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### **Ethical and regulatory challenges with autologous adult stem cells**

A comparative review of international regulations

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# **Ethical and Regulatory Challenges with Autologous Adult Stem Cells: A Comparative Review of International Regulations**

## **Abstract**

Cell and tissue-based products, such as autologous adult stem cells, are being prescribed by physicians across the world for diseases and illnesses that they have neither been approved for or been demonstrated as safe and effective in formal clinical trials. These doctors often form part of informal transnational networks that exploit differences and similarities in the regulatory systems across geographical contexts. In this paper, we examine the regulatory infrastructure of five geographically diverse but socio-economically comparable countries with the aim of identifying similarities and differences in how these products are regulated and governed within clinical contexts. We find that while there are many subtle technical differences in how these regulations are implemented, they are sufficiently similar that it is difficult to explain why these practices appear more prevalent in some countries and not in others. We conclude with suggestions for how international governance frameworks might be improved to discourage the exploitation of vulnerable patient populations while enabling innovation in the clinical application of cellular therapies.

## Introduction

Over the last decade, the use of human cell and tissue-based products (CTPs) in new and innovative therapies has drawn increasing interest from healthcare providers, researchers, patients, and regulators, internationally. However, despite there being few accepted clinical uses (Daley 2012), CTPs are increasingly being prescribed for conditions that have not been demonstrated as safe or effective in clinical trials. In particular, autologous adult stem cells (ASCs) are being offered directly to patients, typically over the Internet, for a wide range of diseases and conditions for which there is insufficient evidence that demonstrates their safety and efficacy (Regenberg et al. 2009, Lau et al. 2008). While evidence has emerged in recent years to reduce initial safety fears about the tumour-forming properties of ASCs, clinical data that supports the efficacy of these products for many indications has been either limited to early Phase I/II trials, or in some cases, non-existent (Power and Rasko 2011).

Until recently, these practices were utilized mainly by patients travelling from wealthy nations to low-to-middle income countries, or so-called ‘stem cell tourism’ (c.f. Lysaght and Sipp 2015). These countries, including China, Thailand, and India (Regenberg et al. 2009, Lau et al. 2008), were assumed to foster stem cell clinics because they lacked the necessary regulatory infrastructure to monitor and control the practices of clinics and healthcare institutions operating within their jurisdiction (Kiatpongsan and Sipp 2008). This picture is, however, no longer adequate, as autologous ASCs are increasingly being offered in wealthy countries, such as the United States (Turner and Knoepfler 2016), Japan (Fujita et al. 2015) and Australia (McLean, Stewart, and Kerridge 2014). The emergence of these domestic markets means that patients need no longer travel long distances to access ‘unproven’ cellular therapies, and that the global escalation of these practices cannot be simply explained as a matter of weak or absent regulation in emerging economies.

In a study funded by the Economic and Social Research Council in the United Kingdom, Petra and Sleeboom-Falkner (2009) describe how disparities in regulatory systems across geographical contexts are being exploited by what they term as ‘bionetworks’. These networks are represented by loosely organized transnational relationships between physicians, science entrepreneurs, researchers and patients, who operate mostly, although not

exclusively, within the private healthcare sector (Sleeboom-Faulkner and Patra 2011). They work in part by exploiting differences and inequalities in the provision of healthcare, standards of wealth, capacity to conduct scientific research, and regulatory infrastructure between rich and poor(er) countries. While this study provides some evidence of bionetworks extending out of Asia and into the protected markets of the so-called ‘West’, most notably through patient recruitment (Patra and Sleeboom-Faulkner 2009), their infiltration into high income countries with lucrative domestic markets for novel therapeutics has not been uniform nor has it been essential for the global proliferation of clinics offering autologous ASCs outside clinical trials.

The global reach of bionetworks is most clearly visible in the recent events in Texas, where the Governor Rick Perry was administered with autologous ASCs processed using technology imported from the Seoul-based company K-STEMCELL, formerly operating as RNL Bio (Lysaght et al. 2013). This intervention followed a similar procedure that had been carried out on Perry’s treating physician at a clinic associated with RNL Bio in Japan (Berfield 2013), one of a number of clinics are purportedly offering autologous ASCs (Fujita et al. 2015). Yet, in Australia, where a sharp increase in such clinics has occurred following the introduction of a new regulatory framework for CTPs (McLean, Stewart, and Kerridge 2014, Munsie and Pera 2014), the connections with bionetworks in Asia or elsewhere are less visible. Furthermore, other countries such as Singapore, Canada and the United Kingdom, have been relatively successful in controlling the use of autologous ASCs within their borders. Hence, there could be differences in regulatory systems between *wealthy nations* with similar standards in healthcare, scientific investment and economic structure that may be influencing the provision of autologous ASCs to patients outside clinical trials.

This paper examines the regulatory systems of five geographically diverse but socio-economically comparable countries with the aim of identifying similarities and differences in how novel uses of CTPs are regulated and governed within clinical contexts. We follow this examination with a discussion about the strengths and weaknesses of these approaches and suggest ways in which international governance may better achieve a balance between the need to protect vulnerable patient populations and the desire to enable scientific and clinical innovation. Specifically, we argue for greater consistency and clarity in regulatory

instruments across jurisdictions and encourage the relevant authorities within the medical profession to take a greater leadership role in sanctioning unethical and irresponsible practices with CTPs.

## **Comparative Review of International Regulatory Approaches to CTPs**

The five countries selected for the comparative review – Australia, Japan, Singapore, the UK, and the USA – were chosen from the extant literature because of their comparability across key socioeconomic and health indicators. They are all structured as capital markets and are among the 46 countries classified by the World Bank as high-income economies (World Bank 2012). They each spend between 1.7 and 3.4% of gross domestic product a year in research and development (World Bank 2008) and have comparably high capacities for scientific research (IMD 2013). While different healthcare systems are in place, the standards of healthcare offered to patients are relatively stable across these jurisdictions. These countries have also invested heavily in biomedicine and medical biotechnologies, including regenerative medicines based on stem cells and other CTPs.

To support this investment, these countries have all established regulatory infrastructure to enable the protection of intellectual property rights and govern research involving human subjects. Regulations for human subject research in each country are based on internationally accepted norms initially set in the Nuremberg Code and later adopted by the World Medical Association (WMA) in the Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) for the International Ethical Guidelines for Biomedical Research Involving Human Subjects. These norms include imperatives for informed consent, privacy, confidentiality, and independent oversight from an Institutional Review Board (IRB) or an equivalent body. Most of these countries have also established extensive frameworks for research involving human stem cells and tissues.

While the five jurisdictions employ different regulatory mechanisms to control the use of human embryos in research, they all generally provide relatively permissive environments for stem cell research (Chalmers 2010). All countries, except the USA, have specific legislation that prohibits the use of human cloning techniques for reproductive purposes and all five jurisdictions have regulations that allow research on human embryonic stem cells (ESC). In

addition, all countries have established regulatory frameworks for the sale of medicinal drugs and governance of medical practice. As the following analysis indicates, there are technical differences in how these regulations are implemented. However, there are also broad similarities with the general approach taken in each jurisdiction that do not lead to simple explanations as to why the use of autologous ASCs appears more prevalent in some countries and not others. In the following, we describe these regulations and provide some critical commentary focusing on provisions specific to autologous uses of ASCs within both formal clinical trials and the practice of medicine.

## United States

In the USA, the Food and Drug Administration (FDA) has jurisdiction over medicinal drugs, devices and biologics that are entered into *interstate commerce*; meaning that products (or products composed of ingredients) that are shipped interstate fall under the federal regulatory authority (FDA 1978). The FDA controls market entry of these products through requirements for premarket testing of safety and efficacy in specified indications, which usually involves a series of registered multiphase (I–III) clinical trials that are conducted after the sponsor obtains an Investigational New Drug (IND) designation. Subsequent market authorisation may include additional requirements for post-market surveillance.

Regulation of CTPs is administered by the Center for Biologics Evaluation and Research (CBER) Office of Cellular, Tissue, and Gene Therapies (OCTGT) within the FDA, and depending on their specific formulation, may be classified as devices, drugs, and/or biologics. CTPs are then subdivided according to criteria set out in the Code of Federal Regulations (CFR) that are intended to establish whether the product is: 1) more than minimally manipulated 2) intended for non-homologous use; 3) combined with other articles; or, 4) if not for autologous use, either exerts systemic effects or relies on metabolic activity. If a CTP meets any of these definitions, it is categorized under section 351 of the Public Health Services (PHS) Act (1944) and regulated as a biological drug according to the CFR as a “351 product”. This categorisation requires pre-market authorisation from CBER and compliance with Good Manufacturing Practices (GMPs). However, CTPs that do not meet any of these definitions are regulated solely under Section 361 of the PHS Act as “361 products”, which do not require the pre-market evaluation required for 351 products.

While the processing of 361 products should comply with Current Good Tissue Practice (CGTP) standards intended to prevent contamination by the spread of communicable diseases (CBER, 2011), their use within clinical contexts, along with ‘off-label’ uses of approved 351 products, constitutes a medical procedure that lies outside the FDA’s jurisdiction. Medical procedures are instead governed within the practice of medicine by medical boards and civil statutes in each of the 50 American states. In 2012, the Texas Medical Board (2012) introduced rules on the investigational use of human stem cells that appears to provide an alternative to the IND pathway by allowing physicians to seek IRB approval to prescribe agents not approved by the FDA in their practice. Despite these rules, federal laws pertaining to manufacturing standards supersede state laws and they are unlikely to provide protection against legal action taken by the FDA in asserting its authority over CTPs that fall within its jurisdiction.

Indeed, the FDA has exerted its authority over the manufacturing of autologous ASCs processed on-site for non-homologous uses in the District Court of Columbia. This court broadly upheld the FDA’s interpretation of CTPs that are entered into interstate commerce as defined in CFR 1271 (see US Court of Appeals 2014). The FDA has also issued a warning letter to a storage facility in Texas over violations of GMP standards for adipose-derived stem cells. In addition, the Federal Bureau of Investigation successfully prosecuted the owner of laboratory in Arizona for unlawfully introducing allogeneic cord blood cells into interstate commerce while investigations into other related cases of mail fraud involving stem cells continue (Callaway 2011). Civil action has also been initiated against the American subsidiary of RNL Bio, RNL Biostar, for allegedly providing misleading information about the efficacy of their autologous ASC product (Cyranski 2012). The outcomes of these lawsuits, and their impact on the availability of ASCs outside clinical trials, remain to be seen.

The USA faces many difficulties in controlling the number of clinics offering putative stem cell treatments, not least because of a federal system that has generated a patchwork of state-based regulations for the governance of medical practice. This system allows physicians who are notified by regulatory authorities to cease and desist in one state, to easily move into another where they hold medical licensure, or partner with other physicians who are

registered to practice in that state. They can also relocate the clinic to another country, such as Mexico, where they can evade regulatory oversight while marketing the interventions to American patients (Turner 2015). Exacerbating this situation are the ambiguities in the FDA regulations on what constitutes ‘no more than minimal manipulation’, which is defined in 21 CFR 1271.3(f)(2) simply as “processing that does not alter the relevant biological characteristics of cells”. Rather than specifying techniques or processes that would count as minimal manipulation, or not, this definition relies on what impacts the processing has on the integrity of the cells or tissues from their original state. This vagueness is open to interpretation and may have encouraged the introduction of invented techniques, such as ‘stromal vascular centrifugation’ of adipose-derived stem cells. While new Draft Guidelines for HCT/PS from adipose tissues may help to clarify these definitions (FDA 2014), without specifying the techniques that constitute minimal manipulation, they may still leave open the opportunity for clinics to circumvent the regulations.

## Japan

Japan has a pre-market evaluation process for drugs and devices that is similar to the FDA system where market approval is generally provided following the evaluation of data from clinical trials that demonstrates safety and efficacy. Clinical trial data is reviewed by the Pharmaceuticals and Medical Device Agency (PMDA) – an administrative agency established under the Ministry of Health, Labour and Welfare (MHLW) under powers conferred by the *Pharmaceutical Affairs Law (PAL)*. In practice, requests and notifications are generally submitted to the PMDA, which reviews the submission and reports its opinion to MHLW, which either grants marketing approval or makes further recommendations.

In May 2013, the Japanese Diet introduced widespread changes to this legislative framework with the enactment of the *Regenerative Medicine Promotion Law (2013)*. The new legislative framework includes amendments to the PAL, which has been renamed as the *Pharmaceuticals and Medical Devices and Other Therapeutic Products Act (PMD Act)*, and the introduction of the *Act on the Safety of Regenerative Medicines (ASRM 2014)* as well as a slew of administrative guidance documents, ministerial ordinances, and guidelines on product quality, safety and efficacy (Azuma 2015). This framework was introduced, in part, to speed-up the approval process for new regenerative medicine products, particularly induced



pluripotent stem (iPS) cells that were first developed in Kyoto; but also in response to the country's growing reputation as a destination for medical tourists seeking out unproven stem cell-based interventions (Konomi et al. 2015).

Prior to these changes, CTPs were not explicitly regulated under the PAL unless they could be classified as drugs or devices according to their mode of action (Azuma 2015). However, this only included *processed* CTPs that were expanded *ex-vivo*, treated pharmacologically for activation, biologically-altered, combined with scaffolds or genetically modified; unprocessed CTPs<sup>1</sup> were excluded and their use presumably fell within the practice of medicine, which is regulated by the Medical Practitioners Law (MPL) (1948). This law, which the MHLW also administers, considers a practitioners' act of producing an unapproved drug and administering it to a patient as falling within the scope of 'physician discretion' in medical practice. CTPs administered in this context thus were not governed by the PAL and practitioners did not need to seek prior approval from the MHLW/PMDA when acting within this zone of discretion. If the CTP was administered in the context of clinical research, as distinguished from a clinical trial (*chiken*), then practitioners were expected only to observe the *2003 Ethical Guideline on Clinical Research*, and the *Guidelines on Clinical Research Using Human Stem Cells (2006 Guidelines)* if stem cells were used.

With the new laws, companies aiming to evaluate the safety and efficacy of CTPs for market distribution in clinical trials will be regulated under the PMD Act, while institutions that use stem cells in clinical research or medical practice will fall under the ASRM (Azuma 2015). The PMD Act provides sponsors of clinical trials with a conditional and time-limited approval to market CTPs once safety and *probable benefit* has been demonstrated in early clinical studies (Konomi et al. 2015). Sponsors will then have a maximum of seven years to submit data from post-marketing trials to evaluate efficacy and may apply to the national insurance scheme for reimbursement, subject to the approval of the Central Social Insurance Medical Council. CTPs that are provided under the ASRM must be processed in a licensed facility for quality assurance and reviewed according to a three-tiered risk-based

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<sup>1</sup> Includes the separation of tissue, mincing of tissue, separation of cells, isolation of specified cells, treatment by antibiotics, rinsing, sterilisation by gamma-rays etc., freezing and thawing. See Guidelines on Ensuring Quality and Safety of Products Derived from Processed Cell/Tissue (PFSB/MHLW) Notifications, 2008.

classification system (i.e. low, medium or high) that is overseen by committees certified to approve the use of these products in medical practice and clinical research. Companies will be permitted to use data from clinical research conducted at medical institutions to demonstrate product safety under the PMD Act.

While it may be too soon to predict the full implications of this framework, early indications suggest that businesses and industry are manoeuvring to exploit the new laws. In September 2015, the MHLW authorised the first conditional approval under the PMD Act for an autologous cell product for use in patients with serious heart failure on the basis of evidence submitted from a single small-scale (n = 7) open-label clinical trial (Sawa et al. 2015). In addition to the approval, the Central Social Insurance Medical Council set a price of approximately \$122,000 USD for a standard course, which has shifted investment risks from the developer to the Japanese taxpayer and patients who still contribute a 30% co-payment for an under-tested product with uncertain safety and efficacy (McCabe and Sipp 2016). Moreover, the ASRM is likely to encourage clinics to continue marketing autologous ASCs with a highly decentralised oversight model that places the responsibility of classifying CTPs with certified committees that interpret the regulations and determine a product's level of risk based on guidance documents that lack enforcement in law (Lysaght and Sugii 2016). With more than 128 committees currently certified with the regulator, there is much room for variation in how this guidance is interpreted and applied to specific products.

## Australia

In Australia, CTPs are regulated federally by the Therapeutic Goods Administration (TGA) under the *Therapeutic Goods Act* (1989) according to the framework for biologicals (Trickett and Wall 2011). This framework categorises CTPs as either being: 1) regulated as therapeutic goods, but not as biological goods; 2) regulated as biological goods under the biologicals framework; and 3) not regulated as biological goods (excluded from regulation).<sup>2</sup> The first category includes biological prescription medicines, such as vaccines, blood, plasma

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<sup>2</sup> Part 3-2A of the *Therapeutic Goods Act 1989* defines biologics as “a thing made from, or that contains, human cells or human tissues and that is used to treat or prevent disease, ailment, defect or injury; diagnose a condition of a person; alter the physiological processes of a person; test the susceptibility of a person to disease; or replace or modify a person's body parts”

derivatives, and cryopreserved haematopoietic progenitor cells that are used for haematopoietic reconstitution. These products are listed as medicinal products on the Australian Register of Therapeutic Goods (ARTG) following pre-marketing assessments of safety and efficacy in clinical trials in a manner broadly similar to the approval processes for drugs in the USA and Japan.

The second category of products are regulated as biologics and include human stem cells, tissue-based products, such as skin and bone, genetically modified and *in vitro* expanded cell-based products, and combined cell and tissue products. These products are classified according to a risk-based framework that is broadly similar that outlined in Japan's ASRM. This framework is detailed in the *Australian Regulatory Guidelines for Biologicals*, which applies oversight measures based on the degree of manipulation or alteration, and the intended use (non/homogeneous, autologous/allogeneic) of the CTPs. All CTPs regulated as biologics under this framework must be entered onto the ARTG following a pre-market approval process, although assessments of safety and efficacy data only apply to products classified as higher risk. Manufacturers of these products must also obtain a licence from the TGA that demonstrates compliance with principles equivalent to the *Australian Code of Good Manufacturing Practice (GMP) or Human Blood and Tissues*. Very low risk products require only a statement of compliance with these standards. At the time of writing, no products had been listed in this class.

Products exempt from both of these categories are not regulated as biological or therapeutic goods. Under the *Therapeutic Goods (Excluded Goods) Order No. 1 of 2011*, these products include fresh viable human organs and haematopoietic progenitor cells for the purpose of haematopoietic reconstitution, reproductive tissue for use in assisted reproductive therapy, and most controversially, CTPs that are collected from a patient who is under the clinical care and treatment of a registered medical practitioner, and manufactured by that practitioner, or under the professional supervision of that practitioner. In this case, the CTPs must be used in the treatment of a "single indication and in a single course of treatment of that patient by the same medical practitioner, or by a person or persons under the professional supervision of the same medical practitioner" (TGA 2011).

The TGA has provided additional guidance of the Exclusion Order, which specifies that the CTPs must be for autologous use, that a single medical practitioner must assume responsibility for the clinical care of that patient, and where the practitioner is not directly involved in the manufacture of the CTP, that there be a “specified relationship with the agent/agency that meets the requirements for professional supervision” (TGA 2011). The use of CTPs that are excluded from TGA regulation would thus fall under the jurisdiction of the Medical Board of Australia and practitioners must comply with the *Good Medical Practice: A Code of Conduct for Doctors in Australia*. At least three practitioners have been disciplined for providing stem cell therapies, with one having their registration suspended for three years (McLean, Stewart, and Kerridge 2015). Most recently, the Deputy Coroner in New South Wales (2016) recommended an investigation into the professional conduct of cosmetic surgeon, Dr Ralph Bright, following the death of a patient who died after liposuction that was done to obtain adipocyte-derived ASC for the treatment of her dementia.

There is little question that the regulatory framework in Australia, particularly the Exclusion Order, has encouraged the proliferation of clinics offering autologous ASCs in Australia. Unlike the FDA regulations, the Australian framework specifies the techniques and products that are excluded from regulation, which implies that everything else would fall under the TGA’s jurisdiction unless otherwise stated. This implication means that practitioners can assume that a CTP processed with a new technique will fall under the regulations because it is not specified as being excluded. The problem with the Exclusion Order, however, is that terms such as “single course of treatment”, “professional supervision” and “manufacturing” may be mistakenly, or willfully misconstrued, as having different meanings as intended in regulatory guidance (McLean, Stewart, and Kerridge 2014). In 2015, the TGA invited public submissions on the appropriateness of the Exclusion Order for autologous CTPs. As of August 2016, the results of the TGA investigation had not been released and no change had been made to the existing regulatory framework.

## Singapore

Singapore does not have specific legislation to regulate CTPs, although they broadly fall within the scope of *The Medicines Act* (1975, revised 1985). Part 1 Section 3(1) of this Act provides laws for the manufacturing, distribution and marketing of medicinal products,

defined as “any substance or article (not being an instrument, apparatus or appliance) which is manufactured, sold, imported or exported for use wholly or mainly [...] for a medicinal purpose”. CTPs are not explicitly included in this definition, but nor are biologics, which the Health Sciences Authority (HSA) defines in its guidance for registering medicinal products, as “products derived from biological systems”, including whole cells or organisms, or parts thereof (HSA 2011). Manufactures of unlicensed products that fall within this definition are required to apply for a New Drug Application through the HSA, similar to an IND in the US, which is assessed following the submission of clinical documents demonstrating safety and efficacy, according to the *Medicines (Clinical Trials) Regulations* (1978, revised 2000).

The Medicines Act provides for exceptions to these regulations. According to Part 2 Section 7(4), restrictions on the sale, supply and manufacturing of medicinal products that are set out in Act do not apply to “the preparation, dispensing and assembly of any medicinal product by or under the supervision of a practitioner for the purpose of administration to a patient or animal under his care”. Thus, as biological medicinal products, the Act would not apply to the manufacturing, sale or use of CTPs within hospitals and medical clinics. The Act also “does not apply to products categorised and regulated as health products under the Health Products Act” (see Part 7 Section 77). Currently though, the *Health Products Act* (2007) only regulates product categories that have been specified in the First Schedule, which is limited to medical devices and cosmetic products, and do not include CTPs.<sup>3</sup>

The HSA has proposed to add CTPs to the First Schedule and are currently drafting regulations to include CTPs as health products. The proposed framework resembles the risk-based classification system used in Australia and Japan (Ong 2013). If adopted in Singapore, it is unclear how CTPs may be used in hospitals as the Health Products Act does not include exemptions for products that are manufactured by or under the supervision of medical

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<sup>3</sup> Medical devices are defined in the Schedule as “any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article” and cosmetic products are “any substance or preparation that is intended by its manufacturer to be placed in contact with the various external parts of the human body or with the teeth or the mucous membranes of the oral cavity”. Thus, while a point-of-care cell processing device may fall within the scope of the Act, the cells processed using this technology would not. Health Products Act (2007) Part 1 Section 4(1)

practitioners. CTPs that are processed and stored for human transplantation in hospitals and medical clinics are covered under the Ministry of Health's (2003) *Guidelines for Healthcare Institutions Providing Tissue Banking*. Sections 1.1a and b of this guidance include "all constituent parts of the human body, including surgical residues" but exclude solid organs, placenta, blood and blood products, and reproductive tissues, as well as tissues that have been "processed in such a manner that their functional, structural and biological characteristics have been altered". These products are classified as biologics, which currently fall under the Medicines Act.

The legal ambiguity may have encouraged a small number of physicians to market stem cells in Singapore without prior approval from the HSA. While these physicians had not clearly broken any laws, the Singapore Medical Council (SMC) took disciplinary action against three practitioners offering stem cells for aesthetic and anti-ageing treatments.<sup>4</sup> All three doctors were charged with professional misconduct, issued with fines and censured, but not removed from the medical register. However, in 2012, the Singapore Court of Appeals overturned the SMC's verdict against one physician on grounds that there were no established or official standards for the practice of 'aesthetic medicine' at the time of the Discipline Committee's inquiry to substantiate a charge of professional misconduct (High Court of Singapore 2012). The SMC has since withdrawn the charges against the physicians in question. No claims have surfaced around the use of CTPs for medical indications.

Legal actions from the SMC may have discouraged other practitioners from offering autologous ASCs, although since the appellant Court decision the SMC has not prosecuted any other physicians and a Google search in August 2016 revealed at least five clinics offer stem-cell based products for aesthetic purposes. Reasons for the lack of clinics offering medically-indicated therapies with autologous ASCs in Singapore are unclear since the regulations for CTPs are less clear than they are in Australia and the USA. This situation may

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<sup>4</sup> In 2007, Drs Georgia Lee and Low Chai Ling were censured for offering aesthetic treatments with stem cell 'extracts' without evidence of efficacy (High Court of Singapore 2012); Dr Martin Huang Hsiang Shui in 2009, for offering therapies involving the injection of xenogenic (animal) foetal cells into patients for anti-ageing and rejuvenation purposes (SMC 2009); and Dr Wong Yoke Meng in 2010, for offering stem cell-based 'anti-ageing' products and therapies that were not medically proven (SMC 2010).

change, however, if Singapore adopts the comparable risk-based frameworks to those in Australia and Japan.

#### United Kingdom

The UK has also adopted a risk-based approach although it differs slightly from the other jurisdictions; partly due to its current status within the European Union. In EU countries, CTPs are regulated as ‘advanced therapy medicinal products’ (ATMP) under a national framework that integrates the regulations and directives of the European Commission: this includes the Tissue Framework Directive (2004/23/EC), the ATMP Regulation (EC No 1394/2007) and the ATMP Directive (2001/83/EC). According to the ATMP Regulation, a centralised authorisation procedure applies to ATMPs that are intended to be marketed within the European Union. This procedure requires approval from the European Medicines Agency (EMA) following review of the safety and efficacy data. This data is initially reviewed by the EMA’s Committee for Advanced Therapies (CAT, 2007), which has the discretion to determine the extent and quality of the non-clinical and clinical data to be included in the marketing authorisation application as well as conduct of follow-up efficacy, pharmacovigilance and risk-management systems. The CAT then makes recommendations to the Committee for Medicinal Products for Human Use (CHMP) for final approval.

The supervisory authority for UK manufacturers or importers of centrally authorised ATMPs is the Medicines and Healthcare Products Regulatory Agency (MHRA). The MHRA defines CTPs according to the ATMP Directive, which may be classified as a gene therapy product, a somatic cell therapy product and/or an engineered tissue product. However, according to Part IV of Annex I Part 4 Paragraph 2.2 of ATMP Directive (as amended), the classification of somatic cell therapies only includes “cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered”.. Thus, ASCs that are not substantially manipulated are excluded from the ATMP Regulations,<sup>5</sup> and if used an

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<sup>5</sup> Non-substantial manipulation includes cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilisation, freezing, cryopreservation and vitrification. EC Regulation No 1394/2007 Annex I

autologous graft “within the same surgical procedure and without being subjected to any banking process”, would also be excluded from regulation under the Tissue and Cells Framework Directive (2004/23/EC Recital 8). Further exemptions are provided under the ‘Hospital Use’ scheme in Article 3(7) of the ATMP Directive, which allows for the ‘non-routine’ use of any ATMP for an individual patient.

Similar to Singapore, the Medicines Act (1968) provides additional exceptions for medicinal products that are manufactured under the supervision of a registered medical practitioner. The UK framework also provides a ‘specials’ scheme, which allows for the manufacture and importation of unlicensed medicinal products. This scheme is enabled under the Medicines Act 1968 and the Human Medicines Regulations 2012, although specific guidance is currently under review. The purpose of this scheme is to ensure that patients are able to access medicines that the MHRA has not approved for marketing. Thus, with permission of the MHRA, holders of a specials licence may supply an unapproved CTP to practitioners and pharmacies regardless of their intended use, although the procurement and processing of such products may still fall under purview of the Tissues and Cells Framework Directive and the prescribing physician must conform to accepted ethical standards which place the interests of patients before commercial imperatives (Department of Health 2010).

Outside the formal regulatory framework for CTPs, the conduct of registered practitioners in the UK is governed under the practice codes and guidelines of the British General Medical Council (GMC). Empowered under the *Medical Act 1983*, the GMC has the authority to place sanctions on practitioners and remove those from the register who’s fitness to practice is found to be impaired. In 2010, the GMC (2010) deregistered Dr Robert Trossel following an investigation by the Fitness to Practice Panel for unjustifiably administering an allogeneic cellular preparation (also found to contain bovine neural cells) to patients affected by multiple sclerosis at a clinic in Rotterdam. In its decision, the Panel stated that the interventions were based on “anecdotal and aspirational information”, and called his actions “unjustifiable” and “exploitative”, and "repeated and serious" breaches of many of the "essential tenets" of good medical practice. However, no investigations have been initiated against practitioners prescribing autologous ASCs outside of the accepted standard of care.



## Discussion

Subtle differences are evident in both the technical language and structure of the regulatory instruments that govern experimental and clinical uses of CTPs in the five jurisdictions examined. Yet, the general approach is the same: each country is attempting to regulate clinical practice so that it is evidence-based. At the same time, the regulations aim to provide sufficient clinical freedom so that innovation can be pursued by clinicians and researchers, and those interventions that lack the level of evidence necessary for licensing or subsidization may still be accessible to patients – particularly those with few other therapeutic options. While these are laudable aims, and the approach may support research, it also creates a number regulatory weaknesses or loopholes that may be exploited by commercial interests and transnational bionetworks.

### Structural Weaknesses in the Regulation of Research and Practice with CTPs

Each of the countries examined in our analysis attempt to provide a clear evidence-based pathway for CTPs that are regulated as medicinal drugs while allowing patients to access interventions with autologous ASCs considered as low-risk under the supervision of their treating physicians. This general approach is designed to provide the necessary protections for research participants while maintaining autonomy for physicians and their patients. To support this goal, all five jurisdictions have implemented, or planning to in the case of Singapore, a risk-based approach to the regulation of CTPs. This approach gives regulators some flexibility in determining the level of oversight and standards of evidence that should apply before these products are introduced into clinical settings.

While autologous ASCs sourced from an individual patient and transplanted back into them have lower risks than allogeneic products, little is known about the safety profile of these cells outside of autologous haematopoietic progenitor cell transplantation. (Herberts, Kwa, and Hermsen 2011). Nevertheless, while details about the level of manipulation and intended use of the cells vary slightly across jurisdiction, the general consensus amongst regulators is that these products do not pose serious safety threats and are thus subject to relatively permissive oversight. Where cells are highly manipulated and there is less certainty about the potential risks to patients, regulators impose greater oversight on these products before they

are introduced into the market. These CTPs are treated as biological drugs, and sponsors are required to obtain an investigational license and demonstrate evidence of safety and efficacy in registered clinical trials.

Yet, even in these instances, there is regulatory flexibility so that patients may have access to CTPs that have not been approved for marketing. All jurisdictions have special programs that allow patients in exceptional circumstances to access unapproved medicinal drugs. The programs differ in name and some of the conditions vary (for example, in the USA, the experimental agent must be the subject of an active IND, and in Japan the drug must be approved in the exporting country, whereas there are no such restrictions in Australia and the UK<sup>6</sup>); but the basic premise is the same – to ensure that patients can access drugs that might save or significantly improve their quality of life on compassionate grounds. This same premise applies in principle to autologous ASCs. In a notable case involving the UK and Spain, a high risk transplantation of a stem cell engineered trachea was done outside of a clinical trial with special permissions from the countries' regulators (Hollander 2010).

Further to these exceptional circumstances, all of the jurisdictions (excluding the USA) have laws that explicitly allow the manufacture of any medicinal drug, including biologics, under the supervision of a registered practitioner within hospitals, by licensed external vendors or imported internationally for local uses. In the USA, the manufacturing of medicinal drugs, including CTPs, is controlled where products, or the ingredients that made up those products, are shipped across interstate borders. The FDA's authority over CTPs made with ingredients sourced entirely within state borders is unclear (Koustas and Fleder 2011). The United States,

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<sup>6</sup> See the Expanded Access Program in the US at <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccessToInvestigationalDrugs/ucml76098.htm>; the Named Patients Access program in Japan; the Special Access Scheme in Australia at <http://www.tga.gov.au/hp/access-sas.htm>; the UK Specials Scheme at <http://www.mhra.gov.uk/Howweregulate/Medicines/Doesmyproductneedallicence/Medicinesthatdonotneedallicence/index.htm> and the Hospital Exemption Scheme at <http://www.mhra.gov.uk/home/groups/es-policy/documents/publication/con065623.pdf>. Singapore does not have a formal program, but the regulator has the discretion to apply similar arrangements; see [http://www.hsa.gov.sg/publish/hsaportal/en/health\\_products\\_regulation/safety\\_information/product\\_safety\\_alerts/2008/update\\_on\\_aprotinin.html](http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/product_safety_alerts/2008/update_on_aprotinin.html)

therefore, appears to be the most strictly regulated jurisdiction, despite the high number of clinics marketing ASCs without FDA approval (Turner and Knoepfler 2016).

In considering how these discrepant practices occur, it is important to realize that *medical procedures* fall within the practice of medicine, which is regulated under separate governance frameworks in all jurisdictions. Thus, the act of prescribing a registered drug or CTP for indications that have not been approved (i.e. ‘off-license or ‘off-label’) falls outside of the jurisdiction of the regulatory authorities. While practitioners, healthcare institutions or manufacturers are not permitted to market or advertise the drug or CTP for any indication that has not received pre-market approval, physicians may lawfully prescribe them within the discretion of their professional judgment. Where interventions do not fall within the accepted standard of care, then practitioners generally need adequate justification and may require special permission from an institutions’ clinical practice, clinical governance or ethics board. In contrast, if interventions are prescribed as part of a research protocol, then they will generally need to be approved by an IRB (except in the US, where the Common Rule is only mandated for research supported with federal funds). However, no permission or oversight is required from the authorities that regulate the marketing of medicinal products in any of these jurisdictions.

Other medical procedures that generally fall outside the control of the regulators typically include human organ transplants, haematopoietic stem cell transplants using autologous grafts or allogeneic tissues obtained from a relative within two degrees of separation, and human reproductive tissues that are used for *in vitro* fertilisation and other artificial reproductive technologies. They also generally exclude procedures with autologous ASCs that have not been manipulated extensively or combined with other articles and are intended for use in functionally compatible tissues. There are, however, important differences in the terms used to describe low-risk products as ‘minimally manipulated’ or ‘non-substantially manipulated’. The processes that characterize minimal or non-substantial manipulation are made explicit in Australia, the UK and Japan, while the USA uses a definition that reflects whether the basic characteristics of the cells are altered in the process. This approach provides the FDA with greater flexibility, and thus control, over CTPs that fall within its jurisdiction. However, because the definition is vague, it is more open to interpretation – and

thus challenge – by practitioners who want to offer autologous ASCs without going down the IND pathway.

## **Conclusions**

Our analysis does not explain why autologous ASCs are being prescribed outside clinical trials more often in Australia, Japan and the US, than in Singapore and the UK. While there are technical differences and ambiguities in the language and implementation of respective regulatory instruments, the general approach in each country is the same – regulating clinical practice so that it is evidence-based while still allowing enough freedom for clinicians and research to innovate with new interventions and autonomy for patients to access low risk CTPs that lack the level of evidence necessary for marketing or subsidization from public and private health insurers. Indeed, across all five jurisdictions, regulators and policymakers are generally reluctant to interfere in the clinical relationship between doctors and their patients. However, while this is historically, culturally and socio-politically acceptable, few would agree that physicians should be allowed to prescribe whatever they want without being accountable to their patients or to the social and political systems that ultimately pay for the provision of their healthcare. In these cases, the professional bodies responsible for the oversight of practitioners may be where one should start looking for effective regulation (and shortfalls) of CTPs.

The challenge in implementing these risk-based approaches is that the contexts that create scientific research and clinical medicine, and the characteristics of their practices, are frequently incompatible. The standards of evidence required to conduct clinical research differ greatly from what practitioners need to make clinical decisions. Scientific methodology is characterized by uncertainty and researchers design protocols to test hypotheses that have inherently uncertain outcomes. The uncertainty that underlies this methodology provides the ethical justification for conducting clinical research in the first place. For example, clinical equipoise, or the presence of genuine uncertainty (Freedman 1987), provides justification for randomization, and trials may be designed to terminate once an acceptable level of certainty is reached regarding the question under study. Health professionals, on the other hand, deal with evidence and uncertainty differently, and the presence of disagreement within the

professional community about treatment options must allow physicians the freedom to exercise clinical judgments (Miller and Weijer 2003).

Regulators attempting to balance the demands of research with professional and patient autonomy may thus create a potentially intractable problem. Whereas uncertainty is a key driver of the scientific endeavor – and regulations, ethical guidelines and governance processes can be designed to minimize harms that may arise from it – regulating clinical decisions in the face of uncertainty is, in many ways, much more difficult. However, regulators do have power to control unethical and illicit clinical practices; and in this respect there are a number of mechanisms that may be used to control the use of autologous ASCs outside clinical trials. All five countries have torts laws in place for medical negligence, and consumer protection laws that restrict false advertising and the provision of misleading information in medical practice. The two countries that have been most successful in limiting unethical practices with autologous ASCs – the UK and Singapore – have also activated respective medical licensing boards into action against offending practitioners. Even though the practitioners in question had been offering allogeneic products, their sanctioning, and particularly the deregistration of one, Robert Trossel by the GMC (2010), would have undoubtedly sent a stern warning to other practitioners considering offering unproven interventions with any stem cell-based product outside clinical trials.

While these measures may, at least in part, explain why the prescription of autologous ASCs outside clinical trials appears less prevalent in Singapore and the UK than elsewhere, similar actions in Australia do not appear to have had any impact on the proliferation of these practices. Therefore, additional steps may be necessary to balance the conflicting demands of research and practice, and control unethical practices with stem cells. For a start, clearer guidance is needed for clinicians who want to prescribe low-risk interventions with autologous ASCs responsibly and access higher-risk CTPs before they have been approved for marketing. Special access schemes are already in place for these purposes, however, to whom these provisions may apply and who should have access to specific cell populations needs to be clarified. Further clarification is also needed on who should pay for interventions that have not been approved for marketing or demonstrated as safe and effective as costs for such treatments are generally not reimbursable under public or private health insurance

providers. The types of skills and expertise required for the isolation and processing of cell populations, as well as the disease being targeted for treatment, are issues that should warrant further discussion.

Beyond professional guidelines, greater consistency and less ambiguity in regulatory instruments across jurisdictions is necessary because even though they provide regulators with a degree of discretion, the vagaries and inconsistencies are also open to willful misinterpretation and exploitation by unscrupulous operators. Relevant authorities should also activate existing laws and regulations that protect consumers from false advertising and the provision of misleading information in medical practice. It is crucial that the wholesale marketing of such interventions without sufficient evidence should be prosecuted under the relevant consumer protection laws and offending practitioners sanctioned by the responsible medical authority. For clinical practice cannot be regulated in the same way as research if the goal is to ensure that patients have access to novel interventions where efficacy is uncertain and that innovation can occur within clinical contexts.

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