Regulation of autologous stem cell therapies: Discussion paper for consultation

About the authors

Chih Wei Teng graduated from the National University of Singapore with a business degree focusing on operations management and e-business. Subsequently worked for IBM where he handled portfolios of Energy and Utilities, Manufacturing as well as Healthcare and Life Sciences industries. Chih Wei has completed his MBA from Monash University and is currently pursuing his PhD studies on collaborative innovation in the translation of regenerative medicine. Research interests include innovation management and commercialization.

Peter O'Neill is a senior lecturer at Monash University where he delivers units in Strategic Management, Process Management and Supply Chains. Dr O'Neill holds degrees in engineering, business administration and management. He has practiced widely in the manufacturing; defence, construction and health supply chain industries. Dr O'Neill's research interests include: Business Strategy - particularly issues surrounding planning for growth, innovation and internationalisation; Supply Chain Strategy - particularly issues surrounding performance evaluation, process improvement, quality & safety in the health sector; Information Systems – particularly the design and deployment of ERP for decision making, process improvement, and behaviour change.

This submission reflects the authors' personal views.

Background

This submission is in response to the call for public consultation (the Call) with regards to the regulation of autologous therapies. The call for public consultation is timely given trends towards stem cell tourism as well as increasing number of stem cell therapies offered by physicians in private practice. While the Call gravitates towards adipose derived autologous mesenchymal stem cells (MSC) treatments that currently fall under the Therapeutic Goods (Excluded Goods) Order No. 1 of 2011 (the Order), the conversation should encompass all autologous therapies associated with the Order.

The question pertaining to evidence of risk is challenging for an observer with a non-bioscience background. Popular media such as television documentaries and often times at scientific conferences, depict both clinical success (cartilage regeneration from Korea and reported cases of muscular dystrophy recovery in India) as well as failures. Most certainly there are local Australian examples, which I will believe other contributing authors will catalogue. While there are many voices attributing both success and failures to stem cell intervention but there are also opposing voices within the same conversation. We have read or was impressed upon that positive therapeutic outcomes may be attributed to factors outside of the autologous treatment e.g. placebo

or delayed effects from prior treatments. On adverse outcomes, failures may be attributed to deteriorating health conditions given advanced onset of diseases or adverse effects resulting from prior treatments. Moreover, a lack of understanding in the mechanism of action for some interventions has not done either any justice.

This response seeks to offer an alternative opinion from a social and business studies perspective. In relation to the question posed about risk to the ***public*** health, this response believes that the risk is low. Autologous therapies affect only the individual and at present are administered by the attending physician. Moreover, autologous therapies that fall under the Order have not completed formal clinical trials. Therefore have no justifications to be listed under the Australian Register of Therapeutic Goods (ARTG), much less under the Pharmaceutical Benefits Scheme. The result is a somewhat prohibitive price point. Often seen are therapies costing above ten thousand Australian dollars. Unless proven successful, it is difficult to imagine that such therapies will be utilized for the least severe of medical conditions or demanded by large number of patients. Lastly, autologous stem cell therapies are not as prevalent in the healthcare industry as say traditional Chinese medicines. Labelled as complimentary medicines, Traditional Chinese medicines are often not as regulated as their Western counterparts despite health concerns (Li et al., 2003). Specific to the Call, adipose derived MSCs are neither sold as over the counter medicine, mass-produced nor labelled as complimentary medicine. Whatever risk is left between the physician and patient is mitigated through the 1) appropriate conduct/behaviour of the attending physician, 2) adequate patient education, 3) availability of appropriate access schemes and 4) adoption of manufacturing guidelines.

The above four points should be viewed as complimentary when addressing the issues in the following discussion section on options. For example, without appropriate access schemes to autologous therapies, heavy regulation of all autologous therapies by private physicians in a time that simply reflects lack of clinical evidence, is an indirect way of shutting the door on innovation, the progress of healthcare and leaving patients vulnerable. Though some may view the hopes of patients being cured by unproven therapies as false or even foolish, their motivation is very much real and not easily dissuaded. Patients who are sufficiently motivated can and will continue to travel in pursuit of a ‘cure’ even if they need to sell their assets or take to

crowdfunding as a means of financial enablement. Getting oneself enrolled in clinical trials or to access experimental drugs, especially overseas trials require a fair amount of luck as featured in recent news on Keytruda (Barham, 2015; Hyland, 2015) while others are not so fortunate (Medew, 2014). Let us not discount the obstacles in conducting clinical trials, which Alliance for Regenerative Medicine (2014) reports Australia as trailing behind the US and Europe in the number of stem cell clinical trials. One such obstacle is securing of funds required to pursue research up to the tipping point necessary to justify human trials. One challenge raised by a physician with regards to securing grants is that medical conditions, such as lifestyle or work related injuries are not as 'sexy' as other chronic or debilitating diseases. Non-headline grabbing breakthroughs such as curing Alzheimer's disease, are not as favoured but nevertheless have huge impact on the quality of life of patients as well as long term economic productivity.

Regulation should be balanced such that illegal and unethical behaviours are discouraged while promoting economic and social progress. This idea is not new but is one that this response strives to communicate.

Discussion of options

If the market is to be segmented in a simplistic fashion, there are physicians who offer unproven autologous stem cell therapies either to differentiate their practice in order to unlock potential profits whilst the other group would represent physicians who are experimenting with new techniques to improve the delivery of healthcare to their patients. Whilst the outcome may seem the same, the motivations are different. The prior group may be afraid of exposure or regulation because it will potentially rein in their new found income stream while the later accepts the risk that the science is not perfect and outcomes whether positive or adverse are part of scientific discovery. However, to simply categorize all autologous therapies offered by private physicians as being vindictive would be a gross overstatement and unfair to the practice of medicine.

This brings up the unique circumstances that we're faced with. 1) Positive reports of success in scientific/medical journals from which physicians get their information. Often we hear about journals being biased towards publishing positive results as

opposed to failures and the failure rate from replication studies are fearfully high (Iorns, 2012; Moonesinghe et al., 2007). From a layperson's point of view, this is justification enough to favour the need for ensure patient safety, conduct clinical trials and establishment of a registry. 2) Patients are becoming increasingly information savvy. Acknowledging that patients may not be easily swayed, harbouring proactive and outspoken view of 'right to try' and demand access to new treatments. There ought to be an increased concerted effort towards patient education. 3) Lack of a reporting framework or preventative checks by pharmacists warrant the establishment of adverse event monitoring systems as well as other means of ensuring patient safety. An ideal option to address issues raised in the call for public consultation should be able to address the above circumstances in a way that also promotes innovation and entrepreneurship.

Option 1: Continue to exclude autologous cells from regulation under the Act

Remaining on the status quo does not benefit public health. Despite having more liberal access to autologous therapies, patient safety is compromised due to, e.g. lack of good manufacturing practices. Leaving aside evidence of efficacy, the literature points to how sensitive cells are to manufacturing (Shaw, 2010; Shirwaiker et al., 2013). It was also highlighted within the Call that there is currently no "*manufacturing principle that specifically governs and manufacture of autologous cells*" (page 21). Therefore even though the practice of medicine does not fall under the Therapeutic Goods Administration (TGA), we ought to consider critical aspects of manufacture. Much is not known about the critical quality attributes and sensitivity thresholds required for technology transfer (Alliance for Regenerative Medicine, 2014; Shirwaiker et al., 2013). At the very least there must be some form of assurance that manufacturing or culturing of cells take place in an accredited cleanroom as opposed to a laboratory within a private clinic unless there are acceptable justifications for the later. Furthermore the lack adverse reporting or a registry is worrisome as both are instrumental tools for patient safety, regulation and furthering knowledge.

It must be mentioned that there are commendable efforts by a handful of proactive physicians in drafting a Code of Practice to guide medical practitioners in providing autologous therapies as medical interventions. This represents a critical step towards

self-regulation but any framework or tools for oversight should be discussed and agreed upon by members of the medical community. When accepted, how this Code of Practice can be supplemented in conjunction with the Act is something that needs to be discussed.

There are no advantages to Option 1 except for the clause that allows advertising of therapies directly to the patients. However, this purely from the point of view of discouraging patients from travel overseas for illegitimate autologous stem cell therapy treatments. The ACCC by itself may not be in the best position to regulate such advertising and will require assistance from the scientific community as well as the TGA. Some patients may not accept that palliative care is only option left for their condition. Having lost faith in their attending physicians and patients will turn to the Internet in search of alternative therapies, which unfortunately are populated by advertisements featuring unproven therapies by international clinics that fall outside of Australia's regulation. Allowing direct advertising to patients is most probably not the best solution in convincing patients to embark on stem cell tourism. But we are faced with the dilemma of having Australian patients treated with unproven therapies within our boundaries under proper clinical oversight versus leaving patients to their own devices with stem cell tourism. Perhaps this consideration ought to have a role in the public consultation.

Option 2: Exclude autologous cells from regulation under defined circumstances

Without the burden of overheads associated with regulation, Option 2 will no doubt encourage physicians to offer low risk autologous to their patients. This will help reduce the financial and administrative burden on the physicians, which in turn simulates innovation as well as entrepreneurship. In addition, when faced with the prospect of having autologous therapies regulated within the Act (i.e. Class 3 or 4), physicians may be swayed to conduct clinical trials, which will benefit patient safety and contribute to knowledge. Conducting clinical trials will also help Australia catch up with the rest of the world in the translation of regenerative medicine. However, when considering commercialization, if the higher risk therapies are proven to be successful, would they be regulated as Class 3 biologics or Class 4 biologics, much like in Option 5?

Medical practice is fundamentally different from pharmaceuticals or biotechnology firms in terms of their organizational structure, human resource and financial capabilities. This raises the question whether medical practices are able to cope with the regulatory and administrative burden imposed on Class 3 and Class 4 biologicals. While the Act remains for autologous therapies outside of the Order, unlike biotechnology firms, the sophistication of Class 3 and 4 regulatory requirements may be overwhelming for private medical practices. In the event of successfully completing the clinical trials, physicians may face the stark reality they must sell their rights to a biotechnology firm or pharmaceutical. One might argue that market potential may be enticing for treating chronic diseases but as highlighted earlier in the paper, some lifestyle related diseases or injuries are often neglected unless there are special incentives to do so. Physician may be left with no potential buyers of their therapies and unable to recover their investments. Patients will again be left to their own devices and at the mercy of international biotechnology firms as to whether or not it is profitable to introduce their therapies in Australia. From a commercial point of view, without adequate development of business models for higher risk autologous therapies in private practice, the adoption of Option 5-like regulation would serve to curb innovation and entrepreneurism.

On the point of restricting advertising, the lack of efficacy in the current context prevents physicians from reaching out to develop a patient base. Unlike pharmaceuticals and biotechnology companies, physicians rarely if never, employ a team of dedicated sales or marketing personnel to engage other medical practitioners. Given their commitment to patient consultations, most of their marketing engagement will be through formal or informal networking events, perhaps also on personal time. This results in delays to achieving breakeven or unprofitable business models. As such, a proactive investigation into viable business models for medical practice ought to be initiated.

Lastly, the issues about how sensitive the cells or manufacturing process can affect clinical quality, safety and consistency remain a cause for concern as mentioned in Option 1.

Option 3: Regulate autologous stem cells under Act, but exempt from registration and manufacturing requirements

With Option 3, we are beginning to see increasing forms of patient safety now that therapies can be regulated and the TGA has the authority to recall products if the therapies do not comply with applicable standards or presented with unacceptable levels of quality, safety or efficacy. In addition, Option 3 is somewhat favourable to physicians in terms of the cost burden since registration and manufacturing licensing as exempt.

Reservations against Option 3 are made for mandatory adverse reporting versus 'could be required to report certain adverse events to the TGA' within the Call (page 23). Given the lack of understanding as well as the risk posed by autologous therapies, what are the arguments against compulsory adverse events reporting especially since the therapies are regulated under the TGA? As with Option 2. the concern still remains for Class 3 and Class 4 biologicals in terms of a viable business model for medical practice. Finally, the issues about how sensitive the cells or manufacturing process can affect clinical quality, safety and consistency remain a cause for concern as mentioned in Option 1.

Option 4 and 5: Regulate under the Act as Class 1 biologicals or regulate under the Act as Class 2, 3 or 4 biologicals

Under Option 4 and Option 5, the minimal of patient safety is achieved through formal registration, compliance to product standards as well as the need to report adverse events. Despite no formal evaluation by the TGA, Option 4 provides the TGA with authority (recall powers) to intervene whenever adverse events occur. Formal registration is also a good preventative measure in preventing physicians from further providing harmful autologous therapies to patients. During the last few months, concerns were raised about the possibility of physicians who are liable for malpractice in one state, simply relocating their practice to other states. Formal registration of therapies at the federal level may be a step in the right direction in preventing the malpractice of autologous therapies. In conjunction with adverse reporting, both Option 4 and Option 5 further contributes to patient safety through proper oversight. Adverse events will require investigations to be carried out to determine causes of adverse reactions, which will in turn contribute to knowledge and uncovering of

contra-indications. Physicians will become more informed when practicing medicine so as to match the appropriate stem cell therapy to the needs of their patients, given the absence of pharmacists. Compliance to good manufacturing practices as well as licensing manufacturing processes ensures appropriate levels of clinical quality, safety and consistency.

Similar to Option 3, only including homologous use and minimally manipulated autologous therapies in Option 4 is a logical because it allows physicians to continue their innovation and treat patients with some level of safety. Higher risk therapies ought to be encouraged under clinical trials given more control is required. Perhaps in that sense, the clinical trial process for physicians ought to be reviewed to see how it can be made simpler and less costly for physicians to undertake.

Reflecting in terms of commercialization and entrepreneurship for physicians in small and medium practices, Option 4 may offer an ideal balance between patient safety and promoting entrepreneurism as the regulatory burden is not as severe on the physicians' practice. This is again assuming that a small to medium practice does not have the necessary human and financial resources to comply with the regulatory requirements of higher risk classes. Moreover, proof of efficacy for Class 1 biologicals is not required, which would allow patient access to low risk therapies through their physicians. Not needing to license the manufacturing process may also spur further process innovations that allow physicians to experiment with and manufacture/produce cells in a decentralized fashion. However, all medical devices used as well as manufacturing facilities should be regulated and comply with Good Manufacturing Practices.

As raised in Option 2 and onwards, the sophistication of Option 5 may be overwhelming for physicians and will likely face resource constraint as well as daunting commercialization prospects. Option 5 also begs the question if the TGA has the necessary resources to regulate large numbers of medical practices, which are outside the scope of the TGA. As rightfully pointed out in the Call, there ought to be and are a number of regulatory organizations, whether formal or informal (AHPRA, Medical Board of Australia, tertiary medical boards etc.), who are more suitable in regulating medical practice so as to capture autologous therapies that fall within the

Order. However, upon hearing feedback from the industry, this is either not happening or progressing at a slow and reactive pace.

Position

At this juncture, the **critical** information that is **missing** is the proposed self-regulatory framework that medical practices can adopt as well as the indication of support by their members. In light of that, a favourable compromised position is that of Option 4 until a more suitable regulatory framework appears. It addresses patient safety, gives the TGA authority to intervene when safety is compromised but at the same time allows physicians offer low risk autologous therapies to patients since efficacy is not a requirement. This encourages innovation and entrepreneurship. If anonymized clinical data is made available, it will also contribute to our understanding of this emerging field of medicine.

Should a suitable self-regulatory framework emerge, there will be grounds for justifying a position along the lines of Option 2 or Option 3. Even so, sensitivities around cell manufacturing remain one of the concerns.

Summary

Accessing and offering innovative therapies is an innovative process, which progresses public healthcare. Patients get access to therapies, which may provide better therapeutic outcomes, which in turn have positive knock-on effects on economic productivity. Clinicians need to be trained (often internationally) in order to understand and administer the therapies. This improves knowledge and skill, foster collaboration and results in innovation spill-overs, which in turn perpetuates the innovation cycle. Adapting manufacturing, storage and distribution processes to local conditions may require new operational methodologies such as decentralized manufacturing with small footprints, which may spur yet another round of inventions. Such activities have positive contributions to the state of public health as well as the economy (Pharmaceuticals Industry Strategy Group, 2008).

Earlier research by Gottweis (2005) into the regulation of genomics highlighted that the political arena is populated by a multitude of autonomous actors who create patterns of structured cooperation despite absence of a central organizing authority.

Local and national patterns of governance blend into transnational and global forms of policy making. Even though traditional government contribute and continue to play a huge part in the support and regulation of research and development, increasingly bottom-up approach of governance are beginning to shape the policy making. This can be in the form of public opinion, contributions from for profit and non-for-profit organizations etc. Alongside the proactive efforts of physicians to develop a Code of Practice, this is integrative approach is likely to hold true for the regenerative medicine industry.

References

- Alliance for Regenerative Medicine, 2014. Regenerative Medicine Annual Industry Report 2014. Alliance for Regenerative Medicine, Washington D.C.
- Barham, A., 2015. Mum wins cancer battle thanks to 'wonder drug', 7 News.
- Gottweis, H., 2005. Governing genomics in the 21st century: between risk and uncertainty. New Genetics and Society 24, 175-194.
- Hyland, A., 2015. 'I don't want to die, I still have things to do': Keytruda wins Ron Walker's war on cancer. The Sydney Morning Herald.
- Iorns, E., 2012. Is medical science built on shaky foundations?, Opinion. New Scientist.
- Li, G.Q., Duke, C.C., Roufogalis, B.D., , 2003. The quality and safety of traditional Chinese medicines. Aust Prescr 26.
- Medew, J., 2014. Cost of life under microscope as new cancer drug on wait list. The Age National.
- Moonesinghe, R., Khoury, M.J., Cecile, A., Janssens, J.W., 2007. Most Published Research Findings Are False - But a little Replication Goes a Long Way. PLoS Med 4.
- Pharmaceuticals Industry Strategy Group, 2008. Final Report. Pharmaceuticals Industry Strategy Group, Commonwealth of Australia.
- Shaw, R., 2010. Industrializing Stem Cell Production, BioProcess International Informa PLC, pp. 10-15.
- Shirwaiker, R.A., Tan, Z.G., Cohen, P.H., 2013. Regenerative medicine manufacturing. Industrial Engineer 45, 32-37.