a number of different bodies (HTA, HFEA, MHRA and EMA). Commentators have also suggested that adaptive licensing, such as that employed in Japan, may be necessary for RM [7]. Additionally, commentators have argued that the apparent heterogeneity across the EU, and the uncertainty this then creates, can be addressed through greater coordination between the EMA and national agencies.

## Manufacturing, scale-up and logistics

Some areas of RM particularly those using bone-marrow derived stem cells [26], have been able to make use of existing infrastructures (such as blood transfusion and transplantation networks) for cell procurement, selection, and preparation. However a significant challenge for RM (such as those utilising pluripotent cells) is a lack of suitable infrastructure for producing the quantities of product that would be required for phase III trials or commercial use. The design of such infrastructure is greatly dependent upon a detailed understanding of cell biology and cell-niche interaction. Maintaining and expanding cell lines requires tightly controlled extracellular conditions, as slight changes can affect the safety and potency of cells [27, 28]. Upscaling thus poses significant challenges [29]. Expansions processes may favour the growth of particular cell subtypes over others, thus reducing or increasing heterogeneity within a cell line in such a way that potency is affected. Undifferentiated cells may need to be identified and eliminated as they may pose teratoma or teratocarcinoma risks *in vivo* [27]*.* Cells within an expanding line may also undergo genetic and epigenetic changes [30]. Suitable bioreactor and cell expansion systems are therefore required that enable the production of large quantities of product while maintaining delicate extracellular conditions [27]. Assay systems for determining the characteristics of expanding cell-lines in real time are also needed [16].

Some cells and tissues, particularly those autologous cells and tissues used in ‘clinician-led’ [31] treatments as part of surgical procedure, will be extracted and prepared in facilities that are near-at-hand to the clinic. Indeed, semi-automated ‘point-of-care’ systems are being developed for such procedures [25, 27]. The implantation of other cell-based therapies, however, will require new logistical infrastructure and manufacturing approaches [29]. Products will need to be transported to the clinic in short time frames and in some cases across considerable distances: some commentators have suggested this will require ‘Intelligent’ transport systems [32], perhaps with smart sensors to monitor and secure quality assurance. Manufacturing facilities are likely to be positioned to make use of existing transport links, (such as the Cell Therapy Catapult’s proposed manufacturing facility in Stevenage, UK [33]). An additional hurdle that has been identified is the lack of ‘Qualified Persons’ (QPs) with the appropriate accreditation to receive cell-based products at clinical sites [7].

## Reimbursement & commissioning

Securing reimbursement has been identified as a major challenge, with some reports suggesting that current health technology assessment methods used by NICE are inappropriate for RM products [7]. The current ‘value-for-money’ assessment used by NICE, which compares the cost of the proposed therapy with a comparator and which involves a sensitivity analysis taking account of particular uncertainties, may disadvantage novel therapies such as RM with high upfront costs and for which there is limited information on long-term clinical effectiveness [34] .. Some RM therapies, it has been noted, are more akin to transplantation procedures than drugs [7], and will have high upfront costs but overall long-term savings [6]. It is also likely that the initial costs of RM therapies will be high, but will reduce overtime as manufacturers are able to improve efficiencies [7]. Additionally, it may not always be possible to find a suitable comparator for highly novel therapies. In order to test the suitability of NICE’s current method of appraisal the RMEG has recently commissioned a study that assesses the application of the NICE methodology to RM, and as a means of overcoming the reimbursement hurdle, the RMEG has recommended the development of innovative business models which would entail sharing financial risk between the government, commissioners, and manufacturers [6, 10]. One possible approach here could be to consider managed entry agreements seen in other countries, such as that used in Japan. A performance-based commissioning scheme may also be suitable.

Some RM products and procedures, which currently include several of those that are further progressed through the translational pipeline, will target small groups of individuals with orphan diseases [35, 36]. These will be eligible for specialised commissioning, with an appraisal route which is perhaps less challenging criteria, though the budget for such commissioning is limited. One possible problem here is the lack of expertise on RM among clinical reference groups (which provide consultation for specialised commissioning) [6]. In light of this the RMEG has recommended the establishment of an RM-specific clinical reference group under the auspices of Commissioner NHS England [6].

## Implementation within the clinic

Ultimately the success of a product or procedure depends on its being prescribed by clinicians and implemented within hospitals [37]. Several challenges have been identified that may hinder the implementation of RM products and procedures within the clinic. Obviously the successful creation of a RM service will require health professionals with sufficient training; without a clear rationale for the therapy, health professionals may lack motivation [6]. Generally a clear business case for the therapy will also be needed to gain the support of hospital managers, and this will depend upon the formulation of payment codes (or ‘tariffs’ in the NHS) or the flexibility of payment codes. Additionally, the new RM product or procedure, along with all the supporting technological infrastructure and protocols, will somehow need to be integrated within existing clinic workflows [6].

In response to these challenges the RMEG has recommended that specialist Cell Therapy Centres of Excellence be formally recognised and established. The basis of these would be the established Centres for Excellence in stem cell translation, and they would contain the appropriate infrastructure and experts with the specific skills for researching and implementing cell therapies [6].

# *The ‘valley of death’*

The challenges outlined above make for an uncertain context for innovation. Commentators have suggested that this uncertainty is discouraging for potential investors, particularly venture capital and large industry which are seen as necessary for translation and eventual widespread adoption of some cell-based therapies [38]. Much of the commercial activity within the RM field tends to be small enterprises with high levels of clinical and technical expertise [39] but with potentially limited access to expertise on regulatory and reimbursement issues. For these reasons, developments within the RM field are considered to be highly susceptible to the so called ‘valley of death’ that links initial investment and product development with downstream business success and eventual payoff [10]. Thus, authorities in several states have intervened in the field with the intention of facilitating translation and commercialisation – the establishment of CIRM, and the establishment of the Cell Therapy Catapult in the UK, are examples of this.

Of course such ‘accelerator’ initiatives are by no means unique to regenerative medicine. In what follows, we critically engage with the notion that RM and cell-therapies are especially novel with particularly highly uncertain futures. Additionally, drawing on various studies of technology adoption conducted within the social sciences, we draw-out parallels between RM and other medical innovations which have also had highly uncertain futures. These provide useful examples that shed light on the way in which translation within RM may be encouraged.

Figure 1 below summarises the argument so far. It outlines the principal challenges, some of the ways in which these have been or could be addressed, and crucially, whether these can be seen to arise in settings other than RM. We have suggested that in terms of the latter, issues to do with appropriate infrastructure and the logistics of delivery, reimbursement challenges, and clinical implementation are seen in a wide range of contexts. Figure 1 identifies three areas where we suggest the field faces especially challenging issues: these relate to the production, stabilisation and use of live cells and tissues, their complex and often uncertain regulatory definition and their manufacturing/scale-up. It is the *combination* of these three features that reflect the perceived complexity and fragility of the various RM therapeutic products not found elsewhere.

**Figure 1 Innovation challenges and their specific relation to RM**

(insert Table here)

# 3. Novelty, technology identity and adoption space

It is clear that some developments within RM differ from other areas of medicine (drugs and pharmaceuticals) in some important ways [40]. The fact that the mode of action of RM products and procedures derives from live cells and tissues which are fragile and unstable is one important difference, particularly given the challenges this entails for manufacturing [17, 27]. The manufacturing and scale-up systems required for producing large quantities of tissues and cells will be quite unlike those used to produce large quantities of pharmaceuticals or those used to produce devices [29]. Additionally, the ‘particularity’ of RM has, in effect, been reified by the ATMP framework that will regulate most developments within the field [41, 42]. However, despite these areas of difference, it is important to understand ‘novelty’ as being context-specific, rather than technology-specific. Novelty, in other words, is a matter of perception, and it is an aspect of what can be called the technology’s identity.

In their study of the adoption of early-emerging technologies within the NHS, Tomlin and colleagues noted that a technology would acquire a particular identity that largely depended on what they described as its ‘adoption space’ [11, 12]. The adoption space of a technology refers to both the wider, social-political environment and the specific, institutional context in which the technology is being mobilised, the latter comprising material-technical elements (other technologies and tools) and social elements (professional interests, institutional goals etc). Together these macro and micro elements frame a technology in a particular way: they foreground certain qualities of the technology and imbue it with meaning and symbolism, and the technology thus acquires an ‘identity’ as being, for example, ‘novel’, ‘revolutionary’, ‘prestigious’, or ‘difficult to implement’, ‘risky’ and so on. These identities are thus relational, they may differ across institutional or clinical contexts, and as aspects of the adoption space change, so too can a technology’s identity [11]. Importantly, Tomlin and colleagues argue that:

*‘…attitudes, practices, interactions and events, together with the technology's material features, shape technology perceptions in ways that are instrumental in decisions about its use* [11]*.*

For stakeholders working within the field of RM and who are interested in seeing the field progress, there are some advantages to understanding how these processes play out. It cautions us against prematurely bracketing RM as being a distinct field with specific translational challenges that require unique solutions, and it encourages us to draw parallels with technological development and adoption (successful and failed) in other areas of medicine. Emerging biotechnologies in general tend to be perceived as having three principal features: uncertainty, ambiguity and transformative potential [43], so, drawing parallels with other examples here and elsewhere can provide insights on how to facilitate developments within the RM field. There is of course considerable variation within the field of regenerative medicine, and some therapeutic developments are notably further along the translational pathway than others. This can, in part, be described by the degree of homology between these therapeutic developments and other, existing therapies and procedures from which expertise and infrastructure can be derived. Examples include limbal stem cell transplantation [44] and the use of hESC-derived retinal cells for the treatment of macular degeneration [45]. In the following section, we provide accounts of several healthcare technologies that have been adopted with varying degrees of success. These particular examples have been included because they share similar features with RM and because each case reflects a typical problem faced by emerging technologies and what was done to address it. They address the two challenges that are not specific to RM (the reimbursement and the implementation in the clinic challenges), and they provide outcomes that we may see for RM in the future. Other examples could have been used which share similar features but which have quite different outcomes (for example, in terms of ‘high-cost’, smart infusion pumps could have been a comparator to the robotics case). Our point is that the outcome reflects the ways in which those involved define and respond to the possibilities provided by the new technology: the technology can never ‘speak for itself’ [46, 47].

# *Examples of challenges of adoption of other technologies/therapies*

Our first case relates to the matter of reimbursement. A recent decision by NHS England to commission a high-cost biologic for an ultra-rare disease is also useful to explore here. In September 2013, NHSE agreed to commission eculizumab (traded as Soliris) for the treatment of atypical haemolytic uraemic syndrome at a cost of around £340,200 per patient per year (treatment is for a lifetime), and at an initial cost to NHSE of £57.8 million per year [48]. The case provides a useful example of how a product that offers clear clinical advantages over the existing standard of care, but which is unlikely to be deemed ‘cost effective’ according to current thresholds, might be appraised (one analysis suggested that the Incremental Cost Effectiveness Ratio (ICER – a comparative measure of the cost effectiveness) for this product over the current standard of care was £521,000 per Quality of Life Years (QALY) gained [49]). It is also a therapy area that, as with some potential developments in RM, has some uncertainties which can deleteriously impact the appraisal process. For example, clinical effectiveness information was based on a small numbers of subjects, and due to the limited population of sufferers, there is limited data on the natural history of the disease and the cost of current care for patients. The manufacturer, Alexion, argued in their submission that because the drug is targeted at an ultra-rare disease, the appraisal should place more weight on a ‘value for money’ rather than incremental cost effectiveness, explicitly drawing on NICE’s *Interim Methods of the Highly Specialised Technology Programme* [50], and, they argued, ‘value for money’ should be appropriately weighted to support improved clinical outcomes and not just lower expenditures [51]. The manufacturer was able to provide a detailed account of the burden of disease to patients, families and careers, supported by submissions from a relevant patient support group, and data from several trials and patient registries were used to illustrate clinical effectiveness of the treatment [51]. It is highly likely that there will be developments within RM that, such as eculizumab, will target small population groups, will offer clear clinical benefits over the existing standard of care, but which may not, at least initially, meet cost effectiveness thresholds. In light of this case, the lesson appears to be that, in anticipation of the appraisal process, manufacturers and investigators would be wise to collect detailed data on the day-to-day impact of the disease on patients and their families, ideally working with support groups, and doing so early in the innovation process. It would also be advantageous to establish a patient registry to capture such information from any patients treated outside of clinical trials (ie, via the ‘hospital exemptions’ or ‘specials’ route). It is worth noting here that therapies targeting common (non-orphan) diseases will obviously need to have much lower costs if they are to be adopted: the current ICER threshold used by NICE is between £20,000-30,000. Therapies that exceed this threshold will not necessarily be rejected, but they will have to be accompanied by a strong body of evidence on its clinical and social benefits [52].

Our next three examples relate to adoption in the clinic. The implementation of the intra-operative breast lymph node assay (BLNA) provides a useful illustration of how payment structures and tariff systems can influence adoption processes [53]. In 2008 the NIHR Technology Adoption Centre took on the project of encouraging adoption of the BLNA among several trusts (NHS corporations responsible for providing secondary services). The clinical case for implementing the BLNA is strong: it entails the quick analysis of sentinel lymph node tissue during a patient’s mastectomy procedure. If cancer is identified within the lymph node, the surgical operation can be extended and the nodes can be removed [53]. This diagnosis and treatment therefore occurs within one surgical procedure rather than the usual two, which results in a reduction in acute hospital admissions, a reduction in a patient’s overall stay, and thus improved efficiency and long-term savings for the NHS. Indeed, the procedure is recommended by the National Institute for Health and Care Excellence [54]. Despite these benefits, only a handful of hospitals throughout England currently offer the BLNA. One of the hurdles to a more widespread adoption of the diagnostic procedure was a lack of financial incentives for providers [53]. While the BLNA will save money for commissioners, under the current payment structure system it entailed a significant reduction in income for individual NHS trusts, as they would only be paid for one operation instead of two: because there was no specific national tariff for the BLNA, it was difficult for advocates to make a business case to individual trusts for its adoption [53]. Some trusts, particularly those that had a good relationship with their commissioners (then Primary Care Trusts) were able to overcome this problem by negotiating a specific ‘pass-through payment’ for the BLNA.

If a new technology is seen to align with institutional strategic goals, then high upfront cost may not discourage adoption, even when the overall cost-effectiveness has not yet been established. Our second case relates to the adoption of the ‘da Vinci’ robot for radical prostatectomy in the NHS [12]. The robot system costs around £1.5 million to purchase and it has considerable operating costs, including an annual service charge of around £100,000. Despite this and despite the fact that there are no specific tariffs that cover the higher cost of robotic surgical procedures over the equivalent conventional procedures, several hospitals and trusts have acquired the robot – by 2011 there were currently 22 in operation [12]. The *identity* of the robot, how it is perceived by key stakeholders, has been a major factor driving its adoption. The robot has been the centre of considerable marketing campaign and it has acquired prestige as a technologically-advanced ‘futuristic’ system. Hospitals and Trusts felt that such a system would align with their vision of being high-status, ‘cutting-edge’ institutions [12]. They have been creative in securing funds, much of which has been obtained via intensive charitable fundraising, and they have also been willing to accept some financial loss as it was felt that this would be outweighed by the status of having the robot [12].

Our final example comes from the field of E-health, specifically E-health patient records. This example is illustrative of the problems that can arise when innovation is imposed upon clinical contexts by ‘top-down’ initiatives driven by government priorities. Globally, there are a variety of approaches to the ways in which such records have been introduced, but in the UK, the NHS model was one of a nationwide, top-down standardised system to be used in hospitals and primary care. This is known as the National Health Service (NHS) Care Records Service, central to the £12.7bn National Programme for IT (NPfIT). A substantial body of literature assessing this programme has been published, principally about the differential take-up of the system and the lessons that can be learned (e.g. see [55]). While there has been some deployment, the overall picture is less positive: as Greenhalgh summarises [56]:

‘Contracted deadlines for delivering key systems were repeatedly missed. Technologies that were meant to make tasks and processes more efficient at the clinical frontline were more cumbersome and time consuming, and in some cases less safe, than their paper equivalent…[O]nly a handful of hospitals can be described as paperless, and most communication between NHS organisations still occurs by snail mail, fax, or patient messenger’ (p. 4130).

Consequently, there has been a move recently towards reconfiguring the system such that local needs and interests of Trusts and hospitals have a much greater role to play in shaping the Service while at the same time endeavouring to ensure that the system is robust in terms of standards and their specification. This model is described as being neither top-down (ie, government-imposed change) or bottom-up (ie, clinician-led innovation) but rather ‘middle-out’ [57]; an approach that is prompted from above and which also incorporates local preferences:

‘A middle-out approach combines central support for national goals and common standards with incentives to encourage incremental compliance with standards at the local level’ (ibid, p.4564).

Here we see the ways in which adoption is as much about institutional structures and the relation between local and global infrastructures as it is about the specific technical components and design of a specific product. Most importantly, that a balance is needed between these elements if an adoption space is to be created.

# Conclusion

The need to be attentive to contextual challenges associated with innovation in healthcare systems is one of the principal conclusions we can draw from the discussion above. In doing so, we can recognise that some of the challenges which are apparently directly linked to RM have been encountered elsewhere, and that lessons can be learned from the way in which these have been managed: As Fig 1 illustrates, general challenges relating to reimbursement, and implementation within the clinic are encountered in other domains. For example, biologics and robotics may also entail reimbursement challenges due to high upfront costs. However, particular attention needs to be directed at those challenges which we have identified as specific to RM. As we have indicated in Fig. 1, these relate to clinical trials, manufacturing and to regulation, and derive from the perceived complexity and fragility of live material which raises various safety and efficacy concerns. The classification of therapies, particularly within the ATMP framework, provides specific challenges for developers and regulators. It is these that will most likely hinder innovation in this area as there is little in the way of precedent in how to manage them.

The many elements (institutions, agencies, policies, scientific developments etc.) associated with the emergence of RM can be considered as inhabiting and constituting an innovation space, and more specifically, the healthcare system ‘adoption space’ of RM [11, 12]. In this space, the more or less specific identity of RM and of its emerging medical applications, are being forged. One important part of this relational context of adoption is the extent to which adoption requires major, long-term infrastructural commitment and systems, as opposed to responsive ad hoc clinical demand-dependent product supply [12]. Those areas that are doing well at the moment tend to be clinician led surgical procedures whose development may require only minor adjustments to existing clinical practices, such as we see in limbal stem cell transplantation. Additionally, it is important to bear in mind that failure to adopt is often a matter of degree, and a technology that is not (widely) adopted in healthcare practice may nevertheless have value for its developer’s enterprise or as a stepping-stone to further innovation. Equally, non-adoption may be due to a variety of factors in the adoption space [58].

Our analysis of the specific and general innovation challenges suggests that emerging RM products and procedures will have to work hard to find or indeed create an adoption space that serves their needs, and cope with financial uncertainty. But it is clear too that without other actors enabling this through longer-term commitment to clinical, regulatory and economic infrastructures, they will have a difficult time. We see some evidence of this longer-term commitment in NHS England’s *Five Year Forward View* [59]. NHSE proposes to establish ‘test bed’ sites for ‘combinatorial innovations’; combined ‘socio-technical’ innovations which may include a new therapy and the new staffing models, payment structures and infrastructure that would be needed to deliver it. In effect, they will enable the testing of the novel service structures that may be needed to deliver highly innovative therapies. NHSE’s *View* thus recognises the need to create a facilitative adoption space, or an initial ‘niche’ for an innovation which will led to its eventual, more widespread implementation.

Our work on the ‘REGenableMED’ project is developing more detailed analyses of the adoption space for RM, and in doing so identifying the main processes that we can say are linked to what we call ‘institutional readiness’, complementing but contrasting too with the notion of ‘technological readiness’, often found in policy literature. Our concept is one that addresses the UK government’s call that the RMEG should prioritise ‘delivery readiness’: we hope that this paper goes some way towards showing how such a challenge can be understood and addressed.

**Future perspective**

A range of translational challenges have been identified within the field of regenerative medicine. The successful development of RM therapies will require stakeholders within the field to strategically create institutional and infrastructural arrangements that provide a foothold for nascent RM therapies and procedures. We believe that it is important not to exceptionalise the RM field, as important lessons can be learned from other areas on how to create such arrangements, particularly in regards to reimbursement and commissioning, implementation within the clinic. However, the perceived complexity and fragile nature of cells and tissues used in RM therapies creates particular regulatory and manufacturing challenges, for which there is little precedent in how to manage. It is the combination of these three that threatens to hinder the field of RM, and which require particular attention. In the UK, such issues are being addressed by initiatives such as the Cell Therapy Catapult and the UKRM platform, and there is some indication that the NHS will attempt to create spaces to trial and accommodate highly disruptive innovations such as RM, as has been outlined in the NHS England’s Five Year Forward View.

**Executive Summary**

**Introduction**

* High expectation surrounds the emerging field of regenerative medicine (RM).
* There is a concern that advancements made in the lab will fail to be translated into clinical applications, or that such translation will be dismally slow, due to various challenges.

**Novelty, technology identity and adoption space**

* While some of translational challenges are specific to RM, there are parallels between RM and other areas of medicine. Important lessons can be learned from these and the way in which such challenges have been managed in other areas of medicine.
* It is important to understand that all novel technologies and procedures are endowed with a ‘technology identity’ within institutional contexts. These identities will affect decisions regarding their adoption.

**Examples of challenges of adoption of other technologies/therapies**

* NHSE’s agreement to commission eculizumab illustrates how clinical effective technologies that are unlikely to be considered cost-effective, might be appraised by Health Technology Appraisal authorities.
* The implementation of the intra-operative breast lymph node assay (BLNA) provides a useful illustration of how payment structures and tariff systems can influence adoption processes. Despite its clinical advantages, adoption depends on creating a financial incentive for hospital trusts.
* The example of the da Vinci robot illustrates that high-cost technologies will be adopted by institutions, if the technology aligns with institutions’ strategic vision.
* The example of E-health patient records illustrates the difficulties associated with top-down innovation initiatives. This top-down approach is being superseded by a ‘middle-out’ approach.

**Conclusions**

* It is necessary to be attentive to contextual challenges associated with innovation in healthcare systems.
* Emerging RM products and procedures will have to work hard to find or indeed create an adoption space that serves their needs.
* Those areas within RM that are doing well at the moment tend to be clinician led surgical procedures whose development may require only minor adjustments to existing clinical practices.
* NHSE proposals to establish ‘test bed’ sites for ‘combinatorial innovations’ may provide important ‘niches’ for RM adoption, which could further facilitate widespread implementation.

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| **Challenges** | **Possible solution(s)** | **Is there a specific challenge for RM?** |
| Clinical trials   * Complex environment overseen by multiple bodies * Uncertainties & risks associated with the use of live tissue * Inappropriate existing infrastructure (ie, Trial costing templates). | Adaptive trialing (AT); revised template | *Yes*. There are particular safety and efficacy challenges deriving from the perceived complexity and fragility of live material |
| Regulation:   * Burden of the many relevant legal provisions * Heterogeneity in implementation of provisions * Major difficulties associated with classification of products | A ‘one-stop-shop’ for regulatory guidance;  EMA/CAT to adopt clearer specification here  Adaptive licensing | *Yes*. Classification of therapies poses specific challenges to developers and regulators. |
| Manufacturing/scale-up:   * Underdeveloped infrastructure for scale-up & transport to the clinic * Lack of consensus regarding quality assurance * Lack of suitable QPs at clinical sites | New bioreactor systems and QA-proof logistics | *Yes*. Although scale-up, quality assurance and related issues are seen in many novel applications, they are particularly difficult for RM products which are based on living tissues and cells |
| Reimbursement:   * Confusion regarding information required for HTA * High up-front costs of therapies * Lack of long-term data on clinical effectiveness | Move to risk-sharing; refine health economic model; introduce managed entry agreements | *No*. High up-front costs seen in other fields (e.g. transplants, robotics) |
| Implementation in the clinic:   * Need for specific training for clinicians * Gaining support from managers * Constructing a business case for trusts/clinics * Obduracy of existing clinical workflows | Cell Therapy Centres of Excellence | *No*. These challenges are typical of novel applications |

**Figure 1 Innovation challenges and their specific relation to RM**