Bringing regenerative medicines to the clinic: the future for regulation and reimbursement

Significant investments in regenerative medicine necessitate discussion to align evidentiary requirements and decision-making considerations from regulatory, health system payer and developer perspectives. Only with coordinated efforts will the potential of regenerative medicine be realized. We report on discussions from two workshops sponsored by NICE, University of Alberta, Cell Therapy Catapult and Centre for Commercialization of Regenerative Medicine. We discuss methods to support the assessment of value for regenerative medicine products and services and the synergies that exist between market authorization and reimbursement regulations and practices. We discuss the convergence in novel adaptive licensing practices that may promote the development and adoption of novel therapeutics that meet the needs of healthcare payers.

Keywords: access with evidence development • adaptive licensing • advanced-therapy medicinal products • cost-effectiveness modeling • horizon scanning • patent landscaping • regenerative medicine • regulation • reimbursement • value of information

Innovation in regenerative medicine must be driven by a pre-emptive understanding of what signifies value to payers of health technologies and services. 'Regenerative medicine replaces or regenerates human cells, tissue or organs, to restore or establish normal function' [1]. Although many regenerative medicine therapies are approaching market authorization, such authorization is not determinative of whether the resulting technology represents a good investment from either commercial or health system perspectives. Achieving a positive therapeutic effect is only one factor in determining reimbursement and health system adoption for a given therapy.

Given significant national and regional investments in regenerative medicine, it is timely to discuss alignment of evidence requirements and decision-making considerations from regulatory, health system payer and developer perspectives. Only with coordinated efforts will the potential of regenerative medicine be realized for the benefits of the public in general and patients. Here we report on such discussions at two Regenerative Medicine Workshops held in December 2014 and sponsored by the NICE, the University of Alberta, the Cell Therapy Catapult

and the Centre for Commercialization of Regenerative Medicine (CCRM). The workshops, entitled 'Regenerative medicine translation – a pathway into clinical practice and methods to support regenerative medicine translation' brought together key stakeholders in regenerative medicine R&D in Europe and Canada. As a summary of the discussions and presentations at the workshop, this article is not an in-depth or comprehensive account of the regulatory and reimbursement frameworks in Europe and Canada. From a reimbursement perspective, we focus on the UK, recognizing that the reimbursement landscape varies by country in Europe. Nevertheless, the UK is the reference price market for approximately 25% of the world pharmaceutical market and therefore has an influence far in excess of its absolute value [2].

The Cell Therapy Catapult and CCRM are examples of organizations designed to support the development of national regenerative medicine industries in the UK and Canada, respectively. Both support clinical translation of therapies and the creation and growth of companies through national and international networking, regulatory expertise and business support. Both are engaged in policy development and raising

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the profile of the industry. Both are building capacity to support the development of new technologies and processes in GMP, in Canada also supported by the creation of CellCAN [3], a pan-Canadian network of cell manufacturing facilities aimed at accelerating cell-based clinical trials. These organizations further assist cell manufacturing through economic modeling of cost drivers for cell processing and manufacture, which impact on the eventual cost of therapies. Now, in recognition of the maturation of the field, both are building capacity to support developers in considering reimbursement issues and leading the dialogue with regulators and reimbursement agencies to ensure that the investment in regenerative medicine R&D results in clinical adoption of high-value products and services. It is imperative that stakeholders in translational research (whether funding agencies that invest public moneys in health R&D, researchers who invest their careers or industry that invest to bring products to market) work to understand the payer perspective before developing new therapies whose value does not resonate with payers. Toward that goal, payers and health system decision makers need to provide guidance on the challenges of clearing increasingly high but uncertain reimbursement and other market access hurdles.

Opportunities & challenges

Regenerative medicine is coming of age in an era of cost-constrained health systems facing an aging population and high-cost new therapies and technologies that do not necessarily improve health outcomes. Recent global landscapes of cell and stem cell clinical trials have identified an expanding number of trials and types of novel products in clinical pipelines [4–6]. Regenerative medicine therapies are reaching patients. From 1980 to 2013, 320,000 patients in the USA had received hematopoietic stem cell transplants [7], and over 300,000 patients received non-hematopoietic stem cell approved regenerative medicine cell therapy products between 1988 and 2010 for a diverse range of conditions, including diabetic ulcers, wounds, burns, cartilage

repair and musculoskeletal defects [8]. Despite increasing success in achieving regulatory approval, many cell therapies struggle to find a market (Table 1). Physicians have balked at the cost of Dendreon’s Provenge for the treatment of prostate cancer at US\$93,000 per therapy course for a 2–4-month mean survival benefit where a maximum cost of US\$30,000 would support this scale of benefit [9]. Indeed, in February 2015, NICE did not recommend Provenge for reimbursement “as it costs too much for the extra benefit it may provide” [10,11]. Physicians in the USA voice concern about the ability of patients to copay and the need for preauthorization from insurance companies. Prochymal for pediatric steroid-refractory graft versus host disease has not yet been funded by any provincial health system in Canada, despite its conditional approval in 2012 and neither the originator, Osiris Therapeutics, Inc., nor the current developer, Mesoblast Ltd, have applied for evaluation by the Canadian Agency for Drugs and Technologies in Health (CADTH) [12].

The high cost of therapies is in part driven by frequent and expensive failures in clinical development. Even for small molecule drugs, whose development pathways and mode of action are simpler than cell therapies, only 15.3% of drugs traverse the pipeline from Phase I to market authorization for lead indications, a percentage that drops to 10.4% for all indications [13]. This cost of failures is not the only problem; many of the technologies that do make it to market provide only marginal improvements over current therapies. For example, the median gain in progression-free survival for new cancer drugs approved between 2002 and 2014 was only 2.1 months. The gain in overall survival was 2.5 months [14]. This massive investment of time, money and resources on marginal therapeutic benefits is ‘promoting a me-too mentality that is stifling innovation and creativity’ [14].

The promise of regenerative medicine is to break out of this marginal value mould with curative therapies for indications with limited treatment options; but these therapies are likely to be costly, in part, driven by higher R&D costs, higher manufacturing costs than for

Table 1. Reimbursement status of advanced-therapy medicinal products with market authorization in the EU.				
Technology	MA holder	EU MA date	ATMP type	Reimbursement status
ChondroCelect [†]	TiGenix NV	5 October 2009	Tissue engineered	Reimbursed in Belgium, The Netherlands and Spain
Glybera [†]	uniQure biopharma BV	25 October 2012	Gene therapy	No national reimbursement
MACI [™]	Genzyme Europe BV	27 June 2013	Tissue engineered	No national reimbursement
Provenge [†]	Dendreon UK Ltd	6 September 2013	Somatic cell therapy	No national reimbursement
[†] As of 1 April 2015. ATMP: Advanced-therapy medicinal products; MA: Market authorization. Adapted with permission from [80].				

small molecule drugs, the personalized nature of some products and higher costs for clinical delivery. Public health systems, such as those in the UK and Canada, have long explicitly considered cost–effectiveness in making coverage decisions and employ health technology assessment (HTA) analyses to do so. A number of recent developments in the USA indicate that, even in that country, cost increasingly factors into reimbursement decisions that determine whether a therapy authorized for market will be paid for [13]. The payer ecosystem in the USA is a complex blend of public and private insurers, and hospital administrators manage budgets closely. Health plans and medical associations (e.g., oncology and cardiology) are increasingly concerned about the high cost of drugs [15] and have called for re-examination of spending and consideration of cost–effectiveness or better use of evidence on comparative effectiveness [16]. In addition, private insurers require co-payment and/or high deductibles, driving expensive technologies out of the affordability range for patients and their families.

Methods to support assessments of value

In this climate, value assessment is an increasingly real and immediate consideration for access to major markets and must be assessed as part of the clinical translation process. Such an evaluation has multiple components, and one example is the Value-Engineered Translation (VET) Framework that formally integrates analytics [17,18]; many of which are already being undertaken by supportive organizations such as the Cell Therapy Catapult, CCRM, technology transfer offices, patent offices, HTA agencies and horizon scanning centers.

Headroom analysis

The first and broadest step of the VET Framework is to examine the potential for headroom – an analysis of any unmet need for a candidate technology for a specific indication to support a price consistent with an acceptable return on the investment in clinical translation. In other words, headroom considers the maximum scope for therapeutic or health system benefits of a technology relative to other existing technologies and those expected to be on the market at the time of product launch. Prospective analyses are needed given lengthy clinical development timelines, even for small molecule drugs with mean clinical development times from Phase I through market authorization over 14 years [13]. Accordingly, the assessment of headroom draws upon insights from clinical landscaping, which maps how the condition is currently managed in target healthcare systems and technology landscaping, which draws upon patent, clinical trials and trade and

publications databases to identify potential competitor technologies that are likely to be on the market at the expected time of product launch.

The UK has developed advanced capabilities in technology landscaping to support the needs and interests of developers and the UK health system – the National Health Service (NHS). For example, The UK Intellectual Property Office (IPO) realized back in 2006 that there was a need to develop advanced capabilities in technology landscaping to support the needs and interests of developers. In 2014, the UK government identified ten areas of technology whose development was identified as a priority in the UK. The IPO was able to provide a series of reports in these areas, one of which was regenerative medicine. Regenerative medicine has been of interest to the UK government for some time now; indeed, this latest report is the third such report that the IPO has produced on this topic [19].

Patents can provide valuable information on time trends in innovation – who is innovating what and where. Patent examiners housed in patent offices, as both technical and patent experts, are ideally positioned to analyze complex patent data and to provide support for technology developers in academic, government and industrial sectors. The UK IPO further provides guidance documents on how to analyze and interpret patent data [20]. In particular, patent offices are well positioned to develop search algorithms that more clearly delineate innovative fields. In its analysis of the global regenerative medicine patent landscape, the UK IPO demonstrated not only a slowdown in patenting from 2004 to 2013, but also the “patenting characteristics of an emerging technology with the potential for much further growth.” Most patent families were first filed in the USA, followed by Japan. Most of the top applicants were academic institutions, government departments and national research agencies in the USA, with the lead UK institutions being Edinburgh University, Cambridge Enterprises Ltd and Imperial Innovations Ltd. However, encouragingly, the landscape demonstrated a global collaborative environment, with considerable coassignment of patents between universities. Separate clusters were apparent in the UK, but UK universities and their commercialization arms had links to UK businesses and the USA. The dominant fields were in cancer and neurodegenerative conditions.

While patents provide a broad overview of development in a field with potential for commercial application, national health systems require an early awareness and alert system for technologies to which they may need to adapt or which they may need to implement [21]. The National Institute for Health Research (NIHR) Horizon Scanning Centre, as part of

Euroscan [22], provides such a service and has reported on regenerative medicine [23]. Horizon scanning supports analysis of technologies identified internally or by health system clients. It filters, prioritizes and quantifies those technologies most likely to have a significant future impact on health, health services and/or society and disseminates that information to support forward planning by reimbursement authorities, healthcare providers and research funders. The analyses rely on information scans of internet search engines, communications by networks and groups operating in regenerative medicine, journal articles, clinical trial registries, regulatory approvals, horizon scanning databases and commercial databases. The information is then filtered based on the innovativeness of the new technology relative to current practice, expected time to availability and potential for clinical, patient, cost and staffing impacts. All analyses are peer reviewed and supported by multidisciplinary expert consultations.

In 2013, the Cell Therapy Catapult approached the NIHR Horizon Scanning Centre to identify new and emerging cell therapies that may enter or have an impact on the UK health market or patients in 5–10 years. The center identified over 32,000 individual records in the categories of cellular therapy and tissue engineering and gene therapy, which was not a manageable dataset for microanalysis. The center has, therefore, focused on specific patient groups and tried to identify technologies, techniques and products in development. The most recent of these reports has focused on new and emerging technologies for inherited retinal diseases [24], in which the UK is a global leader and regenerative medicine in the management of skin diseases, burns and wound care [25]. These specific analyses may inform commissioning and planning decisions, but also identify current research activities in the UK and elsewhere, and the need for further research in support of regenerative medicine innovators.

These examples of technology landscaping inform our understanding of the potential for health and resource impacts at the time a technology comes to market and variations of these may be performed as soon as a technology/indication dyad moves into clinical development, generally as preclinical studies are underway to support a clinical trial application to a regulatory agency. The analysis must integrate information on potential competitor technologies, as headroom may shrink over time as other technologies enter the market. However, considerations of health and resource impact may be modified by other 'social value' considerations. Research has shown that citizens have sets of values they would like decision makers to take into account when allocating health spending. In addition to cost-effectiveness, citizens may be willing

to pay more for pediatric conditions, severe conditions, especially those with unmet need and rare conditions [26]. The latter conclusion is supported by regulatory frameworks that incentivize R&D for orphan, ultra-orphan and rare diseases [27]. Thus headroom may be greater for therapies targeting these areas.

Cost-effectiveness modeling

The data generated to support the headroom analysis can further inform cost-effectiveness modeling. In the VET Framework, such modeling can occur at two stages of clinical development. The first of these can be performed earlier in development, because it is based on best available and analogous evidence from comparable technologies and derived from formal expert elicitation regarding the likely effectiveness and safety profile of the technology being developed [28,29]. As preliminary evidence from Phase II clinical trials on efficacy is generated, detailed cost-effectiveness models can be constructed for a portfolio of markets that integrate the new data on the expected effectiveness and safety profiles. These models can also synthesize emerging information on the key costs drivers of the new technology, including the cost of goods based upon actual scale-up/scale-out manufacturing strategies and the associated cost of regulatory compliance in manufacturing, and developments in the evidence base for likelihood competitor technologies identified through the landscaping work undertaken for the headroom analysis. These models can then be combined with information on postmarket patent life to inform return on investment analyses.

Cost of goods modeling is well supported in the UK by the Cell Therapy Catapult, which aids in evaluating manufacturing strategies for regenerative medicine technologies. Its goal is to determine product pricing by working back from the reimbursement point to a commercially viable cost of goods. The analysis can occur at an early stage in order to drive development direction, or in later-stage development to optimize cell processing methods and options. The analysis interrogates constructed cost models with sensitivity analysis (via Monte Carlo simulation) to identify parameters that have the greatest potential to reduce costs [30]. These parameters include both productivity drivers and cost drivers, such as sales and marketing, raw materials, consumables, facility build, overheads and personnel. The Cell Therapy Catapult is currently developing idealized scenarios to model potential industrial process options to inform investment risk decisions and return on investment, as well as advise developers on potential strategies, such as who should develop the process, what process should be developed (e.g., scale-up vs scale-out), should a company develop its own facility or use a Con-

tract Manufacturing Organization, what is the optimal scale of operation and what is the target dose?

To assess the reimbursement price potential of a cell therapy under development, economists at the Cell Therapy Catapult utilize value based assessments that link price potential to the magnitude of the novel therapy's added value over standard of care [31]. In so doing, they triangulate qualitative and quantitative pricing methodologies, health economic methods and analog analysis. The starting point is the cost-utility framework developed by the NHS that utilizes the incremental cost-effectiveness ratio (ICER) as a threshold to inform price potential. ICERs are comparative between existing and new therapies and are dependent on direct healthcare costs and changes in quality-adjusted life years (QALYs; life expectancy in years X quality of life). The NICE ICER thresholds (willingness to pay) are in the range of GB£20,000–30,000/QALY, depending on the certainty around the ICER, how adequately quality of life is captured and how innovative the technology is. NICE may also consider a higher threshold for end-of-life treatments for small populations, if the therapy extends life by at least 3 months. The ICER model captures health states, time-dependent transitions, outcomes and uncertainty and employs decision trees, state transition Markov models and discrete-event simulation, among other model types [32]. The uncertainty in the ICER quantified using Monte Carlo simulation, and a cost-effective price is identified as one where the majority of ICER estimates produced fall below the 'willingness to pay' threshold. The willingness to pay threshold is likely to vary, depending on the market (e.g., UK vs US health markets), and understanding this variability in market access drivers will be key for developers. In turn, these calculations may support stakeholders in engaging with healthcare decision makers to explain the value proposition of the new technology and to inform adoption decisions and reimbursement options for regenerative medicine therapies.

New methods in cost-effectiveness modeling provide further guidance for technology developers in terms of investments in further research, such as clinical trials, manufacturing processes to decrease the cost of goods or developing the therapy to be independent of other costly therapies, for example, transplanted β -cells require patients to take immunosuppression drugs, and some cancer immunotherapies require infusions of immune boosters, such as γ globulin. Because cost-effectiveness models are inherently uncertain, reimbursement decisions may be wrong – they may fund technologies with negative health impacts or not fund technologies with positive health impacts. Further research decreases decision-making uncertainty and

value of information (VoI) modeling allows determination of whether further evidence is worth collecting [33]. The function of research, from a decision maker's perspective is to reduce uncertainty – and hence the risk of making the wrong decision. Where decision makers specify an explicit willingness to pay for health (cost-effectiveness threshold), this can be used to identify the value of further research. Value of information analysis uses the quantified uncertainty about the ICER, produced by the Monte Carlo simulation to specify the risk of making the wrong decision. If we do make the wrong decision then the cost of that decision is the health lost multiplied by the value of that health. Hence the probability of making the wrong decision allows us to quantify the expected cost of making the wrong decision. The expected value of any research is the reduction in the expected cost of making the wrong decision if the research is completed. The methods for undertaking these types of analyses are becoming increasingly accessible [34] and straightforward to apply [35].

In sum, a convergence of methodologies is in development to assess the potential cost-effectiveness of regenerative medicine therapies. Applied within a coherent framework, such as the VET framework, these have the potential to provide risk information to developers, public and private sector investors and health systems [36,37]. In addition, the results of these analyses may inform the development of novel regulatory and reimbursement models to support the development of the industry, which were the topics of conversation for the second workshop.

Regenerative medicine translation – a pathway into clinical practice

It is clear from the above discussion that synergies exist between market authorization and reimbursement regulations and practices. The second workshop explicitly discussed this interplay and the convergence in novel adaptive licensing practices that may promote the development and adoption of novel therapeutics that meet the needs of healthcare payers.

The regulatory landscape

Meeting regulatory requirements for safety and efficacy of products and manufacturing/processing is a major cost driver for regenerative medicine therapies. As noted by Heathman *et al.*, [4] in his survey of manufacturing technologies and strategies relative to clinical trials of cell therapies, "it is unsurprising that in the race to successfully commercialize cell products, companies have begun to raise the regulatory bar as a tactic to disrupt competitor companies. This action has the potential to hinder smaller companies who do not have the financial resource to comply with this increasing

regulatory burden.” However, regenerative medicine therapies are novel and challenge both applicants and regulators. In many instances, the small molecule paradigm is not appropriate. It may be unfeasible to conduct randomized controlled trials (RCTs), for example, when it is unethical to assign participants to an invasive control arm or for orphan diseases with small patient populations. In these instances, regulatory decisions must be made on a more limited evidence base for safety and efficacy.

Regulators have been working to develop appropriate policy interpretations of existing regulations or, in some cases, new safety and efficacy regulations specifically for regenerative medicine technologies to reduce uncertainties for developers and investors, and to harmonize these across major jurisdictions. The EU has developed a regulation for Advanced Therapy Medicinal Products (ATMPs) [38], which bridges the gap between the directives of medicinal devices (93/42/EEC) [39] and medicinal products (2001/83/EC) [40]. ATMPs include tissue engineering, cell therapy and gene therapy and the new Committee for Advanced Therapies (CAT), in addition to assessing marketing authorization applications of ATMPs in Europe, provides specific scientific expertise to support applicants and the Committee for Medicinal Products for Human Use and the Pediatric Committee of the EMA [41].

The key principles of the ATMP regulation for products which fall within its scope are: no marketing without prior authorization, demonstration of quality, safety and efficacy, postauthorization vigilance and a centralized review procedure. Classification distinguishes between cell-based ATMP, such as a cancer immune therapy product or artificial skin, and simple cell/tissue transplants, such as bone marrow transplantation. ATMPs involve substantial manipulation of cells that may change their biological or physiological characteristics, leading to safety and efficacy concerns. ATMPs are also for nonhomologous use, meaning that a human cellular or tissue product is not used clinically in a manner that is essentially the same as the natural endogenous function(s) that it performed, for example, to repair, reconstruct, replace and supplement. The CAT has performed 116 classification procedures prior to December 2014 and five certifications [41]. It has also published several specific guidance documents for ATMP developers such as the ‘mother guidelines’ on cell-based and gene therapy medicinal products as well as the risk-based approach, good clinical practice and environmental risk aspects to be taken account [42–46].

The Scientific Advice Working Party is available to developers to provide scientific advice or pro-

ocol assistance (for orphan medicines) on quality development/manufacturing issues, nonclinical and clinical studies. There are fee reductions for this service for small- and medium-sized enterprises, for all ATMP developers and additional protocol assistance at no cost for orphan medicinal products. This service may be provided in parallel with the US FDA. The advice from regulators is to consult as early and as continuously as possible to discuss scientific and regulator expectations and requirements to address and technical limitations or regulatory hurdles that might be encountered. Developers of 69 ATMPs sought scientific advice between January 2009–July 2014, and 47 had informal meetings with the EMA/Innovation Task Force office.

Health Canada employs a similar regulatory regime under pre-existing Food and Drugs Act [47] and Food and Drug Regulations [48] in assessing clinical trial applications and eventual market authorization [49]. Health Canada will be engaging with the regenerative medicine community through annual bilateral meetings, and solicited input on a Guidance for Sponsors: preparation of Clinical Trial Applications for use of Cell Therapy Products in Humans on 12 September 2014 [50]. However, calculations suggest increased costs for cell processing facilities to comply with general guidelines (e.g., by increasing the number of infectious disease markers that must be tested for per serum lot) [51]. An estimate suggests that quality control testing represents 17–45% of production costs, illustrating that regulatory burden is an important cost driver, at least for cell therapies [51]. However, Health Canada has taken a flexible approach to infectious disease testing and deviations from regulatory requirements are explicitly allowed when supported by a strong rationale and supportive evidence.

In Canada, certain allogeneic cells and tissues that are minimally manipulated for homologous uses are regulated under the Safety of Human Cells, Tissues and Organs for Transplantation Regulations [12]. If these cells and tissues meet the criteria, the transplant community may conduct research to establish best transplantation practices without notifying Health Canada.

Cells that fall outside the scope of the Safety of Human Cells, Tissues and Organs for Transplantation Regulations may be considered ‘advance medicinal products’ (AMPs). AMPs fall under the Food and Drugs Act and are evaluated primarily by Health Canada’s Biologics and Genetic Therapies Directorate [12]. A number of regulations may apply, including the Food and Drug Regulations [48], and the Medical Devices Regulations [52]. An AMP that does not meet the Safety of Human Cells, Tissues and Organs criteria or definition of ‘drug’, may meet the definition of a ‘device’ and be regulated under the Medical Device Regulations by the Medical Devices

Bureau in the Therapeutic Products Directorate. Alternatively, it may be a combination product and subject to Health Canada's Policy on Drug/Medical Device Combination Products [53] and guidance for Classification of Health Products at the Device-Drug Interface [54] (such as ViaCyte's VC-01, which was recently approved for clinical investigations in the USA and Canada). Since 2006, the Health Canada's Biologics and Genetic Therapies Directorate has reviewed over 110 regulatory submissions for cell therapies, of which 44 were clinical trial applications, two were new drug submissions, and many of the rest were amendments to clinical trial submissions or requests for priority review [49].

In addition, increased regulatory burdens, especially for storage, processing and manufacture of cells may have implications beyond developers, especially for cell and tissue banks (master and distribution cell banks) that will provide cell lines for clinical development of cell-based therapies [55]. When cells/tissues are the starting material for ATMPs, then the European Tissues and Cells Directive governs donation, procurement and testing of cell lines. Human embryonic stem cell lines (hESCs) in the UK and Canada fall under additional sets of regulations covering their derivation and use that must be traceable. In Canada, provisions of the Assisted Human Reproduction Act of Canada apply [56] including prohibitions on creation of embryos for research purposes and permission to conduct research on embryos that are no longer required for fertility treatments upon full, informed consent of donors.

Medical history of donors, risk assessment of cells and tissues and terms for informed consent add layers of regulatory burden. A variety of agencies are developing and standardizing guidelines on the medical history of donors of human embryonic stem cell lines [57] and microbiology, genetics and consent for tissues and cells (e.g., [58,59]). Microbiological risks are broader than blood-borne pathogens and include rapid detection of bacterial and fungal contamination. Genetic testing may be required to assess the accumulation of mutations in cell lines. Expert groups are working on standardization of tests to assess the suitability of cell lines for clinical use and this needs to be done in consultation with developers and regulatory agencies. Core requirements will require traceability, risk assessment, control of cell processing, testing and a master file on the history of each cell line. These files will have high value in supporting clinical trial applications and market authorization for all products derived from that cell line.

Finally, other regulatory frameworks are available to incentivize innovation in regenerative medicine, such as the EU orphan drug framework (Regulation [CE] N°141/2000) [60] (Canada is in the process of develop-

ing an orphan drug regulatory framework) [61]. Internationally, orphan drug frameworks, supervised by regulatory authorities, provide a variety of incentives to develop treatments for rare diseases (incidence of five per 10,000 individuals in the EU and Canada). In all jurisdictions, a developer must first apply for an orphan drug designation to access incentives. Financial incentives reduce development costs through tax credits for clinical trial expenses, research grants from funding agencies and waived administrative fees for regulatory approvals. From a regulatory perspective, orphan drugs are eligible for priority approval programs, which provide expedited approval for drugs that treat serious conditions and fill unmet medical need [62]. Developers also receive additional advice and assistance on technical matters during drug development and approval, compared with regular drugs. Once an orphan drug is released to market, it is granted market exclusivity, which protects it from direct competition for 8–10 years (10 years in the EU; 8 years in Canada). Collectively, these incentives aim to reduce the cost of developing and marketing orphan drugs.

The reimbursement landscape

While recognizing that reimbursement processes and decisions vary between member countries of the EU, lessons may be taken from the the UK experience, which was the focus of discussion at the workshop. In the UK, reimbursement decisions are supported by NICE. Its HTA employs cost utility analysis whereby outcomes (QALYs) and full care pathway costs are compared with the current standard of care [63]. As discussed above, NICE employs a cost per QALY threshold in making recommendations on the value of new technologies to the NHS. In assessing value, NICE considers the evidence for the effectiveness and cost-effectiveness of the technology alongside a number of other factors including the degree of uncertainty, whether the technologies are life extending at the end of life, indirect health benefits to family and carers and whether the technology is innovative, as well as adhering with equality legislation and a broader social value judgments framework. The probability of rejection increases as therapies exceed GB£20,000/QALY. In the range of GB£20,000–30,000/QALY, the additional variables gain in importance in making the determination and costs between GB£40,000 and GB£50,000/QALY may be considered for life-extending and end-of-life treatments. Unlike the UK, Canada does not have a unified reimbursement landscape; each province makes its own reimbursement decisions. However, support for HTA is provided by the independent CADTH through its Common Drug Review (CDR). The CDR provides objective and rigorous reviews of the clinical effectiveness and

cost–effectiveness of therapies [64]. It provides formulary listing recommendations for Canada’s federal, provincial and territorial publicly funded drug plans, with the exception of Quebec. In addition to the CDR, CADTH supports rapid response reviews, the Pan-Canadian Oncology drug review and provides advice on HTA and optimal use therapies in clinical practice. CADTH also plays a major role in methods development. While not explicitly stated, economists have estimated that CADTH appears to consider technologies with ICERs up to GB£50,000/QALY to be cost effective.

HTA frameworks, such as these, are generic and should have equal applicability for regenerative medicines. However, there may be specific challenges, namely, the high cost of manufacture may impact cost–effectiveness, there may be limited evidence of clinical effectiveness at the time of product launch, and benefits may be long term [63]. Due to the likely high cost of these therapies, QALY gains must be substantial to justify the expenditure, and it may be inadvisable to target conditions where there are already effective treatments. For example, in its review of Provenge, NICE indicated Dendreon (now Valeant) was unable to show that its immunotherapy performed better than already available treatments, and unlike current treatments, it did not delay the progression of the disease [11]. In other words, it did not perform at a level to justify a premium price when compared with existing therapies. Nevertheless, despite coming to a similar conclusion initially, Germany’s Institute for Quality and Efficiency in Healthcare reversed this conclusion, but that the added benefit could not be quantified [65]. The dossier prepared by Institute for Quality and Efficiency in Healthcare will be used by the G-BA (the Federal Joint Committee) to make a final decision on benefit and pricing.

Furthermore, when regenerative medicine products first come to market there is likely to be quite limited evidence on clinical effectiveness, which will drive high levels of uncertainty regarding their expected cost–effectiveness. This is one point of potential interplay with regulatory agencies, which are experimenting with adaptive clinical trial designs and conditional market authorization mechanisms (see discussion below). One effect of these will be to further limit the amount of clinical evidence available for reimbursement decisions through small clinical trial size, use of surrogate outcomes and short duration clinical trials. The latter, in particular, requires payers to extrapolate long-term health benefits, from short trials. This is especially problematic for potentially curative therapies. Conversely, short trials are unlikely to identify long-term side effects, such as cancer risks from cell therapies.

To address some of these challenges of managing access to highly uncertain but potentially high value

health technologies, NICE has been participating in multisector discussions with regulatory agencies and the UK regenerative medicine expert group. NICE recognizes the need to develop frameworks and methods to manage uncertainty where products first come to market with relatively limited evidence. Such a framework needs to consider the importance of early patient access to therapies that address an unmet need and important developments in the regulatory landscape that enable such access. This is a second point of intersection between reimbursement and regulatory agencies, and HTA agencies from other jurisdictions, such as CADTH can learn from developments at NICE.

Configuring adaptive licensing frameworks for regulation & reimbursement

Regulatory agencies have led the way in adapting licensing schemes to address challenges faced by novel and complex therapies, including regenerative medicines. In summary, these challenges include deficiencies in safety and efficacy data. In terms of safety, the goal of many cell therapies is engraftment, not rapid metabolism, thus, side effects may only become apparent many years after the conclusion of clinical trials (e.g., [66,67]). For regenerative medicines targeting rare diseases, clinical trial size and duration may be inadequate to calculate efficacy. Furthermore, RCTs for risky and invasive therapies may be prohibitively expensive and unethical from the perspective of participants enrolled in the control arm. On the other hand, small-scale and short-term clinical trials may be insufficient to provide evidence of the curative potential of regenerative medicines.

In response, both EU and Canadian regulators have made provisions for conditional marketing authorization. In the EU, such authorization is available for seriously debilitating or life-threatening diseases, emergency threats and orphan medicinal products (Reg [EC] No 507/2006) [68]. Regulators are empowered to grant a conditional approval in the absence of comprehensive clinical data if: (1) there is a positive benefit to risk assessment, (2) it is likely that comprehensive clinical data will be provided, (3) that an unmet clinical need will be met, and (4) that the benefit to public health of immediate availability outweighs the risks of moving forward in the absence of additional data that would normally be required [41].

Health Canada was the first jurisdiction internationally to grant market authorization for a cell therapy product, PROCHYMAL® under the Notice of Compliance with conditions guidance [69]. This mechanism allows therapies with promising clinical benefits to be expeditiously available for patients with serious, life-threatening or severely debilitating diseases or conditions for which

no drugs are currently marketed in Canada. This conditional approval process was unique to Canada at that time. Health Canada specifically convened an Expert Advisory Panel to review the available quality, safety and efficacy data and to perform a risk-benefit analysis [12]. PROCHYMAL addressed an urgent, unmet need to treat steroid refractory graft versus host disease in pediatric patients. Given the safety profile of the therapy, with risks focused on infection transmission and some toxicology events, the Panel recommended that the potential benefits outweighed the risks. Health Canada granted conditional market approval with the requirement to provide clinical evidence from further confirmatory studies (RCTs or well-designed case-control studies) for full market authorization by June 2016.

To be effective, conditional approval mechanisms must be supported by postmarket surveillance systems whereby regulators have the capacity and power to remove products from the market. While post approval studies have the potential to provide additional data on safety and efficacy, there are serious concerns about postmarket regulatory systems [70]. In Canada, the recently enacted Bill C-17: Protecting Canadians from Unsafe Drugs Act (Vanessa's Law) [71], which amended the Food and Drugs Act, enhances the powers of Health Canada to maintain surveillance on the products, strengthens the reporting of adverse reactions by healthcare institutions and improves Health Canada's ability to collect postmarket safety data and take appropriate action in the event when a serious health risk is identified.

In March 2014, the EMA launched an adaptive licensing pilot project to serve as a platform for early dialogue among stakeholders. The goal of the adaptive licensing approach is to improve timely access for patients to new therapies. It comprises a 'prospectively planned process, starting with the early authorization of a medicine in a restricted patient population, followed by iterative phases of evidence gathering and adaptations of the marketing authorization to expand access to the medicine to broader patient populations' [72]. From March through December 2014, ten products have been accepted to participate in the pilot project, of which two are ATMPs [41]. While such developments by regulatory agencies are supportive of clinical development for regenerative medicines, in isolation they do not guarantee market access. This conundrum has been recognized in the planning of the EU's pilot project. The EMA recognizes that adaptive licensing to improve patient access requires the involvement of all stakeholders, including regulators, developers, reimbursement agencies such as NICE, organizations that issue clinical treatment guidelines and patient organizations.

Since the 1990s, reimbursement agencies have been experimenting with conditional reimbursement programs. Indeed, even in the USA, the Centers for Medicare and Medicaid Services are re-engaged with coverage mechanism linked to the collection of additional evidence to inform subsequent reviews of coverage decisions [73]. Collectively, these mechanisms to assess technologies that fail standard appraisal criteria are referred to as Access with Evidence Development (Figure 1) [74]. Another system, known as value-based pricing (VBP) sets the price of a new therapy at the level that makes it a good value for the health system, and its use may justify a price premium for curative therapies. VBP has been successfully used in Sweden, but plans to implement it in the UK were shelved when research on public values found no support for an innovation premium [75,76]. As a result, a new Pharmaceutical Pricing Regulation Scheme was negotiated, which attempted to put a ceiling on the maximum UK expenditure on branded pharmaceuticals. There remains substantial interest in policy circles in the concepts underlying VBP, for example, France uses value categories to determine new drug prices. Research into risk sharing models between payer and providers through highly innovative models, such as annuity-based pricing or leasing models, is worth exploring further [33].

The VoI framework described above is useful for addressing the question, 'should we delay reimbursement of the technology to allow further research to take place?' The move to accelerate access for highly uncertain but potentially high value technologies, effectively rules out this conventional use of VoI. However, innovative reimbursement models can be evaluated using the same framework. Changes in the upfront cost of the technology reduces the expected cost of making the wrong decision, and linking reimbursement to performance [33] or the provision of additional data [77] reduces the uncertainty about the net value of reimbursement; again reducing the VoI for further research. Further economic modeling is required to assess the impact of different reimbursement schemes on the potential return on investment for a technology developer. Advances in such models related to real world examples of regenerative medicines in development were the topic of the first workshop.

NICE, in collaboration with stakeholders, is considering the development of models to explicitly consider a wider range of patient access schemes to achieve equitable sharing of risks across stakeholders [63]. This includes developing mechanisms to collect and analyze postmarket surveillance data to reduce reimbursement decision uncertainty over time. This will likely involve an increased emphasis on 'recommend with further research' type recommendations in NICE decision frameworks (Figure 1). However, analytic capacity and

advanced methods will be needed to support NICE's ability to assess products and interventions based on real world data supplemented with formally elicited expert judgment. This will require further collaboration and integration with surveillance systems and health records held by the NHS. Problems inherent in evidence generation and analysis based on postmarket surveillance data outside of a controlled clinical trial environment will be common to all systems experimenting with access with Evidence Development frameworks.

Recent developments in Japan that integrate health system and reimbursement conditional licensing schemes for regenerative medicine may provide some evidence on whether such schemes will accelerate clinical development in the field. The new law came into effect in November 2014, but details of its operation in practice are not fully fleshed out (Figure 2). Under the Japanese law, conditional regulatory approvals may be granted based on early Phase clinical trials that demonstrate safety and are likely to predict efficacy. Therapies that receive such conditional approval are then eligible for reimbursement by the Japanese health system, but Japan's universal health insurance system requires up to 30% copayment from patients depending on age and type of condition (unpublished observations) [78]. The scheme is unique in promoting regenerative medicine to the exclusion of other innovative therapies and has been justified both in terms of improving access to regenerative medicines for patients and the Japanese industrial policy commitment to the regenerative medicine sector. The scheme transfers the economic and health risks of experimental regenerative medicine technologies to the Japanese health system, which is

supported by three mandatory insurance programs: the Japanese National Health Insurance, employees health insurance and government-managed health insurance (unpublished observations) [78]. Safety considerations aside, the scheme may negatively impact the ability to collect meaningful efficacy data for final regulatory and reimbursement decisions, in part, because patients with access to therapies have no incentive to enrol in well-designed clinical trials (unpublished observations) [78]. This was the experience with high-dose chemotherapy with autologous bone marrow transplantation for breast cancer in the 1980s [79]. Support from some physicians and legal challenges over insurance coverage from patients enabled access to the experimental therapy. Such access disrupted enrolment in RCTs, which eventually reported no benefit from the therapy.

In addition to undermining the production of robust evidence to support future regulatory and reimbursement decisions, the system requires patients to assume both personal and economic risks with limited likelihood of benefit given the high failure rate in Phase II trials [13]. There is no doubt that the scheme is a bold move to incentivize and support the regenerative medicine industry; however, other jurisdictions will be reluctant to follow Japan's lead, in light of serious ethical considerations for the safety of patients, and without a societal debate over how far industrial policy supporting regenerative medicine should determine the expenditure of taxpayer resources that have been allocated to the health system piece of the taxpayer pie. The Japanese experiment will be closely followed internationally.

Conclusion

Regenerative medicine holds great promise, but that promise challenges regulatory and reimbursement systems worldwide. Proposals for conditional licensing and reimbursement regimes are being discussed cautiously on both sides of the Atlantic, while Japan has committed to a radical and high-risk policy that represents a complete break with the conventional consumer protection principles that have underpinned worldwide licensing processes for the last four decades. Industrial policy concerns push for ever faster translation of regenerative medicine discoveries, while stewardship of listed healthcare resources urges caution and evidence of safety and effectiveness before large-scale funding. Encouragingly, regulators and healthcare payers have started discussions on collaborative support for the translation of regenerative medicine while protecting both patients and budgets. These discussions are increasingly clear on the need for change and the problems that some proposed changes will bring. However, there is considerably less clarity regarding which changes might successfully balance the competing

Figure 1. Reimbursement options available to healthcare payers. Boxes represent the groups to which therapies will be provided with or without the generation of further evidence. The triangle represents the size of the population that may access the therapy.

Figure 2. Market access in Japan before and after the Pharmaceutical and Medical Device Act. The conditional approval of the PMD act allows for market access in Japan earlier in product development [81]. PMD: Pharmaceutical and medical device.

needs of industry, patients, regulators and payers. The challenges are substantial and the time for resolution is getting short. Multistakeholder discussions such as these workshops provide valuable insights into the tensions between conflicting and synergistic objectives, and therefore, present a space to negotiate solutions that meet the needs of each one.

Future perspective

Enhanced methods in horizon scanning and economic modeling will enable developers of regenerative medicine products and services to better assess value for health systems and other payers in major markets. These will support the development of coherent policies and practices between the agencies that regulate regenerative medicine products and services and will aid the clinical translation process. Emerging convergence in novel adaptive licensing practices will promote the development and adoption of novel regenerative medicine products and services that meet the needs of patients, providers and payers.

Author contributions

T Bubela and C McCabe co-organized the two workshops and drafted the manuscript. All other authors provided comments and clarifications and approved the manuscript as an accurate reflection of the discussions at the workshops. T Bubela finalized the manuscript for submission.

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Executive summary

Opportunities & challenges

- Regenerative medicine is coming of age in an era of cost-constrained health systems facing an aging population and high-cost new therapies and technologies that do not necessarily improve health outcomes. The promise of regenerative medicine is to break out of the marginal value mould of traditional pharmaceuticals with curative therapies for indications with limited treatment options; but these therapies are likely to be costly.
- Value assessment is an increasingly real and immediate consideration for access to major markets and must be assessed as part of the clinical translation process.

Methods to support assessments of value

- Multiple agencies and methods support assessment of value. A convergence of methodologies is in development to assess the potential cost-effectiveness of regenerative medicine therapies, including technology landscaping, horizon scanning, cost-effectiveness modeling, cost of goods modeling and value of information modeling.
- Applied within a coherent framework, these methods have the potential to provide risk information to developers, public and private sector investors and health systems and may further inform the development of novel regulatory and reimbursement models.

Regenerative medicine translation – a pathway into clinical practice

- Regulators in the EU and Canada have been working to develop appropriate policy interpretations of existing regulations or, in some cases, new safety and efficacy regulations specifically for regenerative medicine technologies to reduce uncertainties for developers and investors, and to harmonize these across major jurisdictions.
- Reimbursement decisions are supported by health technology assessments. Health technology assessments frameworks are generic and there may be specific challenges for regenerative medicine, namely, the high cost of manufacture may impact cost-effectiveness, there may be limited evidence of clinical effectiveness at the time of product launch and benefits may be long term.

Configuring adaptive licensing frameworks for regulation & reimbursement

- Regulatory agencies have led the way in adapting licensing schemes to address challenges faced by novel and complex therapies, including regenerative medicines.
- Reimbursement agencies recognize the need to develop frameworks and methods to manage uncertainty where products first come to market with relatively limited evidence. Such a framework needs to consider the importance of early patient access to therapies that address an unmet need and important developments in the regulatory landscape that enable such access.
- Synergies exist between market authorization and reimbursement regulations and practices. There is an emerging convergence in novel adaptive licensing practices that may promote the development and adoption of novel therapeutics that meet the needs of healthcare payers.
- Encouragingly, regulators and healthcare payers have started discussions on the collaborative support for the translation of regenerative medicine while protecting both patients and budgets. Proposals for conditional licensing and reimbursement regimes are being discussed cautiously on both sides of the Atlantic, and a novel scheme is being piloted in Japan.

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