

**Special treatment? Exceptions and exemptions in the politics of regenerative medicine
gatekeeping in the UK in global context**

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Abstract

The global field of cell-based and tissue-engineered regenerative medicine is diversifying, as a wide range of biological mechanisms and therapeutic delivery technologies are developed, tested, trialled and, occasionally, introduced into clinical practice. The field has become an international battleground for opposing forces of regulatory gatekeeping and innovation politics. This applies both to the arenas of legal regulation of market entry and to the regulation of healthcare commodities' adoption by technology assessment and commissioning agencies. The UK's legal regulatory activity in the field is conditioned by its position in the EU and especially, though not exclusively, the Advanced Therapy Medicinal Products Regulation of 2007; its (England's) public healthcare adoption activity is undertaken notably by technology assessment-based policy body NICE (National Institute for Health and Care Excellence) and commissioning/service contractor NHS England. Both gatekeeping arenas are the site of a range of contests about whether, and if so, how, regenerative medical technologies might be accorded 'special treatment'. The technical novelty, evidential uncertainty and high promise of technologies in the field exacerbate the normal tensions of balancing innovation and regulation. In what sense might regenerative medicine or cell therapy be treated in market regulation and healthcare system innovation as a special sector or zone? The paper analyses recent and current regulatory and gatekeeping strains of policy discourse and activity in terms of the tension between commensuration with inherited classificatory domains and technoscientific standards on the one hand, set against counter-movements of exceptionalism and exemptionalism on the other. The paper draws on former and current ESRC supported research projects and involvement in UK policy and technology assessment bodies.

Introduction

The global field of cell-based and tissue-engineered regenerative medicine is diversifying, as a wide range of biological mechanisms and therapeutic delivery technologies are developed, tested, trialled and, occasionally, introduced into clinical practice. The technical novelty, evidential uncertainty and high promise of technologies in the field exacerbate the normal tensions of balancing innovation and regulation. Different countries have tackled the regulation of these sciences, materials and technologies in widely different ways, resulting in a segmented marketplace of different regulatory regimes involved in constituting globally the emerging worlds of the new regenerative medicine paradigm.

The well-known starting-points of the societal and economic promises associated with the bioeconomy and the medical revolution heralded by Regenerative Medicine (RM) in its various emerging forms, can be taken as read here. The sociology of technology expectations is relevant, as we consider the performative effects of gatekeeping actors in shaping the emerging technological zone or field, its emerging markets, its clinical and citizen usership, and its rules of engagement (Borup et al; Faulkner, 2009, 2009). Gatekeeping, as I use the term here, has a role in shaping both technological innovation itself, as well as the innovation pathways that technology developers are able to take in attempting to bring products into the marketplace and into healthcare practice.

The field of RM has become an international battleground for opposing forces of regulatory gatekeeping and innovation politics. This applies both to the arenas of legal regulation of market entry and to the regulation of healthcare commodities' adoption through processes of technology assessment and what in the UK are called 'commissioning' agencies, which develop contracts with providers such as hospitals for the delivery of packages of healthcare to the population. This paper addresses both of these two

gatekeeping constituencies, the market/practice entry regulators on the one hand and the healthcare system assessment and adoption agencies on the other. By focusing on these actors and agencies, I am taking what might be called a 'top-down' perspective on the ways in which regenerative technologies might be made available and accessed by patients.

Elsewhere, I have written about the roles of the political negotiation of regulatory categories of different medical products as an important dynamic constituting the innovation environment of new medical technologies (Zhao, 2005; Faulkner, 2009, 2012). Conspicuous amongst these is the issue of how legal concepts and regulatory institutions can be 'matched' to the scientific, technological and industrial categories that emerge, or which are produced, in the development and testing of complex new medical materials, and how these vary in the framings of different, bounded legal regimes such as national political cultures, building on existing regimes. This key issue has usefully been termed 'regulatory connection' (Brownsword, 2008).

The politics of regenerative medicine gatekeeping in the UK

This paper adopts the concept of 'gatekeeping' as a general way of combining the assessment for, and policing of, the market entry of new cellular medical products. I adopt this concept in preference to 'regulation', mostly interpreted to refer to formal statutory law-based gatekeeping, and 'governance', generally taken to refer to looser, network-based, distributed forms of societal shaping of innovation. Gatekeeping also, more than those related concepts, draws attention to the policing of the boundary of entry of products into adoption processes, user practices and the marketplace.

The UK's legal regulatory activity in the field is conditioned by its position in the EU and especially, though not exclusively, the Advanced Therapy Medicinal Products Regulation of 2007; its (England's) public healthcare adoption activity is undertaken notably by technology assessment-based policy body NICE (National Institute for Health and Care Excellence) and commissioning/service contractor NHS England. Both gatekeeping arenas are the site of a range of contests about whether, and if so, how, regenerative medical technologies might be accorded 'special treatment'.

The field is also shaped by policy actions such as the Innovative Medicines Initiative (IMI) which is Europe's largest public-private enterprise, aimed at accelerating the development of safer and improved medicines. IMI is a joint undertaking between the European Union and the pharmaceutical industry association EFPIA and supports collaborative research projects and networks across industry and academia (<http://www.imi.europa.eu/>).

The last few years have seen a major set of policy initiatives and actions to boost the UK's regenerative medicine activity for both 'health' and 'wealth' objectives, including the 2011 Life Sciences Strategy and the 2013 House of Lords report on Regenerative Medicine (Hol, 2013) which proposed a wide range of investments and infrastructural developments specifically to promote regenerative medicine as a sector in which the UK would excel on the world stage.

The last decade has seen the development in Europe of a number of regulatory policy initiatives that can be seen as relaxations, under specific conditions, of the basic gatekeeping frameworks, infrastructures and regulations. This trend appears to be increasing as different regimes struggle with the dilemmas of innovation and potential health benefit that regenerative medicine and its proponents raise. This leads us to ask: In what sense might regenerative medicine or cell therapy be treated in market regulation and healthcare system innovation as a special sector or zone deserving of its own gatekeeping frameworks and support systems? How does the personalised regenerative therapy movement counter and influence the

systemic standardisation embedded in existing, 'inherited' (Stokes, 2012) regulatory regimes? Against this background, therefore, the paper analyses recent and current regulatory and gatekeeping strains of policy discourse and activity, primarily in the UK and European context. I analyse current and recent trends in terms of the tension between commensuration with inherited classificatory domains and technoscientific standards on the one hand (Faulkner 2012), set against counter-movements of exceptionalism and exemptionalism on the other.

I show that there is a trend to create exceptions to the rules of entry to the regenerative medicine marketplace and healthcare systems through various exemptions and exceptions to established paradigms, noting that this flexibility varies across different jurisdictions. But I argue that it would be easy to overestimate the extent of these developments. In concluding I point to some reasons why this is so.

The structure of the paper is as follows. Following a brief description of data sources, I tackle first the gatekeeping regimes around entry of products into the marketplace and usership (Faulkner, 2009), and then move on to consider the specific case of exceptionalism in the UK's national methodologies and institutional practices in evaluating, guiding, and adopting regenerative medical technologies, in the context of the national healthcare system (NHS), which are under debate at the time of writing (Autumn 2014 – Spring 2015).

Method

The paper draws on former and current ESRC supported research projects.¹ These involved extensive document collection, interviewing by research teams of a wide range of stakeholders, and attendance at policy related meetings from 2013 to 2015. Also drawn on is the author's experience as a member of the Department of Health's Regenerative Medicine Expert Group (RMEG) 2013-14, NICE's Medical Technologies Advisory Committee 2009-13, and as Expert Advisor to a National Assembly for Wales inquiry into access to medical technologies during 2014.

Gatekeeping the marketplace

Gatekeeping of entry of medical products to the EU (and thus in principle the UK) marketplace rests primarily on pharmaceutical and 'Advanced Therapy Medicinal Product' (ATMP) law, operational since 2001 and 2007-8 respectively. Here I discuss the exceptions and exemptions that have been introduced with the relevant Directives and Regulations (which I do not detail legalistically at this point), and related measures.

In the EU, applicable to pharmaceutical products, three main 'licensing flexibilities' intended to improve developers' incentives have already been introduced. One such regulation-relaxing development that has emerged for products designated as medicines is the *conditional approval* – essentially a leap-frogging of Phase 3 studies and launching of a Phase 4 study once a product has been marketed. Proponents argue that this might speed up bench to bedside translation by approving technologies with less than 'complete' safety and efficacy data. However, one analysis suggests that approval times are not necessarily shortened (Boon et al, 2010). The procedure is applicable when there is a complete pharmaceutical and pre-clinical data package and an almost complete set of clinical data, if it is considered reasonably likely that the remaining data will be collected in a short timeframe. To qualify, a product must be intended for treatment, prevention or diagnosis of a seriously debilitating or life-threatening disease; have designated orphan

¹ 1. *State strategies of governance in global biomedical innovation: the impact of China and India*. ESRC, 'Rising Powers' programme, 2012-15, Grant ES/J012521/1.

2. *Regenerative medicine and its development and implementation: an analysis of emergent value systems and health service readiness*, ESRC, 2014-17, Grant ES/L002779/1.

status; or be intended for use in emergency situations, responding to European Community or WHO recognised unmet medical needs, and immediate availability is likely to outweigh risks. Conditional MAs must be renewed annually. It is notable that 10%-20% of all drug approvals are now conditional MAs (ref), including in oncology about two approvals per annum since the mid-2000s. *Exceptional Circumstances Licensing* is available when comprehensive data could never be provided, for example because the disease is too rare, the scientific knowledge is too limited, or because of ethical issues such as constraint on submitting seriously ill patients to extensive tests. *Accelerated Assessment* is designed to meet the expectations of patients and to take account of the increasingly rapid progress of science and new therapies. It applies to medicinal products supported by major interest from public health and therapeutic innovation perspectives. Application for an accelerated assessment procedure must justify itself on these grounds. The EMA's Committee for Medicinal Products for Human Use (CHMP) makes a decision based on the justifications presented and recommendations of independent rapporteurs. (This paragraph draws on Mittra et al 2014 and European Medicines Agency information).

These flexibilities are now being recast in terms of a movement toward 'adaptive licensing'. In March 2014 the European Medicines Agency (EMA) launched an adaptive licensing programme, inviting companies to participate in a pilot project (Ranson & Cline 2014). However, in 2013 the European Commission had stated that it was "not convinced" that adaptive licensing was the best way forward (cited in Ranson & Cline, 2014). The European Commission's IMI initiative is currently attempting to consolidate these and other apparent regulatory easings under the umbrella concept of MAPPS (Medicines Adaptive Pathways to Patients). The intended approach may integrate a number of elements such as adaptive clinical trial design, patient centric benefit/risk assessments and the continuous evaluation of a therapy as new evidence 'including real world evidence' becomes available. Interestingly in the context of debate about the role of consumer/patient demand for therapies, the initiative includes an acknowledgment of patient access issues as part of a life cycle approach to the innovation process. The 'expected impact' would be '

'a comprehensive plan of development and exploitation of tools, methodologies, infrastructures that will allow changes in R&D, regulatory and medical practice to enable early patient access to innovative prevention and treatment options'. (IMI, 2014)

Elsewhere, similar issues are being debated in the context of RM commercialization. For example, in Canada at a recent 'Business of Regenerative Medicine course', in Toronto, in July 2014 reimbursement and accelerated approval were debated

"There was particular excitement around accelerated approval regulatory pathways that are being developed to facilitate the commercialization of live cell technologies. As (a CEO of a company) put it, we're experiencing a "magical era of accelerated approval." But he also wonders about the fate of cell therapy technologies upon approval, and what is being done to link accelerated approval with reimbursement" (Curtis, 2014)

(The latter point about reimbursement is discussed further in the section on 'Gatekeeping healthcare adoption' below). Alongside pharmaceutical exceptionalism must be set certain exemptions from centralised European market entry gatekeeping that have been introduced in the 2007 'ATMP' Regulation. On November 13th, 2007, the European Union adopted a *lex specialis* on medicinal products based on genes, cells and tissues: Regulation (EC) No 1394/2007 on advanced therapy medicinal products ('the ATMP Regulation'). This was a new category of medical product established by the law, which covers many, though not all products deemed to be regenerative medicine products. The Regulation applies to products either 'prepared industrially' or 'manufactured by a method involving an industrial process'. This definition

implied that some therapies would be deemed to be produced non-industrially, and thus a so-called “hospital exemption” was constituted, which means that medicinal products not falling under centralised EC regulation by EU law do not benefit from a harmonized regime across the European Union marketplace, though they have to respect national laws (Mahlatchimy et al, 2012)

The ATMP Regulation institutes provision for a central and unique marketing authorization at the European Medicines Agency (EMA) level where a new Committee for Advanced Therapy (CAT) was created, meaning that once authorized, products may be made available throughout the EU member states. Four types of biological medicinal products were defined as ATMPs, based on genes, and/or cells and/or tissues: gene therapy medicinal products (GTMP), somatic cell therapy medicinal products (CTMP), tissue engineered products (TEPs) and combined ATMPs which combine a medical device (legal category) with an advanced therapy. The European Medicines Agency (EMA) through the CAT can provide an informal scientific recommendation on the classification of products, and indeed this has emerged as one its primary activities since implementation of the Regulation. Unsurprisingly, there are difficulties in distinguishing products which are covered and products which are not by the definition of “industrial process”, which appears vague. The European Commission has tried to clarify it as follows: *“This should cover, inter alia: Any ‘mass production’ of advanced therapy products for allogeneic use (batch production, ‘off the shelf’ products etc.); any advanced therapy product for autologous use (i.e. using cells/tissues from a single patient and re-implanting after manipulation into same patient) which, although being patient-specific by definition, is manufactured in accordance with a standardised and industrial process.”* This classificatory distinction is crucial to defining the status and responsibilities of producers of regenerative products, whether in hospitals or in the commercial sector, and was the subject of major debate amongst interested stakeholders in the negotiation of the Regulation. Thus the ‘Hospital Exemption’ has emerged as one of the most controversial features of the Regulation and its implementation in different EU member states. In fact the proposal of this measure was controversial from the start. An internal EU document noted the differing views about the new principle:

“products prepared in a pharmaceutical enterprise not under this exemption would require clinical trials...but similar products prepared for the same use under the exemption (i.e. in a hospital for a single patient) would not”(Council of European Union, May 2006)

The shift in the Commission strategy toward advanced therapies thus brought with it a shift to a new principle in which the mode and locus of TE production, rather than proportionate safety risk, has become dominant. The new organising principle rested on matters in particular of the *scale* of TE activity and the *‘industrial’, repetitive* nature of the enterprise. Here we see a clear attempt to define a borderline between capitalist commodity market and non-market forms of the technical practice of tissue and cell therapy, typically, though not straightforwardly, institutionalised in the distinction between hospitals and commercial enterprises (and leaving aside such difficult issues as the fact that there is no legal definition of a ‘hospital’ in EU law, and the legal entities which constitute healthcare providers vary greatly across the EU).

In UK law, the MHRA has provided guidance on what constitutes non-routine preparation of a product (MHRA, 2010). Two main areas are taken into account: First, is it the same product repeatedly under consideration? Second, what is the scale and the frequency of the preparation of the specific product? The MHRA has also developed guidance on the UK’s arrangements under the hospital exemption scheme (MHRA, 2010) This sets up specific standards as regards good manufacturing practice (GMP) and quality, pharmacovigilance, traceability, reporting requirements, sanctions and penalties, requirements in respect of wholesale dealers, and requirements not specified within the Regulation but which will apply under the

exemption in the UK such as labelling, package leaflet requirements and advertising (Mahalatchimy et al 2012).

It is known that different member states in the EU interpret and apply the hospital exemption in different ways and are creating different criteria to define 'industrial' 'repetitive' production. It has also become clear that some developers/producers see this as an attractive option, and the EMA has expressed concern that the exemption not be over-used (thus distorting the marketplace for commercialised products), nor that member states fail to apply analogous safety criteria to the resulting therapies. EMA's concern includes both market distortion and the safety regarding stem cell products (EMA, 2010).

Alongside the hospital exemption, the UK had previously created a pharmaceuticals "Specials" scheme under 2001 European Union pharmaceuticals legislation which provides: *"A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this (medicines) Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility"*. For such products, no product licence or marketing authorisation is required, but a manufacturer's (Good Manufacturing Practice -GMP standards) licence is required. Under this scheme, doctors and certain other prescribers can commission an unlicensed relevant medicinal product to meet the special needs of individual patients. (Mahalatchimy et al, 2012).

The role of the Committee for Advanced Therapies (CAT) continues to evolve, partly in interaction with other perceived stakeholders. For example, in a summary of its work programme from 2010, its Chair mentioned its role as including: 'a joint conference on ATMPs involving EMA/CAT, EFPIA, EBE, EUROPABIO, (and) Learned Societies to share clinical, scientific and regulatory expertise in the field for the benefit of all stakeholders' (Schneider 2014; author was Chair of CAT). This statement was presented at an EMA conference on regulatory science "Regulatory science: are regulators leaders or followers?" in 2010. Other CAT initiatives were to consider whether to: 'Extend incentives for SMEs to academia, hospitals, trusts and small research groups?'; and to "Promote access and availability for patients': 'Consult (with NCA) on hospital exemption; Encourage development of ATMPs for unmet medical needs without alternative treatments'. The performance of the ATMP Regulation was subjected to public consultation during 2014, and these issues figured prominently in critical comments submitted.

Another alternative to centralised pharmaceutical/ATMP gatekeeping is, arguably, designation of a new cell technology as a medical device. This is seen by some developers as an 'easier' route in Europe for RM products, compared to the pharmaceutical route. This can be a realistic and crucial consideration for developers, because the 'primary mode of action' of given technologies is by no means always clearcut, and indeed is one of the aspects that regulators such as the Committee for Advanced Therapies regularly adjudicates on. Thus the rise of 'closed system' technologies in which a patient's cells are processed within a single operative procedure to isolate 'regenerative cells' (e.g. producers Cytori; Regeneus), which may include adult/mesenchymal stem cells, are regulated as medical devices.

Gatekeepers also appear willing to explore innovations in regulatory science that would enable good quality in vitro data to play a greater role in early stage proof of concept and safety (Mittra et al, 2014).

So there are a range of developments in gatekeeping policy designed to allow potentially beneficial innovative technologies to be used to a greater or lesser degree, under various conditions, in some cases prior to full marketing authorisation.

Gatekeeping healthcare adoption and practice

In this section, I consider the policy discourse and activity of recent discussions and developments in the MHRA, NICE (National Institute for Health and Care Excellence) and NHS England, the National Assembly for Wales, and high-level Regenerative Medicine Expert Group meetings during 2014 (in which the author participated), which was formed on the recommendation of a 2013 House of Lords Science & Technology Committee report on RM. Again, I focus on the apparently relaxative exceptions and exemptions that appear to be being created, and the contested positions, interests and methodologies around them.

In the UK, one of the schemes now being embraced under the MAPPS (Medicines Adaptive Pathways to Patients) concept referred to above is the 'Early Access to Medicines Scheme' (EAMS) (MHRA 2014), which was instigated in the government's 2011 new *Strategy for Life Sciences*. This scheme 'aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need', and allows for designation as a PIM: 'Promising Innovative Medicine'. Regenerative medicine products are within the scope of the scheme: as the MHRA website proclaimed in November 2014: 'MHRA awarded the first PIM designation for a cell therapy product for the treatment of cancer on 8 September 2014.' PIM designation refers to:

'Promising Innovative Medicine' and 'will give an indication that a product may be eligible for the Early Access to Medicines Scheme (based on early clinical data). The PIM designation will be issued after an MHRA scientific meeting and could be given several years before the product is licensed' (MHRA 2014).

The scheme is distinct from the 'adaptive licensing' discussed above which operates within existing market authorisation law, and mandates the producer to provide the therapy outside the marketplace, *at no cost* until licensing is achieved. The scheme has been supported by the British government in consultation with trade associations and other interested parties during 2014, in response to earlier stakeholder consultations by MHRA and the Department of Health (UK Government, 2014). The scheme explicitly addresses 'the landscape for early access to medicines which reflects the UK Life Sciences Strategy and NHS Innovation Health and Wealth reforms', and 'Reflects the profound changes driven by Genomics, Data, and the rise of Stratified and Personalised Medicines' (ibid, p3). Notably also, patient group involvement is explicitly recognised in the early adoption process: 'Encourages startups, patient groups and charities to collaborate within the extensive infrastructure via the National Institute for Health Research (NIHR) funded Clinical Research Facilities and Biomedical Research Centres and Units in leading NHS Trust/university partnerships'. The government response also mandates for 'a newly coordinated NICE technology appraisal and NHS England Commissioning process'.

The first product to be accorded full EAM status was announced in early 2015: Pembrolizumab, a monoclonal antibody produced by US Merck: 'a positive scientific opinion has been awarded for a medicine used to treat advanced melanoma' (MHRA CEO Hudson, March 2015). The data requirements for the EAMS scheme are less onerous than the full marketing authorisation application dossier which would otherwise be required: 'The trigger for an Early Access to Medicines scientific opinion does not necessarily have to be the submission of a dossier for marketing authorisation application, but the availability of a sufficiently compelling case based on the total data and evidence collected to date as assessed by the MHRA' (MHRA, 2014).

While the Early Access Scheme is operated by the market-entry gatekeeper the MHRA, it requires coordination with NICE and NHS England as the commissioner of health services, including especially 'specialised services' (NHSE, 2012). NHSE's Specialised Services' strategy is to have a 'clear focus on a range of rare conditions and low volume treatments ranging from medical genetics, kidney disorders and

uncommon cancers to complex cardiac interventions, burn care and some specialised services for children' (NHSE, 2012). The rationale for this set of services is thus to provide services for relatively rare medical conditions with severe effects, and may thus apply to regenerative products.

The potential for tensions and potential non-alignment between the two forms of gatekeeping that I have been discussing here (noted also in the section above) is high. There are examples of market-authorized products with regenerative claims, which have not been authorised by national HTA bodies such as NICE in the UK. Short of HTA negative opinions, there are examples of national HTA processes resulting in requests to a manufacturer of a cell therapy product to undertake more research to address particular information deficits. An example of this decisional route from NICE is 'ReCell' a spray form product for burn injuries: 'The medical technology guidance on the ReCell Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury recommends further research. This recommendation is not intended to preclude the use of the technology in the NHS but to identify further evidence.' (NICE, 2014). Such policy positions clearly attempt to find a balance between commercial interests, clinician decision-making, and national system-level evidence appraisal.

NICE has been strongly represented in a Regenerative Medicine Expert Group (RMEG) during 2014, constituted to advise the British government on policy to support RM as a sector following the Life Science Strategy and the House of Lords report referred to above (HoL, 2013). RMEG membership has been composed of a wide range of stakeholders including big pharma, SMEs, clinicians, NICE and NHS England policy staff, private health insurers, and social scientists. Its work was arranged into three groups, focused on 'Delivery', 'Regulation & Licensing', and 'Evaluation & Commissioning' (a NICE official was made Chair of the latter group). The overall tenor of the RMEG discussions about technology appraisal of regenerative medicines was that the existing methodology (including QALYs, clinical evidence and cost utility analysis etc) was adequate and was already applied successfully to other innovative medicines. However, the following proposal was agreed, stated to be initiated by NICE and endorsed by RMEG :

"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'. (RMEG Report, 2015)

Also recommended was a high level Ministerial Strategy Group for regenerative medicine (paralleling existing groups for medical technology and pharmaceuticals), however, this proposal was rejected by the Minister for Health.

Alongside NICE and as national commissioner of health services, NHS England undertakes some technology assessments that NICE does not undertake, and contracts with providers in order to secure services for the population, including the aforementioned 'specialised services'. The RMEG report discusses pros and cons of risk-sharing schemes between commissioners and commercial technology providers, noting their drawbacks, and refers more positively to NHSE's recent 'Commissioning through Evaluation' (CtE) scheme, which is applied to a limited number of therapies, and which enables HTA assessment to be undertaken while a technology is introduced in a limited number of sites. The RMEG concludes on this issue with a very general, flexible recommendation, simply that 'an innovative business model' should be developed (RMEG, 2015).

NHSE had set up a working group on regenerative medicine in response to the House of Lords report. The following recommendation is made in the RMEG report, to strengthen this cross-cutting initiative:

'the cross CRG working group for regenerative medicine set up by NHS England to support RMEG should be further developed into a formal 'CRG for regenerative medicine'. It should include clinicians covering a wide range of specialisms and experience in regenerative medicine to provide specific insight and advice on regenerative medicine products to other CRGs and NHS England'.

'Value-based assessment' (VbA) is a methodological HTA/NICE development which arguably extends the possibilities for RM products becoming adopted in the NHS, especially because many of these products promise long-term benefits, that are not easily captured by existing methodologies. VbA has been partially developed by NICE following extensive consultation, highlighting a high degree of uncertainty around the definition of the concept. It is currently unclear if and how this will be incorporated into NICE's assessment methodologies and organisational infrastructure, and how closely it will be tied to, or equated to, the long-established QALY methodology (NICE, 2014). In a former incarnation, the intention was to develop value-based *pricing*, whose three dimensions given the nod for methodological development were: 'burden of illness', 'therapeutic improvement' and 'wider societal benefits':

"...we intend to consider the wider impact of a disease on people's ability to be part of society. We refer to this as the 'wider societal impact' and define it as the loss (or shortfall) in a person's capacity to engage with society as a result of living with the disease or condition, compared with their capacity to engage with society without the condition. We propose calculating wider societal impact by measuring the absolute shortfall in QALYs' (NICE Consultation, 2014: 7)

The tension between existing methodology and the new proposals is evident here (in the proposal to retain the QALY method as the basis for societal impact assessment). Later in the document we see: 'Since loss of good health affects a person's ability to engage in society, societal shortfall can be assessed by measuring the absolute QALY loss' (p11). Nevertheless, if this methodological innovation is implemented, it will imply a widening of the goal-posts or oiling of the hinges of the gate controlling products' entry into the UK healthcare marketplace, by extending the criteria of assessment. In principle VbA thus means that a broader, social-good oriented approach to valuing technologies could be used, an example, crudely speaking, being the inclusion in gatekeeping evaluations of potential knock-on effects of a technology on return-to-work of previously incapacitated patients, with its consequent calculable impact on the economy. However, the development of VbA is stalled on this point at the time of writing, under criticism that it would operate in an ageist way, favouring e.g. formal economic activity over informal caring for example.

A further 'exceptional' route by which novel technologies that have been approved for the marketplace but not for national commissioning is the Individual (Patient) Funding Request, which is available to individual clinicians in cases of exceptional need (IFRs in NHS England; IPFRs in NHS Wales). This is a further route that has recently attracted policy attention in the UK. NHS England has introduced a requirement that should five such requests be received for the identical therapy, then a 'national' policy should be created for commissioning the technology as part of a clinical service at one or more provider centres. A member of Cardiff and Vale University Health Board told a Committee inquiring into access to medical technology (NAW National Assembly for Wales, 2014):

"a meeting of all Welsh IPFR panels, which had discussed the variation in processes across health boards. There had been consensus that assessing 'exceptionality' was problematic, and that the current IPFR process did not take account of "how we best use our funds on the basis of the budget that we have and the remit that we have for the health of the total population" (NAW, 2014)

The Welsh government recently reviewed the implementation of this practice too, resulting in a new, more coordinated policy. The system will apply to the so-called "orphan" and "ultra-orphan" medicines and

treatments for patients with rare diseases (Welsh Government, 2014), a designation that many developers of RM products are known to be seeking.

Thus, as with 'Gatekeeping the marketplace', a range of apparent easings and potential easings appear to be being introduced in gatekeeping of healthcare adoption processes and systems too.

Discussion: UK in broader context

Not all the regulatory easing that we witness is specific to regenerative medicine or cell therapy, although as I have noted there are some aspects distinctive to the RM sector. Also applicable to RM is the international ('Western') policy response to the global slowdown in regulatory approval of new pharmaceutical therapies. Thus far, the US FDA has introduced its "fast track designation" and more recently its "breakthrough therapy designation" for drugs demonstrating a substantial improvement over existing therapies. Both FDA and EMA moves are linked partly to the MIT Center for Biomedical Innovation moderated New Drugs Paradigms (NEWDIGs) international initiative, started in 2010 as a forum for co-ordinating and exploring the movement from the current binary yes/no boundary-keeping decision to a more flexible, stratified approach. The NEWDIGs initiative also involves the UK MHRA, Health Canada, the Singapore Health Services Authority as well as sponsors, health technology assessment (HTA) organizations, reimbursers/payers, patient associations and academics. The initiative is aimed 'on enhancing the capacity of the global biomedical innovation system to reliably and sustainably deliver new, better, affordable therapeutics to the right patients faster' (<http://cbi.mit.edu/research-overview/newdigshomepage/>), a ringing endorsement of current political 'innovation' agendas.

The commensuration-proliferation dynamic (Faulkner 2012) in the cases considered here includes not only the mushrooming of working groups and conflicting interest group forums around the legal/regulatory issues, but also the tension at least in the UK between an attempt to align RM with the existing HTA-based regime focused nationally around NICE on the one hand, and the proliferation of policy-oriented multi-stakeholder working groups on the other. There are escalating calls for increasing dialogue between market regulators and HTA/reimbursement actors/payers more widely in regenerative medicine stakeholder communities. In the UK, there are currently moves to create closer coordination between NICE and the MHRA and between NICE and NHS England. Links between the two gatekeeping arenas that I have discussed here may be increasing more in some jurisdictions but not others. In fact the EMA since 2010 has offered parallel scientific advice with HTA bodies to attempt to allow medicine developers to establish the required evidence base. A draft best practice guidance for EMA-HTA parallel scientific advice was published for public consultation in May 2014 (EMA, 2014).

The tension seen in cases of disjunction between market authorisation gatekeeping and healthcare adoption gatekeeping, can be exemplified by the South Korean case. Here is an example of a country that has been progressive with RM approval, having approved 16 therapies to date – said to be the most of any country in the world – but apparently has not supported these same technologies through reimbursement decisions. So far, not one is reimbursed or exported out of the country (Curtis, 2014). On the other hand, a precedent in attempts to ease this alignment and reduce the tension can now be found with Japan's recent regulatory innovation, where the government has implemented a conditional approval system. Cell therapy developers are only required to have a single, albeit larger, Phase 1 study to achieve marketing approval. (Interestingly, all, though few, cell therapies currently approved in Japan are entitled to reimbursement, a converse of South Korea). In considering this fundamental tension, we can note that 'adaptive licensing' and the 'early access' scheme in the UK, although legally and conceptually distinct in addressing licensing

on the one hand, and adoption on the other, do align with each other in attempting to achieve conditional forms of availability of innovative medicines.

In a more global perspective, the analysis presented in this paper can usefully be set alongside analysis of cell therapy and other RM gatekeeping developments in other parts of the world, which focus on international variations and connections (Sleeboom-Faulkner, 2013), in order to further our understanding of competition in the global bioeconomy and collaborations that are interlacing through it.

Are the developments considered in this paper really about gatekeeping after the cattle have already broken down the fences? In other words, are there now so many exceptions and exemptions to the dominant gatekeeping paradigms— in principle at least, or in terms of visionary scenarios of medical futures - that the onrush of novel RM technologies is unstoppable and irreversible? I conclude that this is not the case. Although, as this paper shows, there are a number of easings and relaxations of the prevailing regimes, various exceptions and exemptions, their scope (in the UK at least) is somewhat limited, in spite of the rare examples of early conditional authorisation. Accelerated approval systems may not result in incentivisation and faster approval times (Boon et al, 2010; Davis and Abraham, 2013). This limited scope of exceptions and exemptions is defined by narrow criteria of rare disease, orphan designation, compassionate use, critical disease such as cancer, emergency need, and individual medical prescription. And the effects of these exceptions and conditional contracts on innovation pathways and approved/adopted product volumes, requires systematic evaluation.

Returning to the notion of 'regulatory connection' mentioned in the introduction to this paper (Brownsword, 2008), it is clear that there is a politics of regulatory connection, in which stakeholder interests interact and compete in various ways and at various levels and in different institutional sites of biomedical governance. The apparent gatekeeping relaxations and resistances that I have reviewed show a complicated, mixed picture of the emergence of regenerative medicine in face of existing institutional regimes, epistemologies and methodologies. The current REGenableMED project (<https://www.york.ac.uk/satsu/regenablemed/>) aims to analyse these dynamics in detail in the UK case to assess business models and the 'readiness' of the UK for regenerative medicine as an economic, biomedical and healthcare enterprise.

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