

Comparative lessons in regenerative medicine readiness: learning from the UK and Japanese experience

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This paper explores how ‘regenerative readiness’ varies between different national research and health-care systems. Here, ‘readiness’ refers to both the readiness of a given technology and the ability of a given setting to adopt a new technology. We compare two settings that have taken active yet dissonant approaches to improve readiness: the UK and Japan. Existing scholarship observes that disruptive technologies such as regenerative medicine require many adaptations to become useable and function along the principles of their design. We incorporate the sociotechnical systems framework to consider the range of adaptive measures taken across elements of the sociotechnical system for novel technological adoption. Building upon existing works on technology readiness and institutional readiness, we also expand the conceptualization of readiness toward system-wide readiness.

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Regenerative medicine (RM) is a novel therapeutic modality that involves replacing or regenerating human cells, tissues or organs, to restore or establish normal functions. The field incorporates a variety of technologies including stem cells, gene therapy, gene editing and related technologies (base editing, RNA editing et cetera), 3D bioprinting and novel biomaterials [1,2]. The therapeutic potential of RM – to cure rather than merely manage chronic diseases – along with the economic benefits of advancing a frontier industry, has spurred many governments and firms to invest in the field [3–5].

Amidst international efforts to realize the transformational potential of RM, this paper responds to a call to examine how ‘regenerative readiness’ varies between different national research and healthcare systems. ‘Readiness’ here refers to both the readiness of specific technologies, typically assessed in terms of technology readiness levels (TRLs) [6] and to the ability of a given environment to adopt a new technology. Scholars across disciplines have noted that radical, disruptive or unfamiliar technologies require users and user contexts to adapt, in order to enable the technology to become usable and function according to the principles of its design [7,8]. RM undoubtedly falls into this category, owing to the distinctive use of cells, tissues and genes to treat disease and repair bodily damage. Acquiring ‘readiness’ requires adjustments across diverse areas. Around the world, various regulatory adaptations have been made to support RM [9,10]. Providing RM also requires an appropriate infrastructure, from sourcing the starting material, through manufacturing, to clinical delivery, as well as clinical skills, business models and reimbursement strategies [6,11–15].

This paper focuses on ‘system-level’ regenerative readiness in two countries: the UK and Japan. Both nations are leading centers of RM, where there has been a collective effort by government, academic and industry stakeholders to advance the field. In both settings, there has been a range of initiatives to improve regenerative readiness: from

the education of healthcare workers; introduction of expedited regulatory pathways; as well as the creation of specialist clinical treatment centers. At the same time, measures to support readiness have reflected the distinct features of the local settings, such as the organization of healthcare, or the existing legal system. The British and Japanese experiences in RM therefore offer an informative comparison of ‘system-wide’ readiness strategies, as the two countries have taken different approaches to enhancing readiness in dissonant health contexts. As works on experimental governance have noted [16], collaboration and mutual learning between countries can help support the realization of promising technologies. Such comparisons help us to learn from experience and improve best practice involving ‘regenerative readiness’ and collectively accelerate translation to the clinic. The international harmonization of such practices may also facilitate the future translation of therapies across borders.

Defining regenerative readiness at the level of national systems

Moving advances in scientific research ‘from bench to bedside’ to develop new clinical products and services is not straightforward. The concept of ‘translational research’ developed in response to the recognition that ‘upstream’ investment in basic or exploratory research, while often yielding important scientific knowledge, requires further work to transform the findings into ‘downstream’ clinical applications [17]. Translational research can also be divided into different components. The first of these, sometimes designated as ‘T1,’ describes the process of developing findings from basic research into a functional product or process [18]. The degree of functional performance can be described in terms of TRLs. TRLs were originally developed by NASA as way of measuring the degree of development of components or systems for the space shuttle [6]. They operate through a scale consisting of nine levels, where level one ‘basic principles observed and reported’ roughly equates to basic research, and level nine ‘actual system flight proven through successful mission operations’ equates to a finished product – similar to a medicinal product that has successfully received marketing authorization and approval from a national regulatory agency. Given that a number of cell and gene therapies are already on the market [19], while many more are in various stages of development [20–23], it clearly makes sense to ascribe different TRLs to specific products within the broad field of RM.

The second component of translational research, ‘T2,’ describes the work needed to promote the dissemination and adoption of new technologies or processes. The challenges to be overcome, and the knowledge and skill sets required to achieve them, are substantially different from T1: “T1 struggles more with biological and technological mysteries, trial recruitment and regulatory concerns. T2 struggles more with human behavior and organizational inertia, infrastructure and resource constraints, and the messiness of proving the effectiveness of ‘moving targets’ under conditions that investigators cannot fully control” [18].

This illustrates another dimension of ‘readiness’: the extent to which healthcare institutions, especially clinical sites, are ready to employ RM therapies in clinical care. This dimension has been captured in the idea of ‘institutional readiness’ (IR) [24]. IR assesses the degree to which a clinical site needs to adapt, in order to successfully adopt RM products, and the extent to which changes have been implemented. For example, hospitals need the capacity [15] to cope with the requirements of these new therapeutic modalities: from appropriate staff training [12]; ensuring access to a GMP-licensed facility [25]; to putting appropriate systems in place to monitor outcomes and costs [24]. While TRLs assess a technology in terms of adequate functionality, IR assesses the degree of compatibility with ‘real world’ clinical sites.

However, most RMs are ‘disruptive’ technologies, in that they are significantly different from conventional small-molecule pharmaceuticals, biological drugs such as monoclonal antibodies, or medical devices. This is due to the novel technological base of RM: in cells, tissues or genes [26]. Accordingly, the challenges involved in translation remain considerable. These include scale up and manufacturing [27–29]; establishing appropriate regulatory pathways to approval; as well as forming viable business and reimbursement models [11,21,30–32]. It also includes ensuring that there are enough people with the right skill sets at all stages of the translational pathway – from biomedical scientists, engineers, material scientists and physicians from medical, surgical, radiological and laboratory medicine specialties, to Qualified Persons capable of signing off on batches of RM products – and the availability of appropriate physical infrastructures [12,24]. In keeping with the move toward patient-centric medicine, there is a recognition that patient charities and organizations have a role to play in developing the way clinical services are structured and delivered, such as providing feedback on how different options impact on the quality of life, and helping to develop suitable patient-reported outcome measures to evaluate treatments [24,33].

All of this requires broader system-level adaptations and constitutes a third dimension of regenerative readiness beyond TRLs and IR, while overlapping with both. It makes sense to consider systemic readiness at the level of

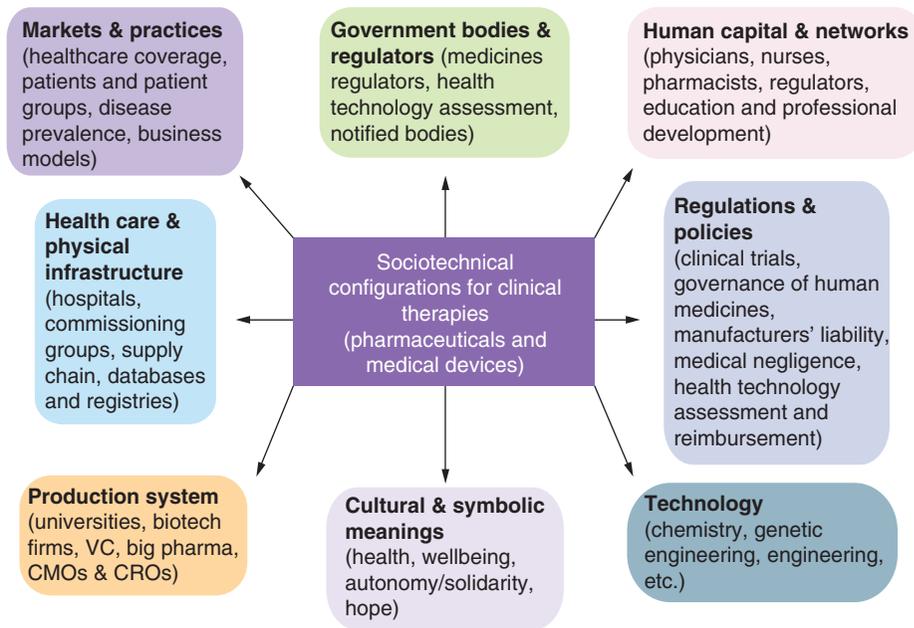


Figure 1. Generic representation of the sociotechnical system for clinical therapies (pharmaceuticals and medical devices).

Modeled after Figure 1 from [36].

CMO: Contract manufacturing organization; CRO: Contract research organization; VC: Venture capital.

nation states, as different countries usually have distinct regulatory and healthcare systems, differing degrees of investment in the academic science base, and differently constituted commercial sectors. This view aligns with recent scholarship on sociotechnical systems [34,35], which argues that system-wide adaptations are necessary to enable the transition to using a new technology. Previous scholarship on innovation and technology transitions has noted that any sector consists of 'an interdependent and coevolving mix of technologies, supply chains, infrastructures, markets, regulations, user practices and cultural meanings' [35]. These elements comprise a sociotechnical system [34–36], which in turn, can be considered as different areas that require adaptation to improve the system-wide readiness needed to support the transition to the use of a new technology. Figure 1 illustrates a generic sociotechnical system for medicinal products, based on that for pharmaceuticals and medical devices.

Figure 1 identifies important supply-side and demand-side elements whose dynamic interactions and coevolutionary processes are key to enabling the system-wide adoption of novel innovations. These include: markets and practices (including reimbursement mechanisms); government bodies and regulators; healthcare and physical infrastructure (e.g., clinical GMP-certified clean rooms, cryopreservation facilities); human capital and networks; the production system; cultural and symbolic meanings; as well as technology. It is important to note that, in practice, these different elements of the sociotechnical system are not discrete but interconnected. For example, specialized physical infrastructure (e.g., cryopreservation facilities) is not functional without appropriately skilled staff to operate it (i.e., human capital). Figure 1 should, therefore, be seen as an idealized, heuristic device to facilitate understanding rather than an account of any given real world situation. To understand the challenges involved in delivering RM, we need to focus on the ecosystem beyond specific projects in RM. We therefore analyze how the different elements of the existing sociotechnical systems for therapeutic products has been adapted for RM in each country.

Rationale for comparing the UK & Japan

There are a number of reasons why the UK and Japan offer good case studies to examine and compare national efforts to enhance regenerative readiness through strategic adaptations of their existing sociotechnical systems for medicinal products. First, both countries are global leaders in the field of RM with robust scientific capacity. For example, the 2012 Nobel Prize was jointly awarded to professors John Gurdon in the UK and Shinya Yamanaka in

Table 1. Major features of the national healthcare systems relevant to regenerative medicine in the UK and Japan.

System feature	UK	Japan	Ref.
Healthcare provision	Primarily public NHS, with some private healthcare provision	Primarily private healthcare system, with access subsidized by the government through NHI	
Reimbursement of approved medicinal products	Provision on the NHS subject to prior cost–benefit analysis by the NICE. Impact of a therapy calculated in QALY and compared with existing standard of care, set against a predefined threshold of cost-per QALY	Provision under NHI follows approval by the Central Social Insurance Medical Council (Chūikyō). Pricing is mostly based on a similar efficacy or cost-based accounting method; some are subject to cost–benefit analysis	
Adaptations for RM?	Alternative options have been proposed and discussed, including VbA, risk-sharing and ‘payment for performance’ schemes, ‘commissioning by evaluation’ and alternatives to direct reimbursement but none of these have been implemented to date	Provisions for insurance coverage for conditionally and fully approved therapies under the PMD Act (2014). Out of pocket payment for unapproved therapies provided by physicians subject to safety review under the ASRM (2014). Mixed billing is permitted under certain conditions	[41–47]
RM industry development	Primarily SMEs, often commercializing discoveries from university-based research. Smaller number of long-standing RM firms and some interest in CAR-T and gene therapy from large pharmaceutical companies	Historically based on in-licensing products from abroad. Currently, a mixture of large, pharmaceutical and nonhealthcare firms, such as Takeda and FUJIFILM, investing in RM as well as recent ‘born global’ SMEs	[5,38,48]
Regulatory agency responsible for medicines and medical devices	MHRA	PMDA	
Product classifications for RM	Advanced Therapy Medicinal Product category, divided into four subcategories: sCTMPs GTMPs TEMs Combined ATMPs (integrating an ATMP and one or more medical devices)	Regenerative Medical Product category within the Pharmaceutical and Medical Devices Act, defined as: (1) Processed human or animal cells intended for: (a) the reconstruction, repair or formation of the structure or function of the human (or animal) body or (b) the treatment or prevention of human (or animal) diseases (2) Gene therapy products for the treatment of disease in humans (or animals)	[43,45,46]
Regulatory mechanisms for conditional approval of RM products?	No RM-specific pathway but ATMPs can be eligible for conditional marketing Authorization, or ‘exceptional circumstances’ approval	Conditional and time-limited approval specific to RM products under the PMD Act	[43]
Regulatory pathway for premarket provision of unapproved RM therapies?	‘Hospital exemptions’: unapproved advanced therapies can be provided through a clinical establishment, provided they are not industrially manufactured or for routine administration ‘Hospital specials’ provision allows a physician or other provider to commission an unlicensed therapy where there is specific unmet patient need	ASRM provides a separate pathway for use of unapproved RM products in research and experimental therapy in a clinical setting, including private practice	[44,49]
Specific to RM?	Hospital exemptions are specific to advanced therapies Hospital specials are a generic provision for pharmaceuticals	RM delivery is subject to review according to a three-tiered classification of risk	[44–46]

ASRM: Act on the Safety of Regenerative Medicine; ATMP: Advanced therapy medicinal product; GTMP: Gene therapy medicinal product; MHRA: Medicines and Healthcare products Regulatory Agency; NHI: National Health Insurance; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PMD Act: Pharmaceuticals, Medical Devices and Other Therapeutic Products Act; PMDA: Pharmaceuticals and Medical Devices Agency; QALY: Quality-adjusted life year; RM: Regenerative medicine; sCTMP: Somatic cell therapy medicinal product; SME: Small-to-medium sized enterprise; TEM: Tissue-engineered medicine; VbA: Value based assessment.

Japan for the discovery of induced cellular pluripotency [37]; and both countries have universities that lead frontier research in this field.

Second, governments in both countries have made dedicated efforts to capitalize on their strong scientific base to advance the field of RM from basic research to clinical delivery. While both countries have struggled to replicate the kind of successful commercialization of biotechnology demonstrated by the USA [38], the UK and Japan have had long-standing industrial involvement in the field of RM [39]. Recent efforts to support commercialization, whether as part of the Life Sciences Industrial Strategy in the UK [40] or as part of Japan’s economic revitalization program, often referred to as ‘Abenomics,’ provide an opportunity to compare different national strategies to support the growth of a home-grown RM industry.

A comparison of the two countries also offers an opportunity to examine the impact of different national systems, from regulation to reimbursement and infrastructure, and the ways they have been adapted to support the adoption of RMs. Some of the key features of existing national healthcare frameworks are summarized in Table 1.

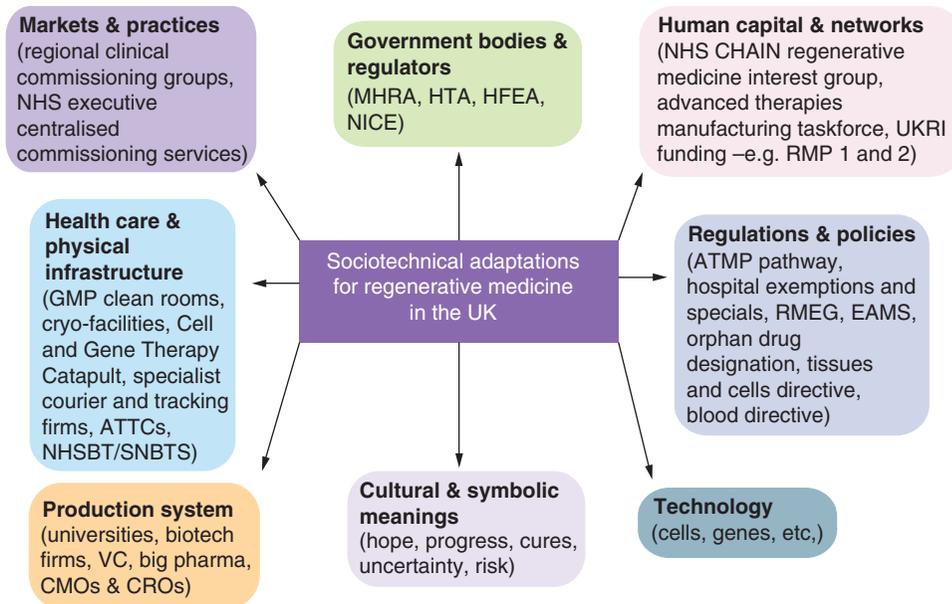


Figure 2. Sociotechnical adaptations for regenerative medicine in the UK.

ATMP: Advanced therapy medicinal product; ATTC: Advanced Therapy Treatment Center; CHAIN: Contact, Help, Advice and Information Network; CMO: Contract manufacturing organization; CRO: Contract research organization; EAMS: Early access to medicines scheme; HFEA: Human Fertilization and Embryology Authority; HTA: Human Tissue Authority; MHRA: Medicines and Healthcare products Regulatory Agency; NHS: National Health Service; NHSBT: NHS Blood and Transplant service; NICE: National Institute for Health and Care Excellence; RMEG: Regenerative Medicine Expert Group; RMP: Regenerative Medicine Platform; SNBTS: Scottish National Blood Transfusion Service; UKRI: UK Research and Innovation.

Enhancing regenerative readiness in the UK

The UK has taken a number of measures to build system-level ‘regenerative readiness.’ Figure 2 highlights the adaptations made from a sociotechnical systems perspective, and identifies specific examples of the UK elements. This section focuses on the measures to enhance readiness in the areas of: regulations and regulatory agency activity; physical infrastructure; human capital; policies and practices; as well as markets and reimbursement.

Developing regulatory readiness: shaped by advanced therapies regulation

The regulatory landscape of the UK has been heavily shaped by the country’s former membership of the EU. The EU legislation set Europe-wide standards for intellectual property in biotechnology, collection and storage of human blood and tissues, orphan drug legislation, among others. The 2007 EU Advanced Therapies Medicinal Products (ATMP) Regulation created a dedicated, centralized European regulatory pathway for cell and gene therapies [50]. Although the ATMP Regulation created a pathway to market, with the first product, ChondroCelect (Tigenix, Belgium) approved in 2009, a limited number of advanced therapies have been approved to date. Furthermore, of the twelve approved products to date, four, including ChondroCelect, have subsequently been withdrawn from the market [19,20]. Data is patchy at best, but the UK does not appear to make much use of the hospital exemptions route (see Table 1) for advanced therapies [20], perhaps because the Medicines and Healthcare products Regulatory Agency (MHRA) takes a tougher stance than some other European national regulators, on what counts as nonroutine use [49]. Most RM provided through these alternative pathways in the UK appears to be one-off, patient-specific treatments [51] or compassionate use/early access to products in development [52]. It is notable that none of the approved ATMP products so far have come from a UK developer.

The UK Regenerative Medicine Expert Group (RMEG), commissioned in 2013, was designed to bring together a variety of stakeholders in the UK RM, including small-to-medium sized enterprises, representatives of major pharmaceutical companies, clinicians, representatives of patient groups, charitable funders such as the Wellcome Trust, NHS England (NHSE) and National Institute for Health and Care Excellence (NICE) policy staff [49]. RMEG was directed to consider three aspects of RM considered potential impediments to successful commercial translation of RM in the UK: regulation and licensing, evaluation and commissioning, as well as delivery and

adoption within the healthcare system [15]. In keeping with this trend of integration and collaboration, the MHRA Innovation Office now acts as a ‘one-stop-shop.’ It gives developers a single point of access to regulatory advice from the Human Fertilisation and Embryology Authority, and Human Tissue Authority – which regulate sourcing of human biological material – the MHRA, and the Health Research Authority – which is responsible for ethical oversight of human subjects research, including clinical trials, in the UK [53].

Creating physical infrastructure: dedicated support to RM development

The UK Cell and Gene Therapy Catapult (CGTC) was founded in 2012 with an initial £70 million funding from the state and an explicit mission to support the growth of an RM industry in the UK [54]. The Catapult’s mission includes supporting technology transfer and IP strategy to better link the university and industry sectors in the UK. It provides ‘translational services’ for advanced therapy developers [31], including advice on financial strategy, business models and clinical trial design, and on occasion acting as a sponsor for clinical trials [54].

The CGTC has helped to enhance physical infrastructure for RM. In 2014, the UK had 13 GMP plants with 56 manufacturing clean rooms, most of which were in the public sector or university based [31]. Noting that the UK’s limited manufacturing capacity for advanced therapies could impede larger-scale Phase III clinical trials [13], the CGTC began developing a £55 million GMP manufacturing plant, which developers can hire out rather than invest in building their own highly expensive GMP-accredited manufacturing sites [31]. The facility opened in April 2018. The government also set up an Advanced Therapies Manufacturing Taskforce, in conjunction with the UK BioIndustry Association and the Association of the British Pharmaceutical Industry, to develop a national strategy to attract and retain further manufacturing capacity for advanced therapies to the UK.

Consideration of clinical delivery and adoption came to fruition in the formation of three Advanced Therapy Treatment Centres (ATTCs) in 2018. The ATTCs are regional hubs involving NHS clinical staff, academic scientists and small-to-medium sized enterprises acting in concert to facilitate clinical delivery of advanced therapies. The ATTC model recognizes that clinical readiness entails more than simply addressing a ‘skills deficit’ in clinical staff. Instead, both the clinical environment and the therapies in development are aligned with one another in a process of mutual development [6,24].

Developing human capital: organizational learning & information sharing

In addition to the recent ATTCs, the UK also has established centers of excellence for the clinical delivery of emerging RM therapies. These are mainly teaching hospitals linked to leading academic institutions such as University College London Hospitals NHS Foundation Trust, Great Ormond Street. A further reservoir of expertise is to be found in the NHS Blood and Transplant service and its Scottish counterpart, the Scottish National Blood Transfusion service. These services have well-developed physical and technical infrastructure and skills to collect, store, track and transport human cells at the quality standard required for clinical use [55]. As well as considerable translational endeavors funded through the first and second iterations of the UK Regenerative Medicine Platform funding schemes for academic research, a limited number of specialist qualifications in ‘translational regenerative medicine’ are beginning to be offered by major UK Universities. The NHS Contact, Help, Advice and Information Network also has a subgroup for health professionals interested in RM to share advice, news and information.

Challenging paths to market & reimbursement: navigating multiple processes

Through the involvement of NICE in the evaluation and commissioning stream of RMEG, policy attention at last began to address issues of health technology assessment (HTA) and the valuation of regenerative therapies. NICE is the primary agency responsible for HTA in England and Wales, although NHSE also conducts some of its own assessments where guidance from NICE is absent. Although a higher threshold of cost-per-QALY (see Table 1) exists for rare diseases, this methodology has been seen as challenging to RM, where large datasets from randomized control trials are rare, patient populations are often small and manufacturing costs are high [14,56]. While several alternative measures have been considered (Table 1), the next steps are not yet clear. Moreover, HTA evaluations from NICE or NHSE are only one part of the challenge. Advanced therapies must also navigate NHS commissioning procedures, which may operate through regional Clinical Commissioning Groups or NHS Executive-centralized commissioning services, under different tariffs and budgets depending on whether the product treats a common or rare condition and the care setting in which it is likely to be administered [56].

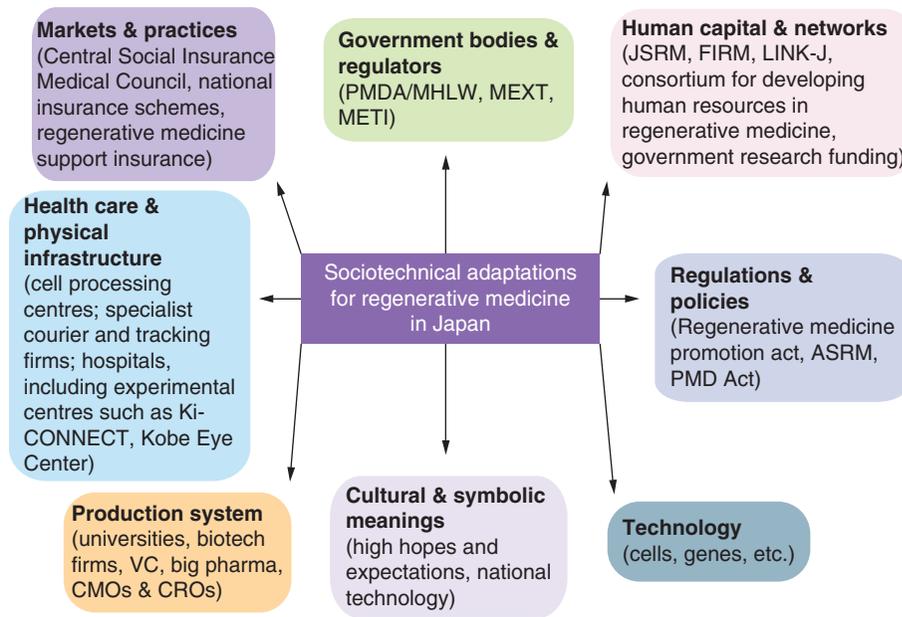


Figure 3. Sociotechnical adaptations for regenerative medicine in Japan.

ASRM: Act on the Safety of Regenerative Medicine; CMO: Contract manufacturing organization; CRO: Contract research organization; FIRM: Forum for Innovative Regenerative Medicine; JSRM: Japanese Society for Regenerative Medicine; Ki-CONNECT: Kyoto Innovation Center for Next Generation Clinical Trials and iPS Cell Therapy; LINK-J; Life Science Innovation Network Japan; METI: Ministry of Economy, Trade and Industry; MEXT: Ministry of Education, Culture, Sports, Science and Technology; MHLW: Ministry of Health, Labour and Welfare; PMD Act: Pharmaceuticals, Medical Devices and Other Therapeutic Products Act.

Enhancing regenerative readiness in Japan

To capitalize on domestic scientific capabilities and 'realize' RM, Japan has also made various adjustments to facilitate its adoption. Figure 3 highlights some adaptations made from a sociotechnical systems perspective. The following sections elaborate on how Japanese initiatives to improve technological readiness were made in much of the same areas as the UK, but often in rather different ways.

Developing regulatory readiness: formulating adaptive laws

Japan has made various adjustments to develop a regulatory framework tailored to the complex technological modalities involved in RM compared with conventional small molecules or biologics [45,46,57]. Following lobbying by the Japan Society of Regenerative Medicine (JSRM), the government introduced two regulations – the Act on the Safety of Regenerative Medicine (ASRM) [44]; and the Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD Act) [43]. The ASRM governs the clinical path to the delivery of RMs, through the regulation of clinical studies carried out in academia and private practice among physicians [44]. The PMD Act governs the industrial path for RM, governing the manufacture of RMs in industry [43,58]. Similar to the MHRA, the PMDA offers consultations on clinical trials [59].

The revised regulations indicated in Table 1 addressed much needed adaptations. First, in the clinical setting, the ASRM provided for the monitoring of experimental cell therapies offered by clinicians, who have long held the authority to offer experimental therapies to consenting patients under the Medical Practitioners Law (1948). Second, ASRM opened up the market in cell processing services, by allowing human cells to be cultivated outside the hospital setting [44]. Third, the PMD Act not only created a new category of regenerative medical products, it introduced a system to approve and reimburse potential therapies on a conditional and time-limited basis after two, rather than three phases of clinical trials. RM firms could market their products, subject to further safety and efficacy tests for full approval [60].

However, the extent to which these adjustments have been transformational in advancing RM has been questioned. For instance, there has been steady clinical provision of unproven RMs [61,62]. Cell manufacturing requires further development, from technology, skills to infrastructure [63]. Many therapies in early-stage development can-

not take advantage of the conditional approval scheme. Furthermore, a new clinical research law was introduced in 2017, while intended to ensure proper protocols for clinical research has made it difficult for many academics to pursue clinical studies [64,65].

Creating readiness in the production system: bridging academia & industry

In Japan, the so-called ‘industrialization of regenerative medicine’ is often considered key to enable the delivery of a large volume of affordable, standardized, quality therapies to a large population [66]. Partly to revitalize the Japanese economy and to support the development of an industry at the technological frontier, the government has played a strongly supportive role in advancing the field, particularly since the discovery of induced pluripotent cells by Shinya Yamanaka in 2007, and his Nobel Prize Award in 2012 [67]. Since the Millennium Project in 2000 [68] to Japan’s recent economic revitalization program, Abenomics [69], the development of RM has involved a recognition that a large-scale, collaborative ‘All Japan’ effort is essential to realize the delivery of RMs [70]. At the same time, reconciling the different end goals between academia and industry for collaboration has remained a challenge. Some have suggested that, in Japan, this distance is exacerbated by a Confucian culture in which academics can be more sceptical of industry [71].

It is worth noting that Japanese RM research has been distinctly oriented to induced pluripotent stem cells (iPS cells, or iPSCs) when compared with other jurisdictions [72,73]. The Center for iPS Cell Research and Application (CiRA), a world leading organization dedicated to iPS cell research, has been involved in the iPSC Stock Project, whose goal is to create a human leukocyte antigen homozygous iPSC haplobank and support associated research [74]. To a certain extent, the additional technical difficulties involved in iPS cell-based therapies [23] compared with somatic stem cell therapies may slow the commercialization of RM in Japan. The coordination between different communities of researchers – such as between stem cell scientists (who tend to prioritize discovery research) and biomedical engineers (who tend to be interested in clinical application) – has also frustrated advancement in this field [73].

Experiments to healthcare infrastructure: exploring paths to clinical delivery

While Japan does not have an equivalent of the ATTC network, experimentation to the healthcare infrastructure is occurring at various levels: at single clinical settings, at specialist hubs, as well as local ecosystems. Examples of clinical delivery in specialist settings include the Kobe Eye Center [75], located in the Kobe Biomedical Innovation Cluster [76], which aims to incorporate various modalities to best treat eye disease. As a specialist hub, KiCONNECT [77], based at Kyoto University Hospital, aims to connect volunteers, pharmaceutical companies and medical organizations to facilitate clinical research and clinical trials of iPS cell-based therapies. A local ecosystem to help develop next-generation medicines is being created at the Tonomachi district of Kawasaki, Kanagawa Prefecture supported by national, prefectural, municipal and local governments, as well as academia (e.g., Keio University, RIKEN) and industry (e.g., ReproCell, FujiFilm) [78]. Support schemes here include assistance for financing, business plans, partnering, IP management, regulatory affairs and skills development.

Developing human capital: from up-skilling to collaborative networks

Japanese stakeholders have recognized that skills development will be essential to the delivery of RM. For example, the Consortium for Developing Human Resources in Regenerative Medicines Research, supported by the Ministry of Education, Culture, Sports, Science and Technology, has aimed to educate cell culture techniques, bioethics and safety among medical technicians at Osaka University, Kyoto University and Tokyo Medical and Dental University since 2014 [79]. JSRM also runs certification schemes for cell cultivation technicians [80].

Various stakeholder networks have also offered a forum for information exchange. These include the industry association, Forum for Innovative Regenerative Medicine, which comprises of firms across the value chain – from equipment suppliers to insurers – and aims to cultivate an industry ecosystem [81]. JSRM, Japan’s academic society, is distinct in its sizeable membership, composition of stakeholders across academia and industry, and its influence toward policymakers. JSRM has also worked to create a national consortium to promote RM as well as a Regenerative Medicine Database – a large-scale clinical data registry [82]. The Life Science Innovation Network Japan, an initiative between Mitsui Real Estate, academia and industry, further promotes stakeholder networking and information exchange, to encourage innovation in the life sciences field, including RM [83,84].

Table 2. Comparison of several key UK and Japanese adaptations to develop sociotechnical readiness for regenerative medicine.

Adaptive activity	UK	Japan	Ref.
Regulation of clinical innovation/unapproved therapies	Strict and limited to hospital exemptions and hospital specials	ASRM establishes basis for clinical innovation separate from industrial pathway	
Manufacturing capacity	State supported capacity building through the CGTC Stevenage facility. Enables SMEs to rent GMP cleanrooms instead of building them, but has been criticized for potential to 'crowd-out' commercial supplier	ASRM enabled growth of commercial cell processing services. Technical staff accreditation provided by JSRM	[32]
Integration of different stakeholders	High-level 'taskforce' approach through the RMEG and Advanced Therapies Manufacturing Taskforce Integration of regulatory advice through MHRA Innovation Office and RM advice service	Network based; LINK-J, FIRM, as well as translational initiatives such as Ki-CONNECT and Tonomachi district RM ecosystem. Integrated policy and funding through 'All Japan' initiative	
Education and up-skilling	Traditionally relies on multiple, local or regional networks such as the Scottish Stem Cell Network or the Manchester Tissue Regeneration and Stem Cell Network. This is replicated in the recent Regenerative Medicine Platform and ATTC funding schemes	Coordinated consortium for developing human resources in RMs to up-skill workforce as well as a very active professional society of RM practitioners	

ASRM: Act on the Safety of Regenerative Medicine; ATTC: Advanced Therapy Treatment Centre; CGTC: Cell and Gene Therapy Catapult; FIRM: Forum for Innovative Regenerative Medicine; JSRM: Japan Society for Regenerative Medicine; LINK-J: Life Science Innovation Network Japan; MHRA: Medicines and Healthcare products Regulatory Agency; RM: regenerative medicine; RMEG: Regenerative Medicine Expert Group; SME: small-to-medium sized enterprise.

Paths to market access: formulating an affordable pricing & reimbursement regime

An important concern in realizing the delivery of RM is the affordability of treatment. Japan operates a universal healthcare system in which most patients pay up to 30% of the costs. Medical expenses are capped for expensive treatments according to age and income [85], and mixed billing is available under certain conditions [47]. While this reduces the cost of RMs, it is still a substantial cost out of the reach of many. In this context, Japanese academics have queried the prevailing pricing and insurance system [86,87], investigating how adaptations to pricing schemes can facilitate the broader adoption of RM [88].

Concluding discussion: advancing regenerative readiness

This paper builds upon existing work on 'readiness,' particularly those that look at the readiness of particular environments to adopt new technologies [12,24]. The specific contribution of this article is to move beyond clinical readiness to look at adaptations at the broader level of national sociotechnical systems of healthcare delivery and medical innovation, and to apply this analytic perspective in a comparative study of the system-level regenerative readiness with the UK and Japan. Reflecting on the different approaches taken in each country illustrates the variety of options available to address common challenges in enhancing system-level readiness. The following table highlights selected actions made within and across the various elements of the sociotechnical system, such as: regulation of unapproved therapies; enhancing manufacturing; integrating different stakeholder groups; and developing human capital through education and up-skilling.

Given the absence of a large number of home-grown RM products in routine use or an RM industry with demonstrated long-term sustainability in either country, it is premature to declare either country's approach to building systemic readiness an unequivocal success. Nonetheless, some evaluations can be made. Japan has taken the more ambitious regulatory approach, in crafting a distinct pathway to support clinical innovation that operates in parallel to, but distinct from, the regulatory pathway for commercial RM products. This creates a supportive environment for clinical translation, but has been criticized for reducing safety standards and potentially exposing patients to dangerous and exploitative practices [62,89]. Japan has also experienced reputational harm from private clinics offering unproven cell therapies on a for-profit basis [61,62]. The UK approach has been much more restrictive of access to unproven RM therapies (see Table 2). This appears to offer greater protection against private clinics providing unlicensed cell therapies, but is also less supportive of clinical innovation beyond the research context. Promoting innovation while limiting the delivery of therapies of unproven efficacy is one of the most difficult aspects of regulating the RM field.

The 'All Japan' national mobilization of funding, regulatory reform and policy initiatives toward RM, with early emphasis on iPSC technology, shows that systemic approaches to readiness can also be orientated to a particular technology [73]. Inter alia, this suggests that a sociotechnical systems approach to readiness is com-

patible with TRLs, in as much as system-level adaptations can be made with the aim of supporting the translation of a specific product type, and even to create the circumstances that would facilitate the testing needed to achieve the later ‘mission ready’ stages of TRL. Similar work has been done elsewhere to integrate the tools of TRLs and IR [6]. Regulatory reform, especially the ASRM pathway for clinical research, combined with generous state funding for translational research, has contributed to Japanese success in achieving many of the world’s first, ‘first-in-man’ trials of iPSC-derived cell therapies in a range of conditions: from macular degeneration and retinitis pigmentosa to Parkinson’s disease and heart failure [23].

At the same time, Japan may be reaching the limits of this approach. Production and application of clinical grade iPSC is proving to be highly expensive, and the government is expected to reduce its financial support for CiRA, its flagship translational organization [90]. By contrast, the UK approach has been more agnostic about specific technologies within the umbrella of RM. While the UK does host some leading work in clinical application of pluripotent stem cells (e.g., first-in-man provision of human embryonic stem cells for macular degeneration), most of the RM products being trialed in the three ATTCs utilize more established cell types. This may be a less ‘headline grabbing’ strategy, but presents a less risky, more expedient measure to get selected RM therapies in routine clinical use.

Japan has trialed a conditional access program for RM, where patients and National Health Insurance both contribute to the costs, but overall, both countries have struggled with alternative reimbursement models for RM products. The type of national RM database developed by Japan to capture data about RM therapies could be a useful model for both countries, if some form of ‘payment by results’ regime is adopted in the future for RM and other high-cost products. In theory, such a database can also serve as a source of ‘real world evidence’ on outcomes from experimental treatments, but collecting high-quality data and enforcing compliance are challenges yet to be overcome. In the interim, patient access to RM therapies through private clinics in Japan risks reducing the available recruitment pool for clinical trials of industrial RM products in development.

This perspective paper illustrates how the UK and Japan have made considerable efforts to realize the adoption of RM. As the sociotechnical systems framework highlights, adjustments have been made across different areas, from regulation to infrastructure. These efforts to advance regenerative readiness have not been uniform, and many of their effects are still yet to be seen. It is worth noting that readiness is not a unidirectional process, and that advances are often accompanied by setbacks, with a considerable amount of ‘learning by trial and error,’ as well as learning through comparative insight into the efficacy of different approaches.

Future perspective

This analysis of ‘regenerative readiness’ of sociotechnical systems in the UK and Japan could form the basis for further empirical investigation in both countries to identify how disparate elements of the system interact. Qualitative social science research can elicit the perspectives and experiences of different stakeholders – academic scientists, clinicians, regulators, commercial developers, policy makers, patients and healthcare payers – about how attempts to translate RM products and services operate in practice. There is potential to clarify the hidden barriers to achieving regenerative readiness. This could include, for example, examining conflicting imperatives between stakeholders or unanticipated disincentives to collaboration and translation.

Much work has already been carried out in the UK, through projects such as REGenableMED (ES/L002779/1, 2014–2017) and Biomodifying Technologies (ES/P002943/1, 2017–2020). Future work could expand on comparative work, including, but not limited to, the UK or Japan. The Institutional Readiness tool currently employed by some of the UK ATTCs could also be adapted to generate quantitative data on clinical readiness in other countries. Taken together, this combination of further qualitative and quantitative data could generate a more nuanced and rich account of regenerative readiness across different national systems and institutions, to better support mutual learning and policy implementation. Future research could also examine readiness in the context of international translational projects, when elements of more than one sociotechnical system are involved, so as to facilitate the delivery of RM across borders.

Executive summary

- This paper responds to a call to examine how 'regenerative readiness' varies between two different national research and healthcare systems: the UK and Japan.

Defining regenerative readiness at the level of national systems

- 'Readiness' refers both to the readiness of specific technologies, typically assessed in terms of technology readiness levels, and to the ability of an environment to adopt a new technology.
- A dimension of readiness, institutional readiness, assesses the degree to which healthcare organizations can employ regenerative medicine (RM) therapies.
- The sociotechnical systems framework helps expand this concept of readiness, and the elements that require adaptations in order to enable system-wide adoption of a new technology.

Comparing the UK & Japan

- The UK and Japan offer good case studies because, while both countries are scientific leaders in the field and have enjoyed government support, their healthcare systems and adaptive measures taken to advance RM have varied.

Enhancing regenerative readiness in the UK

- EU regulation has heavily shaped the UK regulation with the EU Advanced Therapies Medicinal Product regulation. Most RM provided through alternative pathways are one-off patient-specific treatments.
- The Cell and Gene Therapy Catapult has provided a range of translational services.
- Advanced Therapy Treatment Centres were established in 2018 to facilitate clinical delivery.
- The UK has further well-developed physical and technical infrastructure for clinical delivery (e.g., Centres of excellence, blood and transplant services).
- Health technology assessment evaluations and National Health Service Commissioning processes are regarded as challenging to the widespread adoption of RM.

Enhancing regenerative readiness in Japan

- Japan has made various adjustments to develop a regulatory framework tailored to the complex technological modalities involved in RM (e.g., Act on the Safety of Regenerative Medicine; Pharmaceuticals, Medical Devices and Other Therapeutic Products Act).
- Experimentation to clinical delivery occurs at various levels: specialist clinical settings (e.g., Kobe Eye Center), specialist hubs (e.g., Ki-CONNECT) and local ecosystems (e.g., Tonomachi).
- In addition to skills training for medical technicians, various stakeholder networks for information exchange support innovation (e.g., Forum for Innovative Regenerative Medicine, Japan Society of Regenerative Medicine and Life Science Innovation Network Japan).
- National Health Insurance caps maximum monthly payments and allows for mixed billing under certain conditions.

Concluding discussion & future perspective

- The British and Japanese experiences offer an informative comparison of 'system-wide' readiness strategies, and use of the sociotechnical framework expands upon existing conceptualizations of 'readiness.'
- Such comparisons help us to improve best practice and collectively accelerate translation of RM to the clinic. The international harmonization of such practices may also facilitate the future translation of therapies across borders.

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