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To:
Biological Science Section
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

Re: Consultation: Regulation of autologous cell and tissue products and proposed consequential changes to the classification of biologicals

MS Research Australia would like to thank the TGA for the opportunity to provide further feedback in this important process of updating the regulations surrounding the therapeutic use of autologous cell and tissue products in Australia.

In our submission to the consultation in March 2015 we set out the relevance of this topic for people with MS and our concerns regarding the current provision of unproven 'stem cell' therapies for people with MS.

As indicated in our previous submission to the initial consultation in March 2015, MS Research Australia supports the distinction made between the immune-suppressive chemotherapy treatment, Autologous Haematopoietic Stem Cell Transplant (AHSCT), and the other forms of autologous cell and tissue therapies that are the subject of the current regulatory review. We continue to endorse the view that AHSCT for the treatment of certain autoimmune disorders should also be included along with cancer in the list of disorders for which AHSCT can be provided by experienced hospital centres subject to NPAC/NATA accreditation. This would facilitate the continued assessment of AHSCT as a potential treatment for severe autoimmune disorders.

Our comments in this submission relate primarily to the provision of autologous 'stem cell' treatments for MS, most commonly, but not limited to, extraction of fat (adipose) tissue from the patient followed by preparation of a cell extract (stromal vascular fraction) which is then reinfused into the patient.

This situation continues to be deeply concerning to MS Research Australia. Firstly, because there is no standardised or licensed method for the preparation of the adipose tissue, the cell extract that is reinfused is likely to contain a broad mixture of cells, rather than a purified preparation of well-characterised stem cells. It also exposes many people with MS to the potential risks of a medical intervention with no evidence for any benefits which may outweigh or justify those risks.

MS Research Australia acknowledges that the rate of progress necessitated by a rigorous clinical trials process to define the risks and benefits of autologous cell and tissue treatments may leave many individuals with MS and other chronic progressive disorders frustrated. We also understand and respect that all individuals, particularly those faced with a chronic, disabling disease, may have a different perception of, and attitude towards, risk. However it is essential that new treatments are introduced under a process that allows doctors and patients to make a fully informed assessment of the risks relative to the potential benefits.

This process will also ensure that advancements in the provision of new treatments to patients occurs in a safe manner that will also ultimately ensure equitable and affordable access to treatments by all individuals who may benefit from them.

Consultation paper questions

Part B - The Problem

Does the description of the problems adequately reflect the actual or potential problems associated with the existing regulation of autologous cells and tissues?

The list of problems outlined in the consultation paper in 'Part B – The Problem' is very comprehensive and has captured all of the considerable concerns and risks relating to the unregulated uses of autologous cell and tissue therapies.

We would however highlight that focussing only on the problem of direct to consumer advertising in relation to how autologous cell and tissue therapies are marketed to consumers may miss a number of significant methods by which potential consumers are reached – we are aware that word-of-mouth 'advertising' and 'educational' methods are also utilised in promoting autologous cell therapies to potential consumers. Misleading descriptions of the provision of treatments purportedly as part of clinical trials (in the absence of HREC approved, registered clinical trials) have also been used.

The Consultation Paper also states that there is difficulty in quantifying the problem and that this absence of reliable evidence of a problem would support the proposition that the status quo be maintained. We would argue that this lack of data - on who the providers are, what treatments they are providing, efficacy and safety data, and adverse event reporting - in fact supports the opposite proposition, that greater regulation and therefore greater requirements for monitoring and adverse event reporting will lead to much greater assurances for consumers and their healthcare providers regarding the quality of autologous cell and tissue therapy providers, and much higher standards of information regarding the potential risks and benefits of the therapies.

Are you able to provide specific evidence in the Australian context, in relation to the practices outlined [in the consultation paper], that demonstrates risk to patient health?

Every medical intervention comes with a range of risks. However, in the case of evidence-based medicine, these known and documented risks can be assessed and evaluated against the known and documented potential for benefit. This means that patients and their healthcare providers can make fully informed decisions about treatment options. This is not the case for many of the autologous cell 'therapies' currently being offered under the existing exemption regulations.

The recent NSW Coroners Court report (July 2016) mentioned in the Consultation Paper, provides a clear example in which a patient has suffered a fatal surgical complication whilst

undergoing a procedure for which there was no scientific evidence for its safety or efficacy for the disease in question (dementia).

We do have anecdotal evidence of patients foregoing proven treatments recommended by their healthcare providers in favour of pursuing the promise of stem cells.

We cannot currently provide specific examples that demonstrate risks to patients – and this is where one of the key problems lies. The absence of any requirement for follow-up monitoring and adverse event reporting means that any adverse events that may be occurring are not being recorded or reported. As the Consultation Paper points out, 'After biologicals have been included on the ARTG', following appropriate provision and assessment by the TGA of a portfolio of documentation relating to safety and efficacy, 'ongoing (post-market) controls include manufacturing surveillance, targeted review and adverse events reporting.'

The lack of peer-reviewed studies also means that there is no evidence that these treatments do not in fact worsen the condition being treated.

Part C & D – Objectives and Options

Redefining the scope of the regulation to encompass autologous 'cells and tissues' rather than only 'autologous stem cells' – Do you support the proposed approach?
Yes, we agree that using the term autologous cells and tissues is much more appropriate. This is particularly due to the problem identified in the Consultation paper, that preparations currently in use are very poorly defined in terms of their cellular composition (e.g. stromal vascular fraction) – continuing to use the term 'autologous stem cells' would potentially allow this type of product to fall outside of the regulations, and this would not solve the current problem.

Do you agree that the proposed options should also apply to registered dental practitioners supervising the autologous use of human cell and tissue products as part of a single course of treatment?
Yes, the proposed options should also apply to registered dental practitioners. However, if this is in relation to Options 1 and 2 in which the status quo is essentially maintained and autologous cells and tissues continue to be exempted from the TGA Act, then the answer would be 'no' as this would only increase the problem rather than solve it.

Please provide your views regarding the proposal to retain the concept of a 'single course of treatment'. Do you consider that storage of autologous cells and tissues as part of a single course of treatment carry risks of such a nature that should require TGA regulatory oversight?
Storage of cells, if clearly defined (e.g. as freezing) is likely to carry minimal risks. However, some freezing procedures, depending on the carrier fluids involved may carry additional risks. 'Storing' live cells in culture, for example, would also carry much more considerable

risks as cell properties are known to be affected by longer term culture and passaging. Simply exempting autologous human cells used in 'a single course of treatment' may therefore not be satisfactory.

However, limiting the exemption to 'a single procedure' also does not satisfactorily solve the problem either. For example, stromal vascular fraction is generally used in a 'single procedure' (extracted, processed and returned without any storage) and therefore would continue to be exempted, inappropriately in our view, from regulation under this definition.

We do acknowledge however that bringing all forms of autologous cells and tissues 'used in a single procedure' or 'in a single course of treatment' under the regulatory framework, could potentially pose problems for some medical practitioners using certain types of tissues, for example, the current surgical practices utilising bone fragments, skin flaps and blood vessels.

Do you agree that it is unnecessary to distinguish homologous and non-homologous use in the context of the exclusion?
No, we do not agree. Introducing a distinction between homologous and non-homologous use would greatly assist in defining the types of procedures that could continue to be exempted, whilst bringing more concerning practices under the regulation of the TGA Act.

For example, including a clear and strict definition of minimal manipulation and homologous use for products that could continue to be exempted, may help to overcome the issue discussed above for products such as bone fragments, skin flaps and blood vessels that are removed from one area of the body and returned to another homologous area of the body, e.g. bone to bone, skin to skin, blood vessel to blood vessel.

It would also help to remove ambiguity and ensure appropriate regulation under the TGA Act for products such as adipose stromal vascular fraction, which is frequently not used in a homologous manner – e.g. adipose tissue is removed, processed and reinfused into the blood stream with the intention of targeting a diverse array of conditions affecting a range of different target organs or systems including the central nervous system or the immune system.

Are any other cell and tissue products currently in use that:
- **a. are currently covered by the TG Order; and**
- **b. form part of established medical practice; and**
- **c. would be more than minimally manipulated (and therefore would be subject to regulation under Options 3 or 4)?**

This is not our area of expertise and others who currently use such tissues would be more qualified to comment. However, it seems likely that by including a distinction between homologous and non-homologous use, procedures such as those noted in the Consultation Paper, e.g. cultured keratinocytes for burns, and infusion of pancreatic islets following removal of the pancreas could continue to be exempted, despite being more than 'minimally manipulated.'

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The Options

Option 1

Do you support maintaining the current system?

No – as discussed earlier, the Consultation Paper (pages 8-10) has very clearly set out the problems relating to the current system. Option 1 will not resolve any of these problems.

Option 2

Given that advertising a service will still be possible what is your opinion on advertising of autologous cell and tissue products and the impact (including financial impact) of this option on those practitioners currently advertising these products to consumers?

Does this option address the issues presented in this paper?

Continuing to exempt products if they are not advertised may slightly reduce the problem in that the ability for practitioners to market unproven products and therapies directly to patients will be somewhat curtailed. However, there are many ways around this restriction, as mentioned earlier, that include word-of-mouth and 'educational' methods. Practitioners will also still be allowed to advertise their 'services', which means that carefully worded descriptions of services could still promote the type of service on offer without mention of a specific product.

Despite these indirect methods of promotion, there may still be a financial impact for providers of not being able to directly advertise autologous cell and tissue products. However, once the necessary evidence for safety and efficacy of a procedure has been established through the usual clinical trials framework and ARTG listing, providers would be able to promote the product through the usual channels that include promoting the product to other healthcare providers which will allow referral of patients. It may provide potential for re-imbursement of services via PBS/MBS and private health funds which would be likely to restore the financial viability of the service, as well as making the availability of therapies more equitable for patients.

Option 2 does not address the issues presented by the Consultation Paper as existing exclusions for autologous cell and tissue products would continue with none of the safeguards for patients regarding evidence for safety, efficacy and good manufacturing standards.

Option 3

What is the impact (including financial impact) of this option on practitioners currently manufacturing and using these cells and tissues?

This option may have little financial impact on practitioners as there is no requirement for good manufacturing compliance and no evidence for safety or efficacy required. There is likely to be some administrative costs for adverse event reporting. More detailed consideration of the definition and extent of adverse event reporting would certainly be required for option 3 – in many cases the period of treatment by the practitioner providing the autologous cell or tissue therapy is very brief and patients may not be required to return for longer-term monitoring. In this case, only immediate procedure related acute adverse events

would be captured and longer-term adverse events relating to the cells and tissues effects in the body may still go un-reported.

The financial implications of this option for patients will be the continuation of a situation in which considerable financial outlay is made for treatments with no assurances as to their quality, safety or efficacy.

To what extent does the requirement to comply with the TG standards increase regulation or whether the manufacture and use currently comply?
Would a requirement to comply with these standards 'add value' in terms of addressing the risks and issues set out in Chapter 2, Part C? Does this option address the issues? Please provide the reasons why it does or does not.

A requirement to comply with the TG standards TGO88 and TGO87 would be a step in the right direction in ensuring that the products meet minimum standards to minimise infectious disease transmission. We cannot comment on whether the manufacture and use currently comply.

Notification of procedures and autologous cell and tissue uses to the TGA and notification of adverse events would certainly add value in terms of enabling the TGA to gather data on the practitioners, practices and cell and tissue types in use. This would help to inform future reviews of the regulations and their scope as well as gathering some data on adverse events.

The requirement to have in place a system for reporting of adverse events would be very welcome, but may not go far enough. As mentioned above, in many cases the period of treatment by the practitioner providing the autologous cell or tissue therapy may be very brief and patients may not be required to return for longer-term follow-up care and monitoring. In this case, only immediate (acute) procedure related adverse events would be captured and longer-term adverse events relating to the cells and tissues effects in the body may still go unreported. Other practitioners treating the patients in the long-term may be unaware that the patient has undergone such a procedure and therefore has potentially no knowledge that an adverse event or health condition may be related to the procedure and needs to be reported. As the consultation paper also states, there would be challenges around defining and identifying adverse and 'unexpected' events as there would be no requirement for an investigators brochure or product information. Properly conducted clinical trials with adequate follow-up periods, and requirement, as currently exists for biologicals, for 'ongoing (post-market) controls include manufacturing surveillance, targeted review and adverse events reporting' are the most appropriate methods to ensure both the short and long-term adverse events are identified.

Under option 3, as stated in the consultation paper, the products would also not be subject to a requirement for Good Manufacturing Practice or inclusion on the ARTG.

As noted in the consultation paper, the limited power of the TGA, under option 3, to recall or stop supply of a product even when an adverse event is identified, due to a lack of ARTG listing, clinical trial or SAS frameworks, means that we would be no further along in terms of regulating the provision of autologous cell and tissue therapies and protecting the health and safety of patients.

For these reasons option 3 would not meet the majority of the objectives of any government action as stated in Chapter 2, Part C of the consultation paper. The public health and safety

risks would not be minimised; consumer confidence in the regulation of therapeutic goods (quality, safety, efficacy) would not be maintained or increased; Australia would not be aligned with international best practice.

Option 4

What is the impact (including financial impact) of this option, particularly on practitioners currently using these products?
Do you consider that this option addresses the issues? Please provide the reasons why it does or does not.

There is likely to be a negative financial impact of Option 4 on practitioners currently using these products until such a time as clinical trials have been conducted to provide evidence for the products' safety and efficacy and ARTG listing has been approved.

This option would have a positive financial impact for patients as these therapies would likely only be available as part of carefully and safely conducted clinical trials at no cost to the patient. Once autologous cell and tissue therapies have proven efficacy and safety, it is also likely that these therapies would become available in an equitable manner via public hospitals and private providers with reimbursement from PBS, MBS and/or private health funds.

Option 4 largely addresses the issues set out in the Consultation Paper, however, it could be greatly strengthened by the inclusion of the term 'homologous use' for both cells and tissues for autologous use that are minimally manipulated and those that are not more than minimally manipulated. This may, in particular, reduce the impact that Option 4 might have on autologous cell and tissue therapies that are part of established medical practice, such as those identified in the consultation paper. It will also help to reduce any ambiguity around tissues that may fall into a grey area regarding the proposed definition of 'minimal manipulation.' Cells and tissues that might potentially fall into the category of 'minimally manipulated' could still be regulated under the Act if they are not for homologous use.

Changes to the definition of minimal manipulation

Please provide your views on the proposed definition of minimal manipulation
The definition is appropriate. It is also appropriate that a final view on whether or not the defined actions amount to more than minimal manipulation depends on the intended use. The proposal for the TGA to publish guidance materials about how to apply the proposed new definition is also welcome. We would suggest that extensive examples of what the definition does and does not include will be required to remove as much ambiguity as possible and to reduce the risk that established medical procedures are not unduly limited by the new definitions and regulations.

Do you support the proposed changes to the classification criteria as set out in the proposed new definitions?
Yes, we support the proposed changes to the classification criteria of biologicals that rely on the new definition of minimal manipulation and incorporate the concepts of homologous and non-homologous use.

The implications of this for the MS community would be greater protection of the health and safety of people with MS. These changes would encourage the development of innovative new cell and tissue therapies within the framework of clinical trials where risks and adverse events are encountered and addressed within a closely monitored environment and the potential benefits of the therapy are established against appropriate controls.

Do you consider it is appropriate for the requirements for CTX approval apply to the new redefined class 3 generally or just to a subset of Class 3 which represent the higher risk biologicals? Should a distinction be maintained for higher risk biologicals in relation to clinical trials and what criteria should this consider?
Requirements for CTX approval should apply to Class 3 biologicals generally. It would be extremely difficult to define criteria for 'higher risk' biologicals, as the risks of any new therapy essentially remain unknown until they have been tried and tested – that is, we may not know what constitutes a 'higher risk' biological until it has been assessed in a carefully monitored clinical trial environment.

Thank you once again for the opportunity to comment on this important discussion paper.

Dr Lisa Melton, Head of Research, MS Research Australia on behalf of MS Research Australia