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RCPA
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Draft Standards for Faecal Microbiota Transplant (FMT) products Consultation Paper

Response from Royal College of Pathologists of Australasia

The RCPA thanks the TGA for opportunity to comment on the draft standards for FMT products in Australia and also for taking into account many concerns raised by the College. These include the need of validating tests to demonstrate test methods as "fit-for-purpose" and the potential of unnecessary administrative burden that may be imposed on hospitals if there is a requirement for GMP licences for minimally manipulated faeces manufacture.

The RCPA's central position is that the tests deployed for screening fecal donors have to be validated for the said purpose (or working towards being validated). Using tests that are unvalidated in an uncontrolled manner will likely reduce the safety of FMT unsafe in both short and long terms, as well as potentially impact the public's confidence in FMT as well as the Australian's regulatory framework for therapeutic products.

The public rightly expect the tests used in the manufacturing of a therapeutic product will have already been shown to be "fit-for-purpose". Ethical medical practices also necessitate tests used to be

1. validated for the intended use, or
2. in the process of being validated as part of a clinical trial, after the recipient has given an informed consent, or
3. (in the case when the tests are not validated) under the control of a medical practitioner, who is aware of the deployment of the unvalidated tests, is knowledgeable in the limitations of the tests, and will monitor the outcome and take medical responsibility of the tests, after the recipient has given an informed consent, and under the necessary regulatory oversight.

The RCPA recognises that the difficulty for individual laboratory services in validating screening tests for FMT purposes and thus has been an advocate for a multi-centre clinical trial to investigate the safety limits of currently unvalidated tests being adopted for donor screening purposes. The RCPA also welcomes the flexibility of the TGA Authorised Prescriber pathway. It believes the Authorised Prescriber pathway will facilitate access of donor screening tests, which have been performed outside the laboratories' claims, on an individual basis by bedside clinicians (the Authorised Prescriber). The RCPA believes these efforts will form a framework to facilitate a better articulation of risks and responsibilities in deployment of unvalidated tests, and a more stringent follow-up of donors and recipients.

The RCPA believes validation of tests for fecal donors screening purposes is best served by a rational approach. This should include, but not limited to, defining the test detection limit, defining the detection probability relating to sampling error, defining clinically relevant infectious doses, defining potential level of contamination in material, considering the manufacturing process, the amount of product used and the route of administration, and risk modelling. The central theme of test validation for donor screening and product manufacturing relates to the residual risk. The RCPA,

being the peak national organisation for pathology test provision, can provide expertise for such endeavours.

Our more detailed views for selected questions are as follows:

Q1. *Is the application of TGO 87 appropriate to FMT products?*

We support the application of TGO 87 to FMT products. Labelling requirements stipulated in TGO 87 reinforce importance of traceability of FMT product manufacture.

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*

No comment.

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?*

We support the concept of utilising Good Laboratory Practice (GLP) in manufacture of FMT product.

Subsection (2)(c):

We do not think biosafety level 2 facility is required, if the donor has been recently screened.

We support the use of a designated area for processing and storage

Subsection (2)(d):

We fully support the statement ". A designated area for processing and storage should be used to avoid mix-ups and adding to the existing bioburden."

We welcome the recognition of clean trolley as a potentially suitable solution: "The premises should be adequately adapted and of sufficient size including a potential mobile unit (clean trolley)…"

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.*

We believe the stated requirements are essential to safe guard recipient safety. Most hospital based FMT manufacture should already have elements of these requirements and therefore formalising these requirements should not be too much of a burden.

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.*

We support the timeframes proposed, in particular, we support statement 8(1)(c) "An abridged medical and social history (based on a risk assessment) must be collected at the time of each donation."

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.*

We believe the stated requirements are essential to safe guard recipient safety. Most hospital based FMT manufacture should already have elements of these requirements and therefore formalising these requirements should not be too much a burden.

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.*

No comment, except we note that there is a validated assay for screening blood donors so is easy to introduce.

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?*

No comment.

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?*

No comment. However, there is no evidence of this risk as far as we know.

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?*

No comment.

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.*

No comment.

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

No comment.

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?*

No comment.

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.*

No comment.

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.*

In blood donation, sample testing at the day of donation is mandatory.

If the same level of risk management is required for FMT product, then stool testing at the day of donation will be necessary.

This approach will be similar to one of the proposals from the International Consensus Statement, and noting the obstacles over this approach is the practicability of testing stools (and blood) of donors if feces is donated daily.

Therefore it is not unreasonable to consider, for high risk recipients, such as immunosuppressed patients who may be more susceptible to infections, stool testing at the day of donation, as this may be required to provide additional safety margin. The stool testing at the day of donation would allow monitoring and early treatment for the recipient, should the stool testing revealed abnormalities.

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.*

No comment.

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?*

The RCPA strongly supports the proposed pathway. The College believes the proposed pathway achieves a good balance between the donor and recipient safety and feasibility.

Our more details comments are as follows:

Statement (9)(10):

The test kits / methodologies used for screening infectious diseases that are performed in accordance with Section 10 must be:

a. The most suitable technology / methodology for the sample and agent being tested; and

b. Approved by the relevant regulatory authority in the country in which the testing is performed; and

c. Performed in a facility approved by the regulatory authority to perform such testing; and

d. Considered acceptable by TGA.

The RCPA strongly support the Statement (9)(10).

In addition, the RCPA strongly believe that the donor screening tests must be validated for the intended use, and therefore strongly support the explanatory statement "Where test methods are used beyond the test kit manufacturer's instructions, validation to support the extended use must be demonstrated."

The RCPA is aware that some of the existing practices may not be complying with this. For example, the College is aware that some member laboratories (for various reasons) are using diagnostic test kits for the purpose of donor screening, without first being validated as an in-house IVD.

The RCPA welcomes the TGA's effort in advocating the requirement of validating for intended use so as to safeguard donor and recipient safety.

The RCPA recognises the challenges in validating the donor screening tests for their intended use. On the other hand, the RCPA believes it is necessary to articulate the risk and as a minimum requirement the detection limits of the current deployed unapproved tests should be investigated.

Subsection (5)(a) Technology / methodology of testing kits / methods

The RCPA welcomes the flexibility that the most appropriate technology / methodology can be determined and justified by the sponsor.

Subsection (5)(b) Approval of test kits

“Where test methods are used beyond the level approved by the local regulatory body, validation to support the extended use must be demonstrated.”

The RCPA notes that the validation to support the extended use may be difficult for individual laboratories. Therefore the RCPA is a strong advocate for having the testings performed as part of a nation-wide clinical trial to gather evidence to support future test kit approvals.

Subsection (5)(c) Testing facility

The RCPA welcomes the flexibility that individual hospitals can determine the suitability of the facility performing the screening tests for Class 1 (fresh stool).

The RCPA agrees that if the stools are tested as part of a stool bank, then a TGA licence must be required, and agree that NATA accreditation is not sufficient.

Subsection (5)(d) TGA acceptance of testing kits/methods

The RCPA strongly agrees the explanatory statements under this subsection. In particular, the College strongly agrees with the statement “laboratories providing stool testing services to determine donor eligibility for FMT products would need to validate these tests as Class 4 in-house IVDs and include them in the ARTG.”, though noting for some conditions it may not be medically necessary to be tested with assays validated to Class 4 level. Validation to class 3 or lower may suffix in these situations. RCPA does recognise ingestion of large amount of stool as an artificial route of infection, and the effect of ingestion of unnaturally high pathogen load may result in clinical disease presentation not usually seen in clinical practices; and therefore understands the precautionary approach of TGA.

The RCPA is pleased to note the TGA’s initiative described in the statement “the TGA will engage with the commercial suppliers of lower class test kits that are approved for supply in Australia as a diagnostic assay, but have not undergone validation for the expanded intended use as a Class 4 IVD, for use in screening of donors to assess suitability for transplantation.”

The RCPA strongly support the interim solutions proposed by the TGA for the use of unapproved (clinical trial pathway or exemption under authorised prescriber). RCPA supports the exemption to be on individual basis. The RCPA believes these solutions will enable current FMT practices to continue as “business as usual” but with significantly improved recipient safety and regulatory oversight. The Authorised Prescriber Pathway should also facilitate a more considered approach in assays selection, especially for new conditions that emerge as safety concerns. Data can also be accumulated at TGA level to identify the adequacy for the unvalidated assays for the tested conditions.

The College strongly agrees with the TGA that adopting this approach will include "a more stringent follow-up of donors and recipients" and believe this is essential for donor and recipient safety.

The RCPA strongly opposes any actions that will result in unvalidated tests being used for unapproved indications without any TGA regulatory oversight and informed patient consents.

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?*

Currently contracted agreement specifically for FMT is not occurring. However, the RCPA strongly support such agreement because of multiple reasons. Firstly, as stated by the TGA: "to ensure that sponsors have considered the suitability of the tests applied, and would perform a risk assessment when changes to the test methods are introduced." Secondly, to allow the test providers to be actively engaged in the process of selecting the testing methods most appropriate to the manufacture protocol of the sponsors, so that when there is a change in manufacture protocol of the sponsors, the test methods can be reviewed for their continued suitability. Thirdly, to allow the sponsor and pathology provider identify donor screening tests as such with appropriate discussion over costs so that these testings are not inadvertently and inappropriately charged against Medicare. Fourthly, the contractual agreement will also facilitate the sample archiving and look-back testing discussion (as stipulated in Q19). Finally, the contractual agreement can also facilitate the formalisation of a result notification pathway.

While there will be some costs involved in establishing this arrangement, the College believes this to be essential.

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?*

The RCPA is not aware that archiving specifically for FMT related testing is current standard practice, apart from meeting the requirement of retention of specimens as stipulated by NPAAC. However, the RCPA is a strong advocate for such practice.

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.*

Please see our response for 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.

While the current blood test has relatively low sensitivity, a positive result is useful as an exclusion. The same applies to looking for *Strongyloides* (and other parasites) under microscropy and agar plate culture. Furthermore, there are stool based PCR tests under development which may be explored as the sensitivity of these are variable. .

Moreover, *Strongyloides* larvae are highly infectious. Manufacturing FMT products using stools containing *Strongyloides* may pose a significant health risk to the personnel involved. Precautions to avoid this must be in place.

Therefore the RCPA supports the requirement for testing and deferral of donors. If microscopy and plate culture are done, it should be tested immediately on a fresh specimen of faeces with refrigeration.

The RCPA does note that the freezing process of FMT products in stool bank may partly mitigate the risk to the recipient. This will need to be fully validated by the sponsors if the freezing step during the manufacturing process is used as a risk mitigating step 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?*

The RCPA cannot speak for all its member laboratories regarding their practice, but does believe that performing NAT to be common practice. Given there is NAT validated for donor screening purposes available from at least the Australian Red Cross LifeBlood and National Serum Reference Laboratory, the College does not believe compliance for NAT will be a significant hurdle.

***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.*

The RCPA's opinion is represented in the Australian CWG. No additional comments.

***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.*

Asymptomatic gastroenteritis by these agents are known to exist. For Norovirus, please refer to the recent 2018 meta-analysis on global burden of prevalence of asymptomatic Norovirus infection [1] . The RCPA supports testing for Norovirus and Rotavirus.

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?*

The RCPA would like to highlight that diagnostic PCR validated for stool is available and offer a better clinical and diagnostic utility than serological testing, which have quite poor sensitivity for non-invasive luminal disease. Microscopy has low specificity and sensitivity and antigen testing has low specificity leading to both false positives and false negatives.

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?*

The RCPA recognises the limited availability of appropriate traditional diagnostic testing methodologies for Shiga toxin producing *E coli* strains that are common in Australia. There has been a paucity of prevalence study of this pathogen type in Australia.

With the newer molecular diagnostic tests that are not particular for specific Shiga toxin producing *E coli*, the RCPA believes that inclusion of these organisms for testing by molecular testing may increase the safety margin.

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?*

The RCPA acknowledge there are differences in opinions in necessity of Enterovirus testings. Omission of the requirements of Enterovirus testing may appear to be an oversight in the other documents because the presence of Enterovirus is usually not related to gastrointestinal diseases.

While Enterovirus is a major cause of viral meningitis locally and internationally, the pathogenesis of enteroviral meningitis and its relationship with intestinal microbiota is currently unknown. Given the current international consensus documents have included pathogens that are less prevalent and cause less significant morbidity than Enterovirus., RCPA believes screening a pathogen that can

[1] Qi R et al. Global Prevalence of Asymptomatic Norovirus Infection: A Meta-analysis. Lancet EClinicalMedicine. 2018 Sep 17;2-3:50-58 https://www.sciencedirect.com/science/article/pii/S2589537018300269

cause significant morbidity would have its merit. On the other hand, the availability of assay that selectively detects meningitis related enterovirus strains is limited, and the mortality from enteroviral meningitis is rare. Therefore there are some opinions that routine Enteroviral testing should not be included, but a history of potential exposure to polio viruses in countries of endemicity and/or documented history of Polio vaccination should be obtained.

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.*

RCPA was under the impression that MRSA was included in the other Multi-drug resistant organism as a mandatory requirement. The RCPA believes that Methicillin-resistant *Staphylococcus aureus* screening should be included. Gastrointestinal carriage of MRSA is well-known and sufficiently prevalent [2]. MRSA blood stream infection carries high morbidity and mortality.

RCPA believes screening for Gram-negative multidrug-resistant bacteria (such as *Pseudomonas aeruginosa* or *Acinetobacter baumannii*) may be important in selected donor groups (e.g. donors working in hospitals) may be warranted.

RCPA also believes that going forward, screening for *Candida auris* may become an issue. Currently it is not known if transmission can occur by the faecal route but it is known to be present in the gut. Testing should be considered in selected donor group, e.g. if there is an epidemiological link to acquiring *C.auris* such as if donor has been to an endemic area or has been in contact with a case.

[2] Acton DS et al. Intestinal carriage of Staphylococcus aureus: how does its frequency compare with that of nasal carriage and what is its clinical impact? Eur J Clin Microbiol Infect Dis. 2009 Feb;28(2):115-27. https://link.springer.com/article/10.1007/s10096-008-0602-7