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Abstract

The field of regenerative medicine (RM) faces many challenges, including funding. Framing the analysis in terms of institutional politics, valuation studies and 'technologies of knowledge', the paper highlights growing debates about payment for RM in the UK, setting this alongside escalating policy debates about 'value'. We draw on interviews and publicly available material to identify the interacting and conflicting positions of institutional stakeholders. It is concluded that while there is some common ground between institutional stakeholders such as industry and health system gatekeepers, there is significant conflict about reward systems, technology assessment methodologies and payment scenarios; a range of mostly conditional payment schemes and non-mainstream routes are being experimented with. We argue that current developments highlight a fundamental conflict between a concern for the societal value of medical technologies in a resource-limited system and a concern for engineering new reward and payment models to accommodate RM innovations.

Keywords: Regenerative Medicine, valuation, payment scenarios

Introduction

Regenerative medicine (RM) is acknowledged as a potentially game-changing set of innovations that could transform the practice of medicine. This field entails the use of human or animal-derived cells, tissues or genetically- modified cells as interventional therapeutics with the aim of repair or regeneration of damaged or malfunctioning cells, tissues or organs.

RM is championed as a potential source of cure for many medical conditions. Although the field consists of a wide variety of different products and processes, especially spanning the established sectors of both medicines and medical devices, the UK has defined RM *per se* as one of 'eight great technologies' (Willetts, 2013). The field is positioned at the forefront of the 'health and wealth' agendas of UK and global initiatives for the bioeconomy (OECD, 2009; Gardner *et al*, 2016). A range of initiatives has been launched to identify innovation challenges of RM, and to devise strategies for addressing them.

Overall, the RM field is beset with a wide range of uncertainties. These include complex regulatory frameworks; manufacturing issues; research governance; clinical trial methodologies; potential disruption to clinical environments; lack of investment from private funders; and lack of viable payment systems (Gardner *et al*, 2016, Gardner *et al*, 2015). The UK Government's official response to a 2016 inquiry into regenerative medicine included the following recommendation (referring to NICE – the National Institute for Health and Care Excellence, the central national health technology assessment institution):

> The next Government should…work with the biotech sector and with NHS England and NICE to agree new reimbursement payment models which take greater account of the value of regenerative medicine therapies that offer cures, reduce healthcare costs and make treatments available earlier to patients (Department of Health, 2017:11)

This dense and multidimensional statement encapsulates two related concepts, first that of payment for regenerative products, and second, the concept of 'value', which has become key to recent debates and analysis in Western advanced healthcare economies where policy must take account of limited resources for public healthcare systems and of public concern about societal access to and safety of innovative technologies. Further, it conjures three domains of value – curability, cost and access.

This paper, then, investigates the twin issues of payment and value. Needless to say, without viable systems to reward producers in some way, the promise of RM cannot be fulfilled. Such issues have generated significant debate, as only a small number of RM products have actually reached the marketplace, and several high-profile products have been withdrawn by their producers for business reasons. At the same time, a few are being introduced clinically through a variety of non-mainstream regulatory and marketing routes to small numbers of patients. The curative potential of some RM innovations presents technology assessment and payment systems with novel challenges, while others are less disruptive suggesting a possible diversification of subsectors in the future, in spite of the government framing it as a single sector. For example, cell therapies produced by a standardised process are very different from a medical device based, 'tissue-engineered' customised product for a single patient. Developers are typically only able to provide evidence about preclinical and clinical quality, safety and efficacy that is even less than for other novel medical products, because performance metrics for cell-based technologies have yet to be clearly defined.

Payment is not the only means by which producers of RM might be rewarded and its value recognised. It has become apparent, as the above Government statement illustrates, that the debates and proposals about the funding of RM products have become implicated in, and are contributing to, a broader debate about methods and approaches to 'valuing' innovative medical products in society more broadly. As Health Technology Assessment (HTA) leaders internationally have stated: 'Identifying treatments that offer value and value for money is becoming increasingly important, with interest in how HTA and decision makers can take appropriate account of what is of value to patients and to society, and in the relationship between innovation and assessments of value' (Henshall and Schuller, 2013). Such a statement about the multidimensional worth of treatments is significantly broader and indeed

at odds with narrower yet high-profile perspectives of value defined by medical outcomes (e.g. Porter, 2010). Thus, it is necessary to appraise issues of potential payment systems alongside the possible methods of assessing the 'value' of potential innovations in the medicines and medical devices sectors, and beyond healthcare systems, in wider perspectives of society and the economy. A range of stakeholders is thus engaged in debating the imagined future of RM healthcare, and in this paper we focus primarily on the UK where a range of notable recent developments in the institutional and methodological politics of RM payment and broader valuation and reward is evident.

Apart from the move within HTA to take greater cognisance of value, 'valuation' has emerged recently as a major focus in sociological studies of economics processes. Helgesson and Kjellberg (2013) have outlined trends in this field: 'These studies address how actors accommodate and mediate a wide variety of value registers as part of performing markets' (p361). Valuation studies are 'examining the multiplicity and disputability of registers of value, valuation practices, metrics and processes' (ibid, p363). Valuation thus focuses on the processes by which different values are mobilised in the formation of new markets, and 'values' themselves express the multiple and variable worth that actors attribute to products entering into those markets. Relevant values in any given case may thus include, for example, economic, societal, health-related values, and social ethics.

Institutional and methodological politics of value

The innovation landscape for RM is inhabited by a complex array of actors with widely varying aims, expertise and resources. To examine the relevant actors here is to examine what MacKenzie has called 'the politics of market design' (2009). The actors involved include market regulators and health technology assessors (acting as 'gatekeepers' of entry to

healthcare adoption), payers (public health system providers, private medical insurers), innovation intermediaries and promoters, research and opinion publishers, charities, patient groups, industry trade organisations, health policymakers, business incubators and investors, and civil society organisations. These actors attempt to negotiate the valuation of the worth of RM products and businesses, possible payment systems (conventionally called 'reimbursement'), and the associated processes of HTA (Garrido *et al*, 2008).

Given the interaction between interest-driven institutions, an 'institutional politics' approach is appropriate as one conceptual strand for understanding the dynamics of valuation positions that may structure RM's emergence. This approach has been used in analysing other fields of public policy where decision-making methodologies are established around particular measurement technologies (e.g. Porter and Demeritt, 2012). A second strand of our conceptual approach, in work bridging political and economic sociology, assumes that 'contentiousness' is fundamental to the 'legitimation of new market categories' such as industrial sectors (King and Pearce, 2010; Lamont, 2012). Struggles to establish new categories are part of stakeholders' strategies. Actors at the margins may be key to innovation (Mennicken and Sjogren, 2015), as has been described for example in the US grass-fed beef and dairy markets (Weber *et al*, 2008 cited in King and Pearce, 2010). In the RM case, actors 'at the margins' of the central policy regimes are essentially the biomedical innovators - small and large companies and their representative associations, specialist innovation promotion agencies, and clinical and academic research communities, and these actors contend with established, central gatekeeping, health service planning, and technology assessment institutions such as NICE, and their methodologies. A third strand of our approach acknowledges the importance of endemic knowledge practices in valuation processes. Methodological 'machineries' or 'technologies' of knowledge (Knorr-Cetina, 1999) partly

constitute the epistemic cultures that structure particular fields. Epistemological assumptions and methodological tools become deeply embedded in the operations of public policy and planning institutions, providing ways of comprehending their domains and making policy judgments (cf. Porter and Demeritt, 2012). The ascription of meaning, therefore, is a necessary precursor to the constitution of value. As Roscoe has stated, 'value depends upon the epistemic' (2015:27). In the case at hand, multiple meanings or 'identities' (Ulucanlar et al, 2012; Gardner et al, 2016) may be ascribed to different medical technologies by different actors through their technologies of knowledge, and value may be ascribed to them through their institutional tools and processes of judgment of worth. In other words, tools of calculation are implicated in processes of defining 'what counts' or 'what matters'. Here, we will show how the concept of 'reimbursement', deployed in the government response above, is a heavily-laden signifier in scenarios for RM products' future viability, directing the debate to a particular market-based vision of 'what matters' in RM valuation, pointing toward a payment-for-products model of the arrangements between producers and the public healthcare system or insurer as purchaser. A key example of an epistemic valuation technology to be discussed below is the 'Quality- Adjusted Life Year' (QALY)[1] the methodological bedrock of NICE in the UK (NICE, 2014).

Drawing on these related analytic approaches, it will also be instructive to compare the epistemic, methodological and institutional conflicts - understood as divergences of views/perceptions- illustrated in this paper with comparable developments studied in other nascent industries. Notably, Pallesen (2016) has discussed value and payment issues in terms of a 'politics of pricing' in the wind power market (in France), proposing that that case illustrates continuous struggles in four dimensions: the framing of the public interest; valuation as the articulation of the future; alternative possible agencies of governance; and

the role of valuation methods and calculations (Pallesen, 2016). Taking these four dimensions as a starting point, we propose that *all of* our analysis of values, valuation and payment scenarios is about 'the articulation of the future'. We build on Pallesen's notion, noting that the articulation of the future has to take place in the context of 'inherited' (Stokes, 2012) regulatory classifications, organisational infrastructures, budget categories and so on, without which future scenarios have no purchase. Evidence of this was prominent in our study. We refer also to Pallesen's other three dimensions in our analysis, going further to detail the positions, arguments and stakeholder actors in struggles over the healthcare adoptability of RM products, and suggesting that the RM case has become one in which the problematic value politics of the public good has become acute.

Thus, given this methodological approach, we set out to ask which institutional actors are developing what positions and how do they agree or diverge? What quantifiable technologies of knowledge are proposed and defended? And, *pace* Pallesen, what are the values, valuation processes and actors that contest what counts as 'good' public value, and how do these relate to possible payment systems or other modes of reward? As stated, our focus is primarily on the United Kingdom and its National Health Service (NHS) public healthcare system, with some reference to debate in other European Union (EU) states where it is prominent, such as Germany. Reimbursement to producers of medicines and medical technologies is essentially a national responsibility not governed by supra-national political regimes, though recent regulatory developments such as 'conditional authorisation' and 'early access' are supported at EU level (see section 'Valuation through market-building and payment scenarios' below).

Methodology

Our methodology was based on semi- structured interviews with key stakeholders in 2015 and 2016 and documentary material. Ethics approval was obtained from the University of XXXX. We examined the main UK reports on RM, to identify the institutions that have been active in the field and to identify potential interviewees. The interviewees and institutions included service planners, government-related national bodies (such as sections of the government Department of Health) and ethics bodies and agencies, funders, consultants, 'innovation networks' (organisations that promote RM innovation), trade organisations, health professional organisations, clinical research centres, journal manager, and patient research charities. From a short list of stakeholders we selected 1 to 3 key institutions in each category, and 43 interviews were conducted. Our initial interviewees suggested further possibilities (i.e. snowballing). We provided an information sheet, asked for signed consent, including that interview records be archived in the Economic and Social Data Service. We received good rates of acceptance from most categories with the exception of venture capital companies and ethical bodies (although a member of the latter answered questions informally); nevertheless our data contain many stakeholders' considerations of ethical issues). We interviewed one journal manager. 'Civil society organisations' are generally not active in the RM field and were not mentioned in the interviews; a member of the wider research team interviewed representatives of ten patient research charities (e.g. British Heart Foundation), but none of them mentioned reward/reimbursement issues. We classify stakeholders broadly in this paper into three types: 'gatekeepers' (NICE, NHS England, MHRA - Medicine and Healthcare products Regulatory Authority), innovators (companies, academic centres, and innovation networks/ promoters), and 'advisors' (specialist observers and expertise such as IP lawyer, health economists, biotech business consultant). To preserve anonymity we refer in the paper to broad categories only. All interviews were transcribed and coded in NVivo. Publications searches on key institutions yielded their official positions, and

we undertook analysis of recent journal publications on gene therapy. We analysed publication trends on RM 'reimbursement' which is the topic of a separate paper (AUTHORS, 2017). Relevant questions and data for this paper were focused on: the perceived value of RM and RM products, what method stakeholders' believed should reward its producers, and the reasons; whether new methodologies are required to define and assess RM products' value or values; proposals for novel payment schemes or methodologies; and whether specific funds should be earmarked for RM. Drawing on systematically coded interview transcripts and content analysis of key documents, we derived a set of main themes relating to reward/reimbursement in the RM field. These are illustrated and discussed in detail below, and comprise: alternative framings of 'value' itself (for example 'public health', 'equality', or 'market value'), issues of organisational and budgetary infrastructure of the NHS, issues of data collection and clinical 'evidence', potential reward/reimbursement schemes, and the salience of different RM product types.

Valuation devices and healthcare payment

NICE and the NHS Executive are the central institutions that have the responsibility respectively to evaluate new technologies and if appropriate guide their adoption into the healthcare system, and to oversee national-level payment schemes to recompense producers such as device or drug companies. NICE's verdicts on innovations are perceived as crucial to their prospects (Rose and Williams, 2012) and its assessment processes and NHS Executive's existing budget infrastructure form the backdrop to the development and debate of new scenarios for recompense of RM producers. In other words, the articulation of RM products' value and potential future reward depends on this inherited (and continually changing) regime.

Conceptually, NICE's over-riding mission is primarily to 'make things the same' (Mackenzie, 2009) by applying a standard metric, a machinery of knowledge, to identify the technologies most deserving of national adoption. NICE thus acts as a central threshold-setting institution by deploying the long-established 'QALY' methodology. The QALY is a key algorithm in national level gatekeeping. Its methodology has become an established 'mode of coordination' (Moreira, 2012). It enshrines an essentially utilitarian approach to health technology innovations, seeking to produce the greatest public good for the most population. Deployment of the QALY facilitates processes of giving differential value, defined in terms of population health gain, to different technologies, so in turn providing for resource allocation. It can thus also be understood as an 'allocation protocol', to use Roscoe's (2015) term. By using the QALY, NICE's technology appraisal and advisory committees and staff enact a rule that subsumes into its system the contentiousness about 'value' that is characteristic of the political negotiation of market boundary-work.

We now describe the basic features of how the NHS can introduce a new technology, which is defined by NICE and the NHS Executive. It is necessary to bear this in mind when considering the value debates and scenarios for reward provided in our data, analysis of which follows. Decisions to 'reimburse' technologies/services are taken through various different pathways (AUTHOR2, 2016). First, two formal pathways at NICE result in mandatory decisions: for larger target populations the 'Technology Appraisal'[2] and for rare diseases the Highly Specialised Technologies Evaluation (HSTE). If these NICE procedures result in negative decisions, manufacturers can propose a Patient Access Scheme (PAS), usually a lower price. Manufacturers can also negotiate specific performance related agreements (Epstein, 2014). Given the different assessment routes in NICE, the NHS Executive may or may not be legally obliged to provide a novel technology through the NHS.

This is rarely a straightforward matter not least because of the wide range of possible routes of service provision. Most NHS services are paid for under the 'National Tariff' system (conventionally called the 'drug tariff' in spite of not being confined to pharmaceuticals), which annually allocates prices to units of care delivery ('currencies'), enshrined in a complex resource coding system ('Healthcare Resource Groups' - HRGs). The NHS decides on commissioning (contracting and paying for) therapies either at the National Executive level for Specialised Services or locally through 'Clinical Commissioning Groups' (CCGs) led by General Practitioners planning for the local population. It is notable that NHS England (NHSE) appointed a National Clinical Director for Regenerative Medicine in 2016 to advise on policy, joining a set of some 20 such positions for various services. CCGs could in principle decide reimbursement locally including RM treatment, for example treatment for chronic diabetic ulcer including tissue-engineered skin substitute.

Very expensive drugs, devices and particular services, especially where only a few centres provide them, are reimbursed through the NHS Executive additionally by extra price negotiations. Further, certain services can be deemed separate from the tariff as 'Specialised Services', some cancer services being an example. The unique 'Cancer Drugs Fund' (which some of our interviewees referred to), was started in 2011 to make certain expensive drugs more easily accessible, and was reconfigured in 2016 notably to give NICE a larger role in assessing relevant drugs, following criticism from prominent health economists (Claxton, 2015). The existence of such a fund illustrates the constant tension that exists between the kinds of allocation devices deployed by policy institutions such as NICE, and the pull of priorities from the 'political' domain, mobilising different registers of value, cancer being seen politically as a 'dread disease' warranting special, exceptional policy treatment. As one interviewee commented, clearly drawing on a societal level value-concept of fairness : 'I

think the issue with the Cancer Drugs Fund was that it was set up with no value element included in it at all' (Gatekeeper 3, 2015).

As noted in the introduction to the paper and as the Cancer Drug Fund case illustrates, payment or reimbursement is not the only discourse in which the valuation of RM is being conducted. The explicit discourse of 'value' has grown in the HTA, government health department, and health system communities. The NHS Executive refers to 'Commissioning for Value' (website); the Cell and Gene Therapy Catapult aims 'to explore models based on value' (website); NICE committees consider the 'value proposition' of technologies (Campbell, 2012), and economists propose new methods for producing data relevant to healthcare value (Epstein *et al*, 2012). Thus 'value' as a symbolic term is itself part of the emerging valuation of RM, broadening and indeed challenging the narrower discourse of 'reimbursement'. This explicit discourse appeared in our interviews, though it is notable that it came mainly from those we defined as consultants and gatekeepers:

> I think in the highly- specialised treatments, they're in a separate box partly because of evidence issues, but mainly because of a sense that you have to apply different values. (Consultant 2, 2015)

Considerations of societal value are seen at NHS system level as challenging basic democratic values:

> if you start taking account of wider societal benefit and…things like ability to earn money and contribute finances to society, then straight away you start getting into some terrible equality issues. (Gatekeeper 3, 2015)

So the discourse of value can frame the public good in different ways, special cases such as therapies for cancer being informed by different values than curative therapies for relatively rare genetic diseases. 'Wider societal benefit' can be defined in population terms given RM's

curative promise (potentially allowing people to resume a 'contribution to society'), or by contrast in public priorities translating latent hierarchies of 'disease values' into healthcare policies.

Many of our participants approached the RM value issue in terms of the notion of 'reimbursement'. Most believed it to be an important issue, with the exception of most of the research charities interviewed (9 out of 10), and gatekeepers, for whom payment issues are outside their official remit. Most of the innovators, gatekeepers and advisors were aware of ongoing discussion in terms of reimbursement. The 'innovators' were those most vocally concerned about reimbursement. A critical view typical of trade organisation representatives was:

> So I think we have the academic excellence, some significant infrastructure, a growing community... What we don't have is a route to reimbursement. (Trade organisation 2, 2015)

Such statements emphasize the reliance of future scenario- building on participants' understandings of the current valuation and payment environment. Our data reveal a wide range of features of this existing infrastructure and role definitions amongst the gatekeepers, NHS budget structures, and how these impinge on stakeholders' 'articulation of the future'. Most of the institutional stakeholders had views about organisational aspects of payment possibilities seen as problematic given existing infrastructures:

> choosing the right patients to give the right medicine to is going to be problematic. So the (payment) system readiness…is (defined by) the currencies of contracts (which) will be a barrier... (Innovation network 1, 2015)

A perceived divide between market regulation and technology assessment, and in addition conflict between roles, knowledge practices and organisations was a common theme amongst

gatekeepers, including technology assessors, and industry, with a widespread conviction that NICE and NHSE should be more coordinated:

> Currently we have NHS England evaluation capability, we have a NICE evaluation capability and the two are no longer tightly integrated ... (Trade organisation 4, 2015)

Gatekeepers, NHS innovation actors and trade organisations all highlighted the existing special organisational infrastructures referred to above, which could be exploited for RM payment pathways:

> All of these medicines will come under specialised commissioning and there is the mechanism there…for commissioning policies to be developed, for the evidence base to be reviewed and for recommendations to be made. (Trade organisation 4, 2015)

It should be noted however that this perspective elides a number of issues. First, the assumption that all RM products will be 'medicines' with the implication of a pharmaceutical-style market for the NHS is certainly a partial representation of the current developments in RM products, where small-scale, personalised, surgeon-dependent applications, often with a medical device component, are significant. So the powerful agenda-shaping voice of the pharmaceutical medicines industry is evident here. Second, the statement that specialised commissioning will be the norm ignores the likelihood that some RM products will be subsumed into existing 'currencies' funded under the standard tariff scheme. As one gatekeeper noted:

> … if you're going to have an active dressing for a foot ulcer, that's not going to be a specialist commissioning area. That's going to need to be funded under the drug tariff because that takes place in the community…. Whose budget does it come under? (National body 1, 2015)

The design and administration of different NHS (and as the above quote implies, possibly social care) budget regimes act as one form of governance that will structure the market for

RM products. If a product cannot be fitted easily into an existing 'currency', lengthy and expensive negotiations would be needed possibly to extend an existing resource group definition, if a 'specialised' status cannot be given. We reiterate that these regimes are situated wholly within the public healthcare 'reimbursement' system, a point that we will return to below. *Pace* Pallesen (2016) and given the diversity of RM products types, it is clear that articulation by stakeholders of RM's future must take account of the *diverse types* of products in the context of existing budget regimes. Thus, the classification of RM technologies is key to their valuation and potential recompense to producers. Our analysis suggests that this diversity is downplayed in many accounts amongst powerful stakeholders, though some commentators do consider it:

> … cell and gene therapy, I think, will have an easier route into adoption…They will face challenges on cost, I think but they will be straightforward challenges because they will be compared with current (drugs)…as we move forward into the more medical device type areas like orthopaedics and like wound care, I think that's going to become much more complex. (Innovation network 1, 2015)

The complexity referred to here entails different healthcare epistemic cultures, as Roscoe (2015) pointed out, underlying alternate potential valuations:

> … orthopaedic surgeons are used to the type of assessment that occurs for joint replacement…Culturally it will be quite a difficult place for them to understand the rigour of the assessment perhaps that medicines would have. (National body 2, 2015)

Thus, the type of product, RM or not, or type of RM, is seen as a complicating aspect of RM valuation from an NHS system perspective, especially for applications that do not fit pharmaceutical market models. Likewise, physical infrastructure of service provision is related to the potential classifications of different RM therapies, hence shaping the future pathways for market schemes:

> … there are new challenges in applying normal techniques that we use… what are you going to compare, the cost of the cell treatment to the cost of the current treatment…? Is it always going to be in a tertiary centre or is this going to move out into general medical practice? (Consultant 2, 2015)

NICE and NHSE as the primary gatekeepers have to assess various data and 'evidence' for their 'valuational' assessments of RM, as other technologies. As noted, the level of uncertainty of clinical evidence with emerging RM products is unusually high. The appropriate types and 'levels' of evidence for RM products was a widely raised and contentious issue. Promoters of RM technologies argue, and some indeed lobby, for what one interviewee called a 'more forgiving' approach by technology assessors. The trade organisations unsurprisingly were most expansive about a need for new HTA approaches and methodologies:

> we're not going to have large-scale, double-blind RCTs (Randomised Control Trials), we're going to have different kinds of study which, essentially, in front of a NICE appraisal committee, would be viewed as lower-quality evidence. (Trade organisation 4, 2015)

Clinical actors confirm that long-term outcomes of certain RM techniques are simply not known. Referring to knee cartilage regeneration:

> costing the impact of something where you don't know the durability of the product is very difficult… They're not going to build your cartilage forever so we're back at … the limits of the evidence base. (National body 2, 2015)

The novel methodologies being promoted include 'real world evidence', usually taken to mean patient follow-up data from registries, or possibly individual patient records:

> … So we want to be able to see how real-world evidence collection can be used more actively in appraisals…HTA bodies are not used to having to take that kind of

> evidence into account. (Trade organisation 4, 2015)

Indeed, gatekeeper HTA body NICE is robust in defending its existing approaches:

> The NICE technology appraisal methods have very much been designed so that you can evaluate different therapies for different disease areas for different severities all on a level playing field, and we do that through the metric that we use (i.e the QALY) (Gatekeeper 3, 2015)

A number of contentious issues were raised specifically about data that might underpin RM payment schemes. These especially concerned difficulties and costs of collecting appropriate clinical data, practical implementation of recommended therapies:

> There is a great reluctance on the part of both pharmaceutical companies and the NHS on the ground to enter into these schemes that involve collecting data. (Consultant 2, 2015)

Challenging the established valuation mechanism

An important test of NICE's capacity to deal with RM products was conducted in 2015-16. This consisted of an 'exploratory study of the appraisal of example regenerative medicine products' (NICE, 2016; Hettle *et al*, 2016). This highlighted the challenge from various actors, especially the innovators, to the prevailing valuation methodology of the QALY. The study can be understood as a testing of the machinery of valuation knowledge, though not going beyond the 'reimbursement' assumption of market transaction. It concluded that NICE's existing methods were sufficiently robust and versatile:

> These results can support manufacturers and reimbursement bodies in determining potential commercial and health system value. The significant clinical gains provide support for significantly higher value based prices than current

> technologies…However, the potential high upfront costs of these technologies may present additional challenges… (Hinde, 2016).

The 'additional challenges' resulted in the following conclusion:

> Where there is a combination of great uncertainty but potentially very substantial patient benefits, *innovative payment methodologies* need to be developed to manage and share risk to facilitate timely patient access while the evidence is immature …The discounting rate applied to costs and benefits was found to have a very significant impact on analyses… (NICE, 2016, our emphasis)

This statement can be regarded as a concession on the part of NICE, acknowledging as a legitimate value itself the *tradeoff between* 'commercial and health system value', expressed in the form of potentially flexible payment models. In other words, in Pallesen's terms, conflicting definitions of the public good have been welded together in a 'compromise' position.

Reviewing these data, we see that an explicit discourse of broadly defined societal value or the public good is not prominent. Industry interests press for more flexibility around types of assessment data, NICE in particular as a governance actor is resilient in maintaining its gatekeeping role around the 'allocation protocol' (Roscoe, 2016) of the QALY, implicitly at least maintaining the utilitarian value on population health as public good, and the classification of different types of RM product emerges as key in 'articulating the future' of RM in the context of existing budgetary infrastructures and professional medical cultures. However, we also see NICE accepting that more flexible methods of recompense for producers might be acceptable from both a public good point of view as well as being compatible with its own machineries of knowledge that construct 'what matters'.

Valuation through market-building and payment scenarios

Still within the 'reimbursement' paradigm, many of the institutional stakeholders discussed non-mainstream payment possibilities that NICE's exploratory study pointed towards, noting a range of apparent flexible 'gateways' proposed or emerging (AUTHOR1, 2016, 2017). These flexible schemes include conditional authorisation and 'early access', payment by results, 'risk-sharing' and other 'managed payment' schemes, ring-fenced RM funding, and recompense on condition of further data. Here, for reasons of space, we present a small selection from our data on these alternative scenarios and methodologies.

Trade associations showed major concern with the development of a RM market, outlining the basic principle of a financial 'risk-sharing' approach:

> There needs to be more flexibility to say, 'Okay, so maybe the medicine will be provided at a different in-market commercial price for this period,' but then, if the data supports it, the price should go up.... and it's only if we accept that that we're properly accepting that value should be linked to price. (Trade organisation 4, 2015)

Risk-sharing schemes, in which the NHS can reclaim payments from companies in case of lesser than projected medical outcomes, raise issues for existing payment systems:

> some companies are sufficiently confident that they will want to sell their product on a 'you won't get billed unless we deliver that benefit to you' and that allows multi-year (payments) (Innovation network 1, 2015)

Similarly:

> we're going to say 'if that's all it does we're going to pay 10% of what you set the price as it just hasn't fulfilled its promise'. (Service 1, 2015)

An 'Early Access to Medicines' (EAMS) scheme was introduced by market approval regulators in 2014, aiming to speed up clinical access to medicine deemed to have good

potential in the case of life threatening conditions with no alternative ('unmet need'). The medicine is provided free by the producer pending data collection and licensing authorisation (Office for Life Sciences, 2016), which is a point of contention:

> we maintain that for the Early Access to Medicines Scheme to fully benefit patients it must be centrally funded and reimbursed (UK Life Sciences, 2014).

Gene therapy, of which there are already examples on the market, represents the most extreme medical form of RM, where cure for life-threatening, intractable disease is envisioned. Here, we see stakeholders' considerations of value principles and valuation methodologies highlighted, and conventional payment regimes most challenged. Developers of genetic therapies that fulfil the criteria of 'unmet need' can gain regulatory incentive advantages (Hyry, 2015), and numerous options for funding gene therapy products are being debated. However, it has been opined that tackling this will require a 'revolution in the reimbursement environment' (Carr and Bradshaw, 2016). Health economists have noted that 'Willingness to pay is typically higher in smaller patient populations', and that outcomes modelling and risk-sharing agreements can address the uncertainties of trials (due to small numbers) in niche populations (Jorgensen and Kefalas, 2015). The endorsement of modelling techniques by health economists and NICE is a very concrete example of the 'articulation of the future' through machineries of valuation knowledge.

Payment options that have been discussed for gene therapy RM range from payment-by-results to up-front lump sum payments to capped annuity with risk sharing, which Touchot and Flume (2015) believe is the most likely approach, noting that this would allow 'health systems to spread the cost over several years and to limit risk if efficacy is not maintained'. However, they also opine that most healthcare systems cannot implement such an approach

currently (2016: 902). Notably, flexible clinical outcomes-dependent schemes necessitate accurate and systematic follow-up of patients, hence the emphasis on 'real world evidence' as mentioned above. While dedicated national funds for RM as a special technology are appealing to producers (proposed in the 'VALUE' report, Biolatris 2012), if anything there is a retreat from such approaches, as shown in the UK case with the recent reform of the Cancer Drugs Fund, where the socio-political allocative priority accorded cancers has been reined in by the cost-utility arguments of HTA and NICE (NHSE, 2016).

In summary, we can see a wide range of flexible, conditional payment schemes being discussed and contended between the key institutions as RM and its proponents challenge existing infrastructures, some of which are specific to RM and some more broadly applicable. These scenario debates formulate schemes which would make valuation of RM products possible, showing a growing trend of provisional measures that would satisfy values of the public good in terms both of enabling access to special therapies and of providing innovation and market incentives to therapy developers and producers.

Where value and payment meet – a clash of paradigms

The previous sections have shown how the reimbursement market paradigm for RM has dominated the contentious policy discourse and option appraisals between the central institutional actors and the innovator stakeholders. Concern about broader, society-wide value regimes became acute over the last few years, with the emergence of advocacy for a putatively fairer system for pricing drugs – 'value-based pricing' – and subsequently for 'value-based assessment' (VbA).

> The terms of reference (i.e. from the government Department of Health) asked NICE to introduce 'a simple system of weighting for burden of illness that appropriately

> reflected the differential value of treatments for the most serious conditions, encompass the differential valuation of treatments designed to extend life at the end of life… within a new system of burden of illness weights and include a proportionate system for taking account of wider societal benefits (NICE, 2014).

Value-based pricing, however, has not been implemented. The Parliamentary Office of Science & Technology (POST) has stated that it floundered because:

> there were concerns over how to determine price, including how to price a drug that can be used to treat different conditions or patient groups (for which its value could be varied). Other concerns included potential discriminatory effects and how unmet need…, innovation and real world evidence could be taken into account… Measures that attempt to capture WSI (Wider Societal Impact) and BoI (burden of Illness) will discriminate in favour of those treatments that provide the highest value to society …. Conditions that predominantly effect older people … may discriminate against older people ... (POST, 2015).

Although for example, drugs that help older population groups with chronic conditions to lead a better quality of life might be seen to have 'high value' in society, in fact the policy concern expressed here is that value accorded 'contribution to society' as societal impact might all too easily be gauged in economic terms of employment and productive work, thus neglecting less measurable contributions such as family and caring activity. The stalling of VbA is significant because it shows the difficulties that conflicting institutional stakeholders have in defining the public good, the societal value of novel technologies such as RM products, via ethically acceptable methodologies. So VbA as a methodology or machinery of knowledge has failed to find a place in the accepted repertoire of valuation methodologies. In Pallesen's terms, we can understand VbA as an attempt to square societal-level public good principles with a quantitative allocative valuation tool, both of which attract controversy

between different stakeholder groups. Value-based assessment extended the definition of the public good, but some scenarios in the RM valuation debate extend beyond this. The recent 'value turn' highlights this, and we briefly note broader value criteria below.

Non-payment approaches to valuation

We have been careful in this article to frame reimbursement as one possible means by which RM producers seek reward for their products, but other modes of reward lie outside the NHS as a marketplace. 'Value' might not lie within the bounds of healthcare-related transactions or even calculations of 'societal impact'. Although a relatively rare view amongst our interviewees and in the key documents we have reviewed, recompense or worth in general was sometimes defined in a more holistic, systemic way, and this was also evident in gene therapy scenarios. For example, from an innovator's point of view value might lie in adjunct materials to an active health technology:

> there could be a piece of plastic, software, glass, metal, or a…standard operating procedure… those things remain every bit as valuable, and it means that there is a lot of value to be had …. (Consultant 3, 2015)

Likewise, economic consultants envision approaches that take a broader view of the public good and methods by which innovation can be rewarded, such as intellectual property-based payment including 'prizes for patents, out-licensing of technology rights or prolonged patent rights' in the case of gene therapy innovation (Carr and Bradshaw, 2015). Such a formulation of value breaks the mould of the conventional healthcare-centric view of reimbursement, taking it to a broader societal level of the overall innovation ecology. It is notable that some health economics thinking within the HTA community is starting to recognise this type of valuation approach, for example as 'scientific spillover' (Marsden et al, 2016), although policy outcomes of such considerations are yet to be formulated.

Discussion and conclusions

A growing policy concern with the societal value of medical technologies in a resource-limited system is clearly evidenced by the current turn to a value debate in the regenerative medicine field. We have placed the discourse of reimbursement in context of emerging movements mobilising different value registers in medical technology planning. We have illustrated how valuation is multidimensional, with institutional stakeholders mobilising their views on NHS and technology assessment infrastructures, the definition of RM's appropriate value regimes, the methodologies and data of technology evaluation, on evidence and on payment scenarios. Thus differing epistemic cultures (Knorr-Cetina, 1999; Roscoe, 2015) shape 'what matters' in the stakeholder politics of RM products' markets design. Specific tensions are evident between central and contending institutional stakeholders, between future scenarios of RM products' introduction into public healthcare and existing inherited infrastructures, and between different medical specialist cultures of innovation. While there is some common ground between institutional stakeholders such as industry innovators and health system gatekeepers, there is also significant conflict. The inertia of existing payment systems and tariff structures is a clear impediment to reimbursement of novel technologies. Not only are most RM technologies themselves expensive, but 'real world' data collection is too. There is a degree of experimentation and scenario-building with novel systems, with different forms of 'risk-sharing' receiving particular attention, although with no clear dominant model.

Within the reimbursement paradigm, the QALY as a machinery of valuation knowledge and managed market device remains resilient in spite of its history of controversy (Schwappach, 2002), although the potential use of alternative valuation pathways expressing different sets

of value principles is a notable development. Exceptions to the mainstream assessment and reimbursement routes in the form of the 'specialised' technologies and services are diversifying the potential healthcare adoption pathways and payment scenarios, and responding to different societal and political regimes of public good values. We have shown clear divergence between the pharmaceutical market model in the reimbursement discourse and the recognition that some RM will be embedded in existing tariff structures, budgets and clinical service packages. Also notable is the increased attention within NICE to a role for modelling and discounting techniques in the face of clinical and cost-effectiveness uncertainties and data challenges, increasing the flexibility of the reimbursement paradigm.

Turning more closely to the analytic themes that have guided our discussion, we have recognised Pallesen's four dimensions of struggle in the case of RM valuation and payment scenarios. First, we have seen valuation as 'the articulation of the future', especially in the proposal and debate over payment scenarios, the value-based assessment debate and the exploration of the applicability of NICE's machineries of knowledge to RM technology. And NICE's 'exploratory study' extends the articulation of the future via proposals for further economic modelling and future outcomes-dependent payment scenarios. Further, we have extended this analytic theme by analysing the many features of the existing inherited assessment and budgetary infrastructures that innovatory fields such as RM must contend with. Second, we have shown alternative framings of the public good and economic benefit: while the wind power technology that Pallesen analyses addresses a problematisation about the natural environment, RM valuation is construed to address problematisations of 'unmet needs', life science industry development, and the societal value of aggregate population-level healthcare. Third, stances toward market governance are clearly shown in the RM case. Rather than 'feed-in tariffs' (state incentives guaranteeing companies' payments for

providing electricity) in a liberalised market, we see the much more state-steered market of national healthcare services grappling with complex biomedical innovations under constrained budgets in conditions of scientific and clinical uncertainty. Flexible schemes such as conditional authorisation and early access combine governance by incentives with oversight, and regulatory control over innovation – a hybrid and provisional form of innovation governance, that attempts to address that state-steered market. Further, the level of the 'marginal' stakeholders' participation in reimbursement debates illustrates a level of albeit contentious 'partnership governance' with state and gatekeeping agencies, conflictual though it may be. Finally, Pallesen's analysis of the struggle over the ability of valuation methods and calculation to produce fairness and efficiency in the system, is echoed by our analysis of the disputed role of the QALY as a valuation method and allocation protocol, and the evident calls for more flexible and adaptable valuation machineries for RM through 'real world data'. Adding to this point, we can note the high complexity of contemporary healthcare provision and the high level of commercial medical innovation exemplified by RM that is resulting in a more diversified set of pathways including state-legitimated conditional exceptions and special considerations for certain types of product with high promise, and certain classes of patient such as those with rare, hitherto 'incurable' disease. The failure of Value-based Assessment can be accounted for by the different incommensurable value principles brought into conflict by this complex version of the public good.

Unlike the case of wind power technology, which produces electricity with a high degree of certainty, the market of medical products is massively diverse and effectiveness of the products largely uncertain. Thus, in the RM cases examined here, the political discourse on the RM market at this stage is focused more on valuation, societal and healthcare values, and the infrastructures of assessment and payment systems rather than on pricing per se. RM

treatments for common conditions such as chronic ulcers address different markets and different potential payment pathways than gene therapy products offering cure for rare diseases. Such structures embed deep value positions that delineate subsectors of the market. In the RM case we have seen a plurality of non-aligned values informing the political negotiation of RM products' future, notably innovation promotion and medical need on the one hand, and healthcare resourcing and population medical provision on the other. It is worth noting that the heightened entanglement of such values may be greater in the UK context than some other advanced states where the value of 'unmet need' may be accorded higher priority (INCa, 2018).

In summary, our analysis shows that valuation debates and market- building are the sites of interplay of different value principles and regimes – social, ethical, economic, and health-related. Conflict is evident between gatekeepers and innovators over the definition and operationalisation of 'value' in payment systems, as well as there being some recognition that RM producers may access alternative modes of reward altogether. RM producers can obtain reward through systems other than commodity markets. Here, our data on reward systems for RM has some kinship with that of Birch (2012; 2016) who has proposed that the bioeconomy is developing through processes of assetization and financialization, rather than a 'biocapital' market in material, biologically derived commodities. Our data on the multiple RM stakeholders' positions include some stakeholders countenancing his view, for example, that royalties rather than simply payments may be required as part of (some of) RM's incentive structures for creating 'value' (Birch, 2012:198). However, our analysis shows that the current valuation debates around RM in the UK encompass not only capitalist value, whether through assetization or through commodity markets, but also broader 'egalitarian' (Gardner, 2017) social public good values such as fairness, non-discrimination, equity, speed of access,

and population health. The extent to which this complex interplay of values can be steered and aligned through policy and institutional infrastructures to achieve an acceptable mix of medical, healthcare, economic and social goals for the range of regenerative medicine products, remains an open question.

Notes

[1] 'A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.' (https://www.nice.org.uk/glossary?letter=q)

[2] Although the literature generally refers to 'Health Technology Assessment', NICE's term is 'Technology Appraisal'.

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