Submission in response to draft standards consultation paper for FMT products

Executive summary

1. We believe that the screening guidelines are well developed and evidence based and we support most of the suggested screening criteria with several caveats

2. Our view is that FMT requires bespoke regulation because stool is vastly different to human blood, tissue and cell transplantation with very different safety and quality issues.

3. By classifying FMT as a class 2 biological, all the blood and stool laboratory screening tests are classified as class IV IVDs. Many of the tests do not currently have class IV IVDs. The cost and length of time required (many years) makes this level of validation impossible and effectively precludes the provision of FMT in Australia.

4. We are concerned that the class-IV IVD regulation, that have been applied to testing for human blood products donors, where there is a very high public health risk of transfer of a **small** number of serious blood borne infectious diseases, has been transposed onto FMT where the list of potential pathogens is **very broad** but in almost all cases represent a low public health risk.

5. Evaluating the public health risk associated with the pathogens that do not already have class-IV IVD we cannot see that they represent a high enough public health risk to warrant class-IV IVD according the TGA risk stratification.

6. Epidemiological risks can change quickly and to optimise safety and quality stool donor screening programs require the flexibility to undertake a range of different laboratory tests dependant on the current epidemiological (and medical risks) of the potential donor. This is determined from a clinical assessment that is far more thorough than is undertaken for most other tissue transplantations to ensure the optimal safety and quality of the screening program.

7. There must be a much greater emphasis on the **clinical** aspects of screening and application of the best available diagnostic tests. This is the approach used in every other major jurisdiction that conducts FMT elsewhere in the world. Many tens of thousands of FMT have been provided using this approach with excellent safety records.

8. For reasons of safety and public health, identical evidence-based regulation should apply to both hospital and non-hospital based providers.

9. The requirement for a full dossier for FMT products is un-necessary and imposes unreasonable costs for no clear benefit given the necessity for GMP production and the widely available evidence supporting the use of FMT for *C. difficile* infection.

10. The requirement for GMP processing standards is appropriate for FMT used in routine clinical practice, however we believe that FMT used in the clinical trial setting should be excluded from full GMP compliance as this would limit research that may lead to new indications for FMT and the development of microbial based therapies.

Q1. Is the application of *TGO87* appropriate to FMT products?

Yes our view is that TGA 87 labelling standards are appropriate to FMT products. However, we do not agree that FMT should be regulated as a class 2 biological as this imposes class IV IVD status on all donor stool testing and this is currently unworkable.

Q2. 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.

Cost impact:

The changes to current FMT practice outlined in the draft standards will have significant cost impacts that will impact the supply of FMT to patients. To meet the GMP standard we have spent $710,000 during 2019. This cost includes capital costs for equipment, consumables and establishing a clean room as well as hiring laboratory staff and TGA advisors and constructing a Quality Management System and Validation Master Plan and protocols. This does cost does not include TGA fees for GMP inspection or dossier assessment.

We have sought a quote on the cost of producing a dossier for our FMT product based on the biological framework and this has been quoted as costing $120,000. The TGA fees are also likely to be more than $110,000. These costs are far too high for a start-up company producing a small volume product. We currently supply 30 FMT treatment aliquots to South Australia annually for the treatment of *C. difficile* infection. This extrapolates to approximately 450 treatments nationally. These additional expenses will add significant cost to the end product. This is a particular problem because currently there is no funder for FMT in Australia and hospitals will therefore need to purchase FMT using operational funds. The regulatory costs will also increase the price of FMT product beyond what most patients could afford without subsidy.

12-month transition period:

We are preparing to be ready for GMP inspection in April 2020 and could prepare a limited dossier prior to January 2021.

Dossier:

We believe that a full dossier for FMT products is not necessary given the widely available evidence for efficacy and the need to comply with GMP standard ensures a high-quality product. The dossier would seem to provide no additional benefit and would be a significant cost that would increase the cost of the product and hence access and availability of FMT to patients. If a dossier were required we would suggest a very limited version that did not impose an unnecessary regulatory burden.

Class 2 Biological

We believe that FMT should be regulated in a different manner to other biologicals. A bespoke approach to FMT is required that does not impose a class IV IVD requirement on all screening tests as this is unworkable. As recognised in the TGA draft standards human FMT products are sufficiently different in nature from other therapeutic goods of human origin (blood, cells and tissues) and as such the new product specific TGO was drafted. This has used TGO-88 as starting point. Stool consists of a mixture of water, undigested food, micro-organisms and epithelial cells released from the wall of the GI tract. Unlike other transplanted “tissues” human tissue cells only forms a tiny fraction of its composition. The classification of FMT as a biological has important implications

regarding donor screening, in particular the requirement for Class IV IVD status for each donor stool test. There are currently no stool screening tests that have class IV IVD status. SA pathology and other laboratories have indicated to us that the cost and recourse to validate stool tests as class IV IVDs is too high and they will not do this given the low throughput of donor stool testing required and their lack of resources to meet the requirements.

We believe that dedicated clean room facilities not attached to hospitals are preferable to hospital-based stool banks. This is because of the increased risk of multi-drug resistant organisms and cross contamination within hospitals. We therefore believe that imposing a higher regulatory requirement on non-hospital based stool banks (Class 2 biological) poses an increased risk to patients as it will push FMT to be preferentially manufactured within hospitals. It is also not equitable that higher standards (Class 2 biological) be applied to purpose built laboratories rather than in hospital laboratories. The discrepancy in regulatory burden is likely to make the cost of production significantly higher for stool banks located outside of hospitals.

Q3. For hospital-based providers of FMT products, do you envisage any problems with meeting these requirements outlined? Do you need further guidance from TGA?

For reasons of safety and public health, identical evidence-based regulation should apply to both hospital and non-hospital based providers. We see no rationale for imposing a greater regulatory burden on non-hospital-based stool banks. This is especially so given the increased risks associated with hospital-based stool banks.

International stool banking guidelines (Cammarota et al. Gut, 2019) recommend transport of donor stool product on dry ice and on delivery checking that the stool product is frozen and adequate dry ice remains in the transport container. Temperature monitoring in transit would impose an unnecessary cost burden and is not recommended anywhere in the world.

Q4. 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 changes to current FMT practice outlined in the draft standards will have significant cost impacts that will impact the supply of FMT to patients. We have outlined these costs in response to question 2 and in summary they are.

1. We have already spent $710,000 during 2019 with the aim of equipping our laboratory to meet the GMP standard. This does cost does not include TGA fees for GMP inspection or dossier assessment.
2. We believe that the costs of TGA assessment and producing a dossier for a biological agent are too high given the small number of FMT aliquots required to treat Australian patients with *C. difficile* infection.
3. The regulatory costs will increase the price of FMT product to the point where it may limit access to the therapy

We feel that a 12-month transition period is sufficient time to update current practice to a GMP standard. The exception to this is the requirement for new Class IV IVDs for all stool and some blood screening tests. This validation process will take many years at significant expense and we believe is un-necessary.

Q5. 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. The proposed time frames for collection of medical and social history for both the initial assessment and repeat donors are appropriate.

Q6. 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 clinical aspect of donor screening (medial interview and examination) is critical to the safety of the FMT product. Clinical screening is cost effective and reduces the pre-test probability of a donor having transmissible disease prior to blood and stool testing. This is particularly important as we do not and cannot screen for every potential pathogen transmissible via stool. We believe that the proposed medical interview is a minimal requirement and medical examination should be added as a requirement.

The cost impact of this is minimal and necessary and can be implemented easily within the required time frame.

Q7. 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.

Faecal transmission is not considered to be an important route of transmission for HTLV-1/2. On review of the literature, our group could not find any evidence evaluating whether HTLV-1/2 is shed in stool to any significant degree. There is however, no currently available evidence to support transmission of <u>any</u> of the blood borne viruses via FMT. In the absence of supporting evidence, our group have elected to keep our screening in-line with internationally published stool donor screening programs with strong safety records. As such we support screening for HTLV-1/2. An approach to screen based on epidemiological risk, taken by Cammarota et al. (2017) is a reasonable alternative strategy.

Q8. 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?

One of the key strategies to mitigate against the risks of transplanting unstandardized material containing complex, and in many cases unknown microbiological populations is to select for the healthiest possible stool donor. A history of receipt of non-human cells or tissues may well pose little risk to the FMT recipient however given the potential (unknown) safety signal it poses we would exclude any donors with this history.

Q9. 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?

Most transmissible spongiform encephalopathies are ingested and the prion protein is absorbed by the gut. In animal models, prions have been shown to shed in the faeces, likely due to shedding from Peyers patches. It is therefore theoretically possible to transmit prion disease via FMT. The risk of transmission of prion disease is likely to be very low but, like much of the donor screening criteria, there is no supporting evidence to help guide the decision. We have chosen to exclude donors who are at risk of prion disease including those that are a recipient of human derived pituitary hormone.

Additionally, as we are looking to select the healthiest possible stool donor and separate to prion disease risk the past requirement for human derived pituitary hormone would provide a sufficient safety signal to exclude the potential donor from our program.

Q10. 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?

On our review of the literature, there is an association between close contact with animals and risk of both gastrointestinal pathogens and multi-drug resistant organisms. Introducing a microbiologically complex material into a recipient has inherent dangers and much of what constitute this risk is not known. Additionally, testing for the known stool pathogens, no matter how well the test is conducted, is not 100% sensitive. A safe and effective donor screening program must not be over reliant on laboratory tests to determine donor safety. The most important strategy to mitigate against this risk is to select the healthiest possible stool donor with the lowest known epidemiologic risk profile. As such we have chosen to exclude any donors who work closely with animals.

Q11. 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.

Malaria, Trypanosomiasis, Tuberculosis: No, we don't think these conditions need to be specifically included in the TGO however there does need to be a strong emphasis on the importance of a high quality medical and social interview and examination. Given the wide range of infectious diseases that are potentially transmissible via FMT, a thorough evaluation of epidemiological risk and medical history and a physical examination by a highly-trained medical physician to detect and exclude any donors with any safety signals related to potentially transmissible infectious diseases is critical. Laboratory testing in this setting only has limited value.

Chronic therapy with proton pump inhibitors: Yes. Imhann et al. (2016) found proton pump inhibitors (PPIs) had a significant impact on the gut microbiome. When compared to non-users, PPI users consistently had changes associated with a less healthy gut microbiome. On a population level, the effects of PPIs were more prominent than the effects of antibiotics or other commonly used drugs. PPIs are amongst some of the most commonly used medications in Australia. In 2017, it was estimated that 15% of Australian adults were dispensed at least one PPI. We consider that a reliance on a history of functional GI disorders is insufficient and specifically screen for PPI use. In our program donors are excluded if they have taken a PPI in the preceding 3 months.

History of receiving growth hormone or insulin from cows: No, not specifically. A well conducted medical interview should detect and exclude any donors with any past medical history requiring such treatments or recreational misuse.

Family history of colon cancer: Yes, we would include this. There is no evidence to date that shows colon cancer is transmissible via FMT. There is however emerging evidence that there are changes in the gut microbiota in patients suffering colorectal cancer suggesting a possible role of host-microbe interactions in the origin and development of this malignancy. There is evidence with regards to some degree of heritability of our gut microbiome and we know that the relative risk of developing colorectal cancer is increased with at least one first degree relative affected. As such we would exclude potential donors with a family history of colorectal carcinoma involving 1 or more first degree relatives.

History of neurological/psychiatric/pain conditions: Yes. There have been associations between the gut microbiome and disorders related to the brain including anxiety, depression and autism. It has been shown that commensal bacteria modulate symptoms and pathology in mouse models of neuropsychiatric and neurodevelopmental diseases. Much of this area is unknown and as such our preference is to select for the healthiest possible donor. Our program excludes all potential donors with a past or current history of a neurological disorder including stroke, chronic pain syndromes, fibromyalgia, neurologic, neurodevelopmental (including autism) or neurodegenerative disorders, or psychiatric disorders.

Q12. How common are autologous FMT transplants in Australia, and is the drafted concession appropriate?

Autologous FMT is not common in Australia. We are involved in a clinical trial of autologous FMT for patients following chemotherapy. The risk of disease transmission with autologous FMT is clearly low given the donor and recipient are the same person. Minimal stool screening is required and this should be left at the discretion of the treating physician.

Q13. 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?

We believe it is reasonable and understood and this requirement reflects our current practice. As highlighted in the document this area continues to evolve. New knowledge (like the US FDA warning in June 2019) will become available and a stool donor screening program must be able to rapidly and effectively respond to new safety and quality concerns.

Q14. 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 clinical aspect of donor screening (medial interview and examination) is critical to the safety of the FMT product. Clinical screening is cost effective and reduces the pre-test probability of a donor having transmissible disease prior to blood and stool testing. We believe that the proposed medical interview is a minimal requirement and medical examination should be added as a requirement.

The cost impact of this is minimal and necessary and can be implemented easily within the required time frame.

Q15. 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.

The blood test requirements of less than one month before the stool donation period and 1 month after completion of the 60-day stool donation period (for serology tests) to allow for a seroconversion window is considered reasonable.

The stool testing (which does not include any serology tests) is reasonable to be performed within 1 month prior to the stool donation testing. 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.

Q16. 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.

Our stool bank already undertakes the "top and tail" screening approach with a quarantine period. As such there will be no cost impact and the transition period will be sufficient.

Q17. 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?

No, we don't believe it is appropriate. As noted in the consultation paper, FMT products are sufficiently different in nature from other therapeutic goods of human origin (blood, cells and tissues) that a stand-alone TGO for FMT products is merited. We believe that it is not appropriate to impose the IVD regulatory framework, that was developed for other "therapeutic goods of human origin", on FMT stool donor and exposes the stool donor screening process to unmanageable risk. The issues around test validation highlight the important differences between screening stool for FMT and other human tissues.

1. **The public health risk is different**. Our understanding is that historically class-IV IVD regulation was focussed around incurable blood-borne viruses. Whilst it is unknown if it is possible to even transmit these infections via FMT, these tests already have class-IV IVD validation in donor populations. All the stool pathogens that are screened for in potential stool donors are either treatable infections or short lived illnesses and would not be considered high public health risk. This is recognised in the consultation paper: *"Q24. 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 would not be required."* It appears incongruous that there is a question as to whether the test even needs to be performed and at the same time a suggestion that it meets the highest public health risk criteria if it is performed.
2. Such validation requirements **limit the capacity of donor screening programs to respond rapidly and effectively to changing safety and quality concerns**. The evidence base to support the list of organisms that are screened for in FMT is overall weak. A vital component of an effective donor screening program is the ability to accurately track and respond to safety signals. The choice of laboratory tests for donor screening has evolved over time, in response to emerging evidence and epidemiological risks. Testing also must be tailored to an individual donor's risk based on their clinical assessment. Given the wide range of potential pathogens this represents many different potential tests. As recognised in the case of ESBL transmission via FMT, reported in the New England Journal of Medicine in November 2019, many of the risks of FMT are yet to be recognised. New resistance mechanisms will develop, new pathogens will be detected. The existing laboratory tests required for stool donors are all performed according to the standards required by NATA and NPACC for in-house tests. If the additional validation requirements are too demanding it will dangerously slow down the capacity of donor screening programs to respond to new risks. We cannot see the benefit that this extra layer of validation adds but see real risk if it limits our capacity to perform the tests that are needed.
3. The cost required to meet the class-IV IVD validation requirements is too high for the revenue that would be generated from FMT given the relatively low number of FMT that are currently performed nation-wide per annum (approximately 450).

4. The donors that reach the laboratory testing point of the screening program are already at extremely low risk of pathogen detection having no medical or social risk factors, a normal physical examination and a formed stool with no evidence of any pathology. The number of people required to validate the test in this very specific setting would be large and given the number of stool donors required we have been advised that this would not likely to be possible to undertake.
5. Promoting the development of enhanced screening tests such as stool metagenomic screening may provide much more useful data about risk and benefit than requiring existing tests achieve class IV IVD validation.

Q18. 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?

We currently have a financial contractual arrangement with our pathology provider but not a quality agreement. The pathology provider has indicated that a quality agreement would involve increased work and cost and this may be borne by our organisation.

Q19. Is archiving of blood and stool samples currently being undertaken? If not, are there any problems or anticipated costs associated with establishing this arrangement?

We currently archive stool at BiomeBank. We have commenced archiving blood tests with our pathology provider at an additional cost to our organisation.

Q20. 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.

See response to Q7.

Q21. *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 support the requirement of testing for *Strongyloides stercoralis* and exclusion of donors who test positive for this helminth. Clinicians that administer FMT product need to be aware about the sensitivity of currently available strongyloides testing and make an individualised decision regards to the need for pre/post FMT-treatment.

We believe testing for strongyloides testing provides an excellent example of where the cost and resources required to meet class-IV IVD requirements for a test that overall performs poorly could be far better spent in development of better quality testing for this pathogen (ie: potentially development of a stool NAT for strongyloides).

Q22. 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?

Our facility currently performs “top and tail” serology with a quarantine period and not NAT testing for blood borne viruses. We therefore believe that this requirement will not add additional cost. If NAT testing was performed then a quarantine period to allow for seroconversion would not be necessary. Most stool banks world-wide perform repeat serology with a quarantine period.

Q23. 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.

We perform Hepatitis E screening because this infection is transmissible via stool.

We perform CBE, LFTs and CRP as screening tests to detect donors who have unrecognised illness.

We do not believe CMV or EBV status should exclude donors, however treating physicians should be aware of the risk of primary CMV in vulnerable recipients of FMT and the consent should reflect this.

Although we believe some of these tests increase the safety profile of FMT, none of these tests warrant class IV IVD status as they do not represent the highest public health risk. **Mandating these tests as class IV IVDs would effectively prohibit FMT in Australia.**

Q24. 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.

Acute gastroenteritis is common and stool donors are, on average, going to experience 0.5-1.3 cases per year. While transmission of enteric pathogens through faecal donor material is rare, instances of post-FMT norovirus gastroenteritis have been reported. Even though the window is relatively short, more prolonged asymptomatic shedding can occur and we believe that screening for these common infections is necessary. We do want to emphasise that these infections are usually short lived and do not represent the same high public health risk such as pathogens like HIV and hepatitis B do.

Hence, there should not be a requirement that tests for Norovirus and Rotavirus be class IV IVDs.

Q25. 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, we consider stool testing the best approach for detection *of E. histolytica*. NAT is the most sensitive approach and this is the strategy we have chosen.

Q26. 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 that this testing should be undertaken in the Australian setting and see no reason why we should vary from the international position.

Q27. 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 support the routine testing for enteroviruses in stool and can see no reason why we should vary from the international position. We agree with the consultation paper that the most appropriate approach is to monitor for epidemiological situations and institute testing in the setting of an outbreak associated with more severe disease.

Q28. 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.

We do not think that at present any additional tests need to be added routinely. Additional testing may well be necessary in the setting of an individual donor's risk (travel history, occupation etc). An emphasis must be on a thorough medical interview and assessment. The regulation around testing must allow the flexibility to add on any additional tests as required to ensure the safety and quality of the screening program.

There is evidence that *dientamoeba fragilis* and *blastocystis hominis* are prevalent in significant proportion of the healthy Australian population. There is also evidence that these organisms are more common in healthy individuals than those with gastrointestinal symptoms (Dullaert-de boer et al 2019) and when *Blastocystis sp* are transferred via FMT the recipient patients do not experience symptoms as a result (Terveer et al 2019). In short these are likely to be commensal organisms and should not be included as screening tests.