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Submitted online: https://www.tga.gov.au/consultation/consultation-draft-standards-faecal-microbiota-transplant-fmt-products

Draft standards consultation paper for faecal microbiota transplant (FMT) products (Version 1.0 Nov 2019) – Response from the Gastroenterological Society of Australia (GESA)

Thank you for the opportunity to respond to the TGA "Draft standards for faecal microbiota transplant (FMT) products" (Version 1.0, November 2019). The GESA membership acknowledges the importance of developing an evidence-based regulatory framework for this emerging therapeutic field. We hope the TGA will take on board our feedback to develop balanced standards that guarantee patient safety while also maintaining sensible regulations that are not so onerous and burdensome on FMT manufacturers and providers that access to this potentially lifesaving therapy and future research/innovation is compromised.

We agree with the TGA classification of FMT as a biological. The predominant concern amongst GESA members active in the FMT field is the requirement that all FMT donor screening tests be class IV IVDs. Biopharmaceutical entities and industry with an interest in microbial therapeutics have also communicated similar concerns to GESA membership. The issues, some of which are readily acknowledged in the draft standards, include the following:

- No ARTG-registered Class IV IVDs are currently available for donor stool screening or blood testing for Hepatitis A or Strongyloides.
- We do not believe such tests would become available within the 1-year transition period (i.e. by Jan 2021). Our understanding is that this will likely take several years.
- The cost associated with developing and validating such tests would be prohibitively expensive for all public hospital-based FMT centres, and potentially eliminate in-house hospital-based FMT services. Many laboratories (hospital-based and external) have communicated it is not financially viable for them to justify the cost of validating such tests based on the relatively small number of donor screening tests they expect will be performed.

- Given the costs associated with validating each test utilised for donor stool screening, there would be a significant financial motivation amongst FMT manufacturers to implement bare minimum product testing and resist additional testing even as the field evolves and new infectious risks become apparent. Thus, while the intent may be to improve safety, the opposite effect may result.
- There is a concern that if over-regulation severely limits FMT availability/affordability, patients will resort to unsafe and unregulated do-it-yourself home-based FMT outside a supervised medical setting with increased risk of adverse events
- To date, FMT has been demonstrated to be an extremely safe therapy when administered by Gastroenterologists in the treatment of refractory or recurrent *Clostridioides difficile* infection and in registered Clinical trials. It is likely to be impossible to reduce risks of any therapy to zero.

In section 9 (subsection 5 – page 42), the draft statements state:

> "As a potential interim solution, while validation studies are being performed, it is proposed that existing exemption provisions could be utilised where testing laboratories can seek access to use the unapproved IVD. If the testing is being performed as part of a clinical trial, then laboratories would need to ensure that the unapproved Class 4 IVDs (or Class 4 in-house IVDs) are covered under the clinical trial exemption. Alternatively, if testing was not being performed for the purposes of a clinical trial, laboratories could seek an exemption under TGA's Authorised Prescriber scheme for the unapproved Class 4 IVD (or Class 4 in-house IVDs) donor screening tests being used. Testing laboratories would need to request such exemptions on an individual basis. However, it is not clear at this time the level of evidence and commitments required to utilise this pathway, but is expected that utilising this approach will include a more stringent follow-up of donors and recipients and therefore further discussions will be initiated with the sector soon, to work towards short-term and long-term solutions."

At a minimum, much greater clarity is required from the TGA regarding this including official formalisation that this is a TGA-sanctioned option until validated tests are available/accessible so FMT manufacturers, pathology centres and FMT providers are protected.

Clarification was also sought by GESA membership regarding the need for GMP processing standards for investigator-initiated clinical trials of FMT. We believe that mandating this would substantially compromise research and innovation in the field, including development of future potential indications for FMT and microbiome-based therapeutics.

Please find attached below our responses to the specific questions raised in the draft FMT standards.

Yours Sincerely,

[redacted]

Assoc. Prof. Simone Strasser President	Dr Sudarshan Paramsothy Gastroenterologist	Assoc. Prof. Jake Begun, Gastroenterologist (Chair, GESA Inflammatory Bowel Disease Faculty)

PS: For your information, the Australian FMT consensus statements referenced in the TGA draft standards have now been accepted for publication and are best referenced as below:

Haifer et al. Australian Consensus Statements for the Regulation, Production and Use of Faecal Microbiota Transplantation in Clinical Practice (accepted for publication in Gut 27/12/2019)

FMT Standards			
#	**Page**	**Question**	**GESA Response & Recommendations**
1	10	Is the application of *TGO 87* appropriate to FMT products?	Yes, *TGO 87* labelling standards is appropriate for FMT products.
2	10	If changes to current FMT practice are required to comply with these requirements, what is the expected cost impact? Is a 12-month transition period sufficient to update current practice? Please provide enough information to allow us to understand any impact.	The cost impact to comply with *TGO 87* should not be significant as all FMT centres should already have in place some form of labelling and traceability. A 12-month transition period is sufficient.

Appendix 1: Guidance on Draft Therapeutic Goods (Standard for FMT Products) Order			
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Part 2 – General Requirements			
3	14	For hospital-based providers of FMT products, do you envisage any problems with meeting these requirements outlined? Do you need further guidance from TGA?	Yes, many hospital-based providers will encounter difficulty complying with all the requirements. The proposed requirements are time-consuming and costly, and a 12-month transition will be insufficient for many centres.
4	14	If changes to current FMT practice are required to comply with these requirements, what is the expected cost impact? Is a 12-month transition period sufficient to update current practice? Please provide enough information to allow us to understand any impact.	Additional funding will be needed for equipment and personnel at many hospital-based FMT centres to implement these requirements, with significant one-off set-up as well as ongoing costs. A dedicated laboratory technician would need to be employed at most hospital-based centres (where currently work related to FMT services have generally been distributed amongst existing staff members), costing $50,000–$100,000 annually which would be prohibitive for most hospital-based providers. In the longer term, we suspect these requirements will ultimately lead to a shift from hospital-based FMT manufacture to a few select dedicated stool banks or commercial suppliers. A 12-month transition period is likely insufficient to update current practice to comply with these requirements for all hospital-based FMT centres though this is probably feasible for dedicated stool banks. We recommend extending the transition period unless it can be ensured that alternative stool bank sources (e.g. Red Cross/Lifeblood) are operational in time so there is no compromise in FMT availability and patient care.

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Part 3 – Specific Requirements			
5	17	Are the timeframes proposed for the initial collection of donor medical and social history and for repeat donors appropriate? If not, then please provide justification for alternative requirements.	Yes, these timeframes are appropriate and consistent with most current practice.
6	17	If changes to current FMT practice are required to comply with these requirements, what is the expected cost impact? Is a 12-month transition period sufficient to update current practice? Please provide enough information to allow us to understand any impact.	We do not envision major changes to current FMT practice or significant cost impact. A comprehensive medical physical examination should be included as part of the initial donor work-up. A 12-month transition period is sufficient.
	17	ADDITIONAL COMMENT – Table 1a	A patient with evidence of prior exposure to/resolved Hepatitis B (i.e. HBsAg negative, anti-HBc positive and anti-HBs positive) should be eligible to donate. HBV DNA nucleic acid testing should demonstrate HBV DNA not detected. A patient with evidence of prior hepatitis C infection who is demonstrated to be HCV RNA negative following spontaneous resolution or following antiviral therapy should be eligible to donate.
7	18	Is infection with HTLV-1 HTLV-2 considered relevant to screening of stool donors? The faecal route is not a known mode for transmission, and the level of evidence to support screening is low.	While we are unaware of any data supporting faecal transmission of HTLV-1/2, we suggest it is safer to remain consistent with other international screening guidelines and include HTLV-1/2 testing until further data becomes available justifying it not being included.
8	19	Is the risk of FMT recipients being exposed to xenogenic infections as a result of receiving viable, non-human cells or tissue sufficiently low in Australia at this time? Should this donor requirement be retained or removed?	It is reasonable to retain this donor requirement given the potential unknown risks, though in reality such donors would likely already be excluded due to the presence of other medical comorbidities that led to the xenogenic transplant in the first place. An overarching philosophy with donor selection is to use the healthiest possible candidates, ideally with no significant medical co-morbidities to minimise transmission of known or, as yet, unknown infections and microbial associated disease phenotypes.

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9	22	Is the risk of prion transmission from donors that have received human derived pituitary hormone sufficiently negligible in Australia at this time? Should this donor requirement be retained or removed?	Based on the information provided in the draft statements regarding last use of human derived pituitary hormones in Australia (1985) and the incubation period (30 years), one would assume that this risk is negligible. Again, such donors would typically be excluded anyway due to the presence of significant medical comorbidities. Retention of this exclusion criteria is unlikely to impact donor recruitment.
10	32	Is the risk of donor being exposed to xenogenic infections as a result of working closely with animals sufficiently low in Australia at this time? Should this donor requirement be retained or removed?	While the risk is probably low, there is a theoretical risk of cross-species transmission of known and, as yet, unknown pathogens. It is also unlikely that such a requirement would compromise recruitment of faecal donors (who are predominantly urban residents). As such, we have no issue with this donor requirement being retained.
11	33	Should any of the donor screening ineligibility criteria listed above under 'other criteria', or any others, be included in the draft TGO? If yes, please outline your evidence-based reasoning.	We would suggest exclusion of patients on chronic PPI therapy, as these medications are very commonly prescribed, are known to significantly alter the gastrointestinal microbiome, and may not always be captured simply based on exclusion of patients with functional GI disorders. We suggest excluding donors if they have used PPIs in the preceding three months. We also would recommend exclusion of patients with a history of neurological, psychiatric and pain conditions given developments in our understanding of the gut-brain axis and emerging associations between gastrointestinal microbiota disturbances and these conditions including supporting mechanistic animal data. These conditions also commonly co-associate with functional GI disorders. There is insufficient evidence at present to otherwise expand the mandated exclusions. It is not possible or practical to test for every potential infection, and a thorough history and examination is sufficient and more cost-effective to exclude such rarer infections in the Australian context.
12	33	How common are autologous FMT transplants in Australia, and is the drafted concession appropriate?	While autologous FMT is not employed at present in routine clinical practice, its potential role is being studied in patients undergoing haematopoietic stem cell transplants/chemotherapy to restore eubiosis post treatment. Autologous FMT is also sometimes used to serve as a surrogate placebo in FMT trials. The theoretical risks of autologous FMT are minimal and the drafted concession is appropriate.

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13	35	Is the obligation of providers to determine a list of diseases or conditions that could impact the quality, safety or efficacy of the product reasonable and understood? Does this requirement reflect current practice?	This requirement is reasonable and reflects current practice. FMT centres when developing their protocols, will consider which diseases/conditions could impact safety or efficacy of FMT and make a judgement call on whether the risk is sufficient to mandate exclusion. However, this is a rapidly evolving field so such a list should probably be reviewed on an annual basis, or sooner if significant new developments come to light (e.g. US FDA warning re MDRO deaths) It is unclear whether the TGA is requesting each centre to separately maintain such a formal list of conditions.
14	35	If changes to current FMT practice are required to comply with these requirements, what is the expected cost impact? Is a 12-month transition period sufficient to update current practice? Please provide enough information to allow us to understand any impact.	No significant cost impact is anticipated. A 12-month transition is sufficient.
Part 9 – Donor Blood and Stool Testing			
15	40	Are the proposed timeframes for the initial collection of blood and stool samples for testing, and the frequency of repeat collections and testing for repeat donors, appropriate? If not, then please provide justification for alternative requirements.	Yes, the proposed time frames are appropriate, and consistent with the recent Australian consensus working group statements. The follow-up testing at the end of the stool donation period should be undertaken as close as possible to the end of the 60-day donation period to best reflect the risk of pathogen acquisition during that time.
16	40	If changes to current FMT practice are required to comply with these requirements, what is the expected cost impact? Is a 12-month transition period sufficient to update current practice? Please provide enough information to allow us to understand any impact.	No change should be required to current FMT practice for established FMT providers. A 12-month transition is sufficient.

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17	42	A definitive solution is not provided here as to the appropriate validation of test methods used on stool samples for FMT products, but is the proposed pathway for continued engagement with the sector appropriate?	Ongoing stakeholder/sector engagement is essential as this is probably the biggest issue in the current draft statements and there are flaws in the current proposal that may impact ongoing clinical use and research with respect to FMT. There are currently no ARTG Class IV IVD tests for screening donor stool while those for screening blood are limited to a few select centres. At present, it is unclear who would be willing to undertake the financial burden associated with validating such tests. It would be prohibitively expensive and logistically impractical for hospital-based FMT/pathology centres to develop and validate such tests, given the relatively low numbers of donor's tested. The TGA would need to accept that such a requirement would likely ultimately result in centralisation of FMT manufacture to a few select stool banks nationally. Based on our discussions with industry, it is highly questionable whether even well-resourced commercial entities will be able to validate such testing before the transition period ends. Given the low pre-test probability of some of these pathogens in healthy stool donors, some feedback we have received suggests the numbers required for validation may not be logistically feasible. As a result, patient access to this potentially lifesaving treatment may be compromised. Even if/when commercial entities or alternative stool banks (e.g. Red Cross/Lifeblood) are operational with validated screening tests, it is also important to ensure that the cost of FMT is not prohibitively expensive due to the costs of validating such testing. In the meanwhile, at a minimum the TGA would need to officially sanction the process listed on page 42 where "As a potential interim solution, while validation studies are being performed, it is proposed that existing exemption provisions could be utilised where testing laboratories can seek access to use the unapproved IVD." and that "...laboratories could seek an exemption under TGA's Authorised Prescriber scheme for the unapproved Class 4 IVD (or Class 4 in-house IVDs) donor screening tests being used". The current draft lacks detail and clarity with respect to this "Authorised Prescriber" pathway. We hope that this process can be streamlined and simplified to minimise burden on clinicians.

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18	42	Is the requirement for testing to occur under contracted arrangements currently occurring? If not, then are there any problems or anticipated costs associated with establishing this arrangement?	This does not currently occur in most hospital-based FMT centres. Many pathology centres would not agree to contracted utilisation of their tests for non-approved purposes such as donor screening due to potential legal ramifications and possible loss of license. We have been informed as much by colleagues from the Royal Australian College of Pathologists.
19	44	Is archiving of blood and stool samples currently being undertaken? If not, are there any problems or anticipated costs associated with establishing this arrangement?	Most current FMT providers (especially hospital-based FMT centres) in Australia are not archiving donor blood and stool samples. We agree that it is a necessary requirement, but it will have associated costs in terms of logistics and need for additional freezer capacity for long term storage.
Part 10 – Donor Physical Assessment and Testing			
20	47	Is testing for HTLV-1/HTLV-2 considered relevant to screening of stool donors? The faecal route is not a known mode for transmission, but the level of evidence is low.	As per point 7, while we are unaware of any data supporting faecal transmission of HTLV-1/2, we suggest it is safer to remain consistent with other international screening guidelines and include HTLV-1/2 testing until further data becomes available justifying it not being included.
21	47	*Strongyloides stercoralis* transmission has been demonstrated in organ donation and is likely to be transmissible via stool transplants. However, it is possible to pre-treat susceptible patients (e.g. with low T cell counts), which may be more appropriate than the testing of donors. In addition, the current blood test has a relatively low sensitivity (70–95%). Do you support the requirement for testing and deferral of donors that test positive for this helminth? If not, then please provide your justification.	We agree that all donors should be tested for *Strongyloides stercoralis,* and if present deferred from donation until treated and repeat testing is negative. We would not suggest empirically treating all susceptible patients as this is unlikely to have a favourable risk-benefit ratio. Rather, such a decision should be individualised by the treating clinician.

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22	47	Is the requirement for repeat serology to be performed in the absence of NAT likely to have a significant impact on facilities manufacturing FMT products from fresh donors? Does your facility, or those you are aware of perform NAT, or will repeat serology need to be completed before a donor can be accepted? If NAT is not being performed, what are the process and cost implications of this requirement?	The number of FMT centres utilising fresh FMT is limited and we do not see this as a long-term modality. Most FMT centres use frozen / banked FMT and have regular stool donors who undergo serial testing including repeat serology, negating the need for NAT testing. We understand the need to have NAT testing performed when fresh FMT is utilised given the inability to account for the serologic window. NAT testing would increase cost of screening in such cases. Based on current MBS fees, the 3 NAT tests (HIV, HBV, HCV) will add $424 to screening costs.
23	48	Should any of the blood tests listed above under 'other criteria', or any others which are relevant, be included in the draft TGO? If yes, please outline your evidence-based reasoning.	Inclusion of general blood tests (FBC, LFT, UEC, ESR, CRP) is inexpensive and can identify relevant common undiagnosed pathology / conditions that may not otherwise be captured (renal impairment, liver disease, anaemia, infection or inflammatory disorders) and should thus be mandatory. Such testing is included in all other FMT consensus statements. We agree that all other tests do not need to be mandated but should be considered.
24	52	Is there a need to test for Norovirus and Rotavirus? If there is a very limited window where an infected individual would present asymptomatic, then testing may not be necessary. Please comment.	We would recommend testing for Norovirus and Rotavirus as while they are self-limiting infections, they are also quite common and prolonged asymptomatic shedding can occur. A proportion of healthy individuals infected with these viruses also may have minimal symptoms depending on inoculation load, so symptoms alone is not always sufficient to identify infected individuals. There have also been reports of Norovirus transmission post FMT. Furthermore, testing for these viruses is also recommended by all other international FMT consensus groups.
25	52	The prevalence of *Entamoeba histolytica* in Australia is unknown and likely to be rare, although it is known to be present in specific groups of individuals. The Australian CWG chose detection of this organism in stool (microscopy or ELISA for antigen), presumably because it is more relevant than the blood test for antibodies to the organism which cannot distinguish current from previous exposure. Is this considered appropriate?	Yes, stool testing for *E.histolytica* is appropriate as this is often asymptomatic and blood testing cannot distinguish active infection from prior exposure. PCR testing is the most sensitive approach and should be included as a test option along with microscopy or ELISA for antigen.

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26	52	Shiga toxin-producing types of *E. coli* is a common cause of acquired gastroenteritis in Australia. Despite this organism not being listed in the Australian CWG, it is recommended in all other consensus statements and the prevalence in Australia does not seem to justify varying from the international position. Is this considered appropriate?	We agree testing should be performed for Shiga toxin-producing *E Coli* as incidence in Australia is similar to those reported internationally and it is included in all other consensus statements.
27	52	Testing for enteroviruses was listed in the Australian CWG statement so has been listed in the draft TGO at this time but is not recommended in most consensus documents. Are there any factors that make explicit testing of potential donors for enteroviruses relevant in the Australian context?	No, we do not believe there is sufficient justification for mandatory testing for enteroviruses in the Australian context and see no reason to vary from the international position. It is reasonable to omit this, and simply have it on the "to be considered" list.
28	53	Should any of the stool tests listed above under 'other criteria', or any others which are relevant, be included in the draft TGO? If yes, please outline your evidence-based reasoning.	No, not at present though this may change in the future as this is a rapidly evolving field.