Australian Government
Department of Health
Therapeutic Goods Administration

Draft standards for faecal microbiota transplant (FMT) products

Consultation paper

Version 1.0, November 2019

TGA Health Safety Regulation

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Purpose and scope

The purpose of this consultation paper is to outline the proposed standards for faecal microbiota transplant (FMT) products in Australia. Submissions received in response to this consultation will inform the final decision by the Australian Government regarding the most appropriate standards to apply to the therapeutic use of FMT products in Australia. This area will be regulated by the Therapeutic Goods Administration (TGA).

In this consultation paper, detailed guidance and justification is provided (Appendix 1) on a new draft *Therapeutic Goods Order (TGO): Standards for Faecal Microbiota Transplant Products* (Appendix 2). This has been provided to assist your review and consideration of the proposed requirements that will apply to all providers of FMT products.

Note that the versions of the TGO and associated guidance provided in this consultation are not the final versions, and may be subject to change following feedback from this consultation.

Your input is sought on specific questions raised within the consultation paper, as well as specific feedback on the applicable standards.

Your views are sought

TGA invites comments from interested parties. Comments can address any of the issues in this consultation paper.

To submit, complete the online consultation submission form to upload your submission in either PDF or Microsoft Word format.

Alternatively, hardcopy submissions with a printed coversheet may be mailed to:

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

Any questions relating to submissions should be directed to TGA's Biological Science Section by email to:

bloodandtissues@health.gov.au

Alternatively, by telephone to 1800 678 799 (free call within Australia).

The closing date for comments is COB Friday 31 January 2020.

Background

Faecal microbiota transplant (FMT) is the process of transplanting gut microflora either in human stool or products processed from human stool, from a healthy human donor into the bowel of a recipient with a medical condition. FMT products include fresh or banked human stool that may be introduced to the bowel by rectal enema, sigmoidoscopy, colonoscopy, nasogastric or nasoduodenal tube. The products also include human stool that has been freeze-dried, or otherwise prepared, to allow oral ingestion. Methods of manufacture for FMT products can vary. However, in principle the process involves collection of donor sample, dilution (using either water, sterile saline or milk, with cryoprotectants such as glycerol added for frozen FMT

product), homogenisation (blending), filtration to remove large particles, and storage by freezing (banking).

Given the uncertainty among medical practitioners, hospital systems, and industry regarding the regulatory status of FMT products in Australia, a clear regulatory position was needed. In October 2018, TGA hosted a FMT stakeholder forum in Melbourne, and in January to March 2019 performed a public consultation on options for the regulation of FMT products. TGA received 22 submissions to the consultation.

After considering the stakeholder responses and conducting individual discussions with some groups, the Minister for Health determined a model by which the collection, manufacture and supply of FMT products are to be regulated in Australia. Details of the new regulatory model for FMT products are published on our website. It is anticipated that the new regulatory amendments for FMT products will be implemented on 1 January 2020 with a transition period of 12 months, i.e. commencement from 1 January 2021.

Under the new regulatory model, most FMT products will be classified as either:

- **Class 1 biologicals**, in the case of minimally manipulated FMT products from appropriately screened donors which are manufactured **in a hospital** and used in that hospital under the supervision of a registered medical practitioner who has clinical care of the recipient patient. Sponsors of Class 1 biologicals will need to comply to applicable standards and have an appropriate quality management system in place. The sponsor will need to submit an application for the FMT product to be included in the Australian Register of Therapeutic Goods (ARTG). However, the manufacturer does not need to hold a Good Manufacturing Practice (GMP) licence, and does not require pre-market assessment of supporting data by TGA.

- **Class 2 biologicals**, in the case of minimally manipulated FMT products from appropriately screened donors which are manufactured in a facility that is **not a hospital** or manufactured in one hospital and used in another different hospitals or clinics. For Class 2 biologicals, these are required to be included in the ARTG and have GMP licensing for all manufacturing and testing facilities.

Relevant to this consultation paper, standards applicable to donor selection and testing, storage and traceability needs to be developed and implemented. The current traceability requirements under *Therapeutic Goods Order No. 87: General requirements for the labelling of biologicals (TGO 87)* will apply for these FMT products. However, the current TGO to determine donor suitability and testing of biologicals – *Therapeutic Goods Order No. 88: Standards for donor selection, testing, and minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products (TGO 88)* – does not provide sufficient controls for the screening of stool donors, given that human FMT products are sufficiently different in nature from other therapeutic goods of human origin (blood, cells and tissues). As a result, a separate, stand-alone TGO for FMT products is merited, and will outline the minimum quality and safety requirements with which biologicals derived from human stool must comply.

FMT standards

Background

To ensure the reliable and safe delivery of FMT products to patients, there is a need to define minimal screening criteria for donors and resultant product. There is plentiful starting material available, so the emphasis of any program should be on the careful screening of potential stool donors to ensure the quality and safety of the stool, with current donor acceptance rates between 1-10%.[1] Other control measures are also necessary such as manufacture in a controlled environment, traceability, and appropriate storage conditions.

In determining appropriate standards to apply to Australian FMT products, careful consideration was given to recent international consensus statements on FMT products from the EU,[2] the US,[3] the UK,[4] and an International consensus group[5] which aims to unify the industry. Similarly, a multidisciplinary steering committee known as the Australian Consensus Working Group (CWG) was formed with the aims of discussing and recommending FMT donor selection and screening, FMT indications, the development of FMT centres, and future FMT research.

Based on the work of these papers and consideration of the local environment, it is proposed that the following standards will apply to all FMT products:

- *Therapeutic Goods Order No. 87*: *General requirements for the labelling of biologicals (TGO 87)*
- *Draft Therapeutic Goods Order*: *Standards for Faecal Microbiota Transplant Products (Appendix 2)*

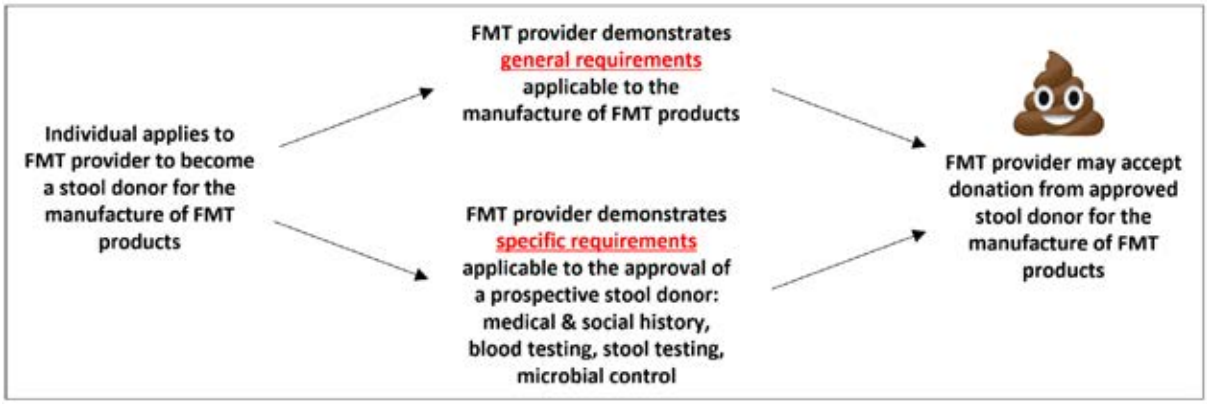
The current *TGO 87* will apply to all FMT products as it stands. In addition, a new product-specific TGO has now been drafted titled *Standards for Faecal Microbiota Transplant Products* (Appendix 2).

The starting point for the draft TGO was *TGO 88*, which states the requirements for donor selection, testing and minimising infectious disease transmission applicable to blood, cells and tissues. Key definitions are included in the draft TGO, such as 'fresh stool' versus 'banked stool'.

As shown in the figure below, the draft TGO outlines:

- **General requirements** that are applicable to FMT providers for the manufacture of FMT products, such as having documented procedures in place, manufacturing facility requirements, and critical material control; and
- **Specific requirements** that outline the need for comprehensive donor work-up by FMT providers of prospective stool donors (clinical assessment, medical and social history, blood and stool testing) as well as requirements for microbial control.

[1] Cammarota G, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* (28 Sep 2019), pii: gutjnl-2019-319548, doi: 10.1136/gutjnl-2019-319548
[2] Cammarota G, et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 66: 569-580 (2017).
[3] Woodworth MH, et al. Laboratory Testing of Donors and Stool Samples for Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection. *J Clin Microbiol.* 55: 1002-1010 (2017).
[4] Mullish BH, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *Gut* 67: 1920-1941 (2018).
[5] Cammarota G, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* (28 Sep 2019), pii: gutjnl-2019-319548, doi: 10.1136/gutjnl-2019-319548.



Australian setting

This TGO has been considered **in the context of Australian donors**; additional requirements may need to apply to FMT products manufactured from stool donors outside of Australia. For example, a number of the testing requirements have considered the epidemiology of infectious agents in Australia only (e.g. Hepatitis E testing), but may be applicable to donors outside of Australia.

Additional or higher requirements may be included at a sponsor's discretion or may also be required by other applicable standards. Further testing as clinically relevant for specific products or target patient populations may also be necessary.

Australian Consensus Working Group

A multidisciplinary steering committee known as the Australian CWG was formed with the aims of discussing and recommending FMT donor selection and screening, FMT indications, the development of FMT centres, and future FMT research. CWG sought endorsement from the Gastroenterological Society of Australia (GESA), Australasian Society for Infectious Diseases (ASID), Royal College of Pathologists of Australasia (RCPA), and Royal Australasian College of Physicians (RACP), and have representatives from each of these organisations. Panel nominees include gastroenterologists, infectious diseases specialists, and pathologists from across Australia and overseas. Using a modified Delphi technique, an accepted method of developing consensus based on an unbiased systematic review of the published literature, there was a voting on statements for FMT products during the middle of 2019. Outputs of this body of work will soon be published.[6]

Other jurisdictions

Along with the Australian CWG recommendations on FMT products, careful consideration was given to numerous other recent international statements on FMT products. These include

[6] Haifer C, et al. Consensus Guidelines for the Production and Use of Fecal Microbiota Transplantation in Clinical Practice. Manuscript submitted for publication (2019).

articled published from the EU,[7] the US,[8] the UK,[9] and an International consensus group[10] when writing the draft TGO.

Much like the Australian CWG, the EU consensus statement (Cammarota et al.) stemmed from separate working groups and an evidence-based process. Statements developed by each working group were evaluated and voted by all members, first through an electronic Delphi process, and then in a plenary consensus conference. The US publication (Woodworth et al.) reviewed the background of the US Food and Drug Administration's (FDA) regulation of FMT products and donor selection and laboratory screening recommendations of six separate groups.[11] The UK working group (Mullish et al.) reported on the outcomes of a joint dialogue between the British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS).

Published in September 2019, the 4th edition of the *Guide to the quality and safety of tissues and cells for human application* by the European Directorate for the Quality of Medicines (EDQM) recently adopted the recommendations by the EU consensus group in Cammarota et al. for FMT products.[12] These published recommendations are referenced in the guidance below.

Commencement of draft TGO

The finalised *Therapeutic Goods Order: Standards for Faecal Microbiota Transplant Products* is likely to be published in January 2020, with a commencement date of 1 January 2021, allowing a 12-month transition period for sponsors to meet the requirements. A similar transition period will be introduced in *TGO 87* to allow sponsors to comply with the requirements for labelling and traceability.

Sponsors and manufacturers of FMT products who wish to do so may begin complying with the standards before 1 January 2021.

FMT products both collected and released for supply prior to 1 January 2021 are exempt from the standards. Where product has been collected prior to 1 January 2021 but released after this date, the product must comply with the standards.

[7] Cammarota G, et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 66: 569-580 (2017).
[8] Woodworth MH, et al. Laboratory Testing of Donors and Stool Samples for Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection. *J Clin Microbiol.* 55: 1002-1010 (2017).
[9] Mullish BH, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *Gut* 67: 1920-1941 (2018).
[10] Cammarota G, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* (28 Sep 2019), pii: gutjnl-2019-319548, doi: 10.1136/gutjnl-2019-319548.
[11] Bakken JS, et al. Treating *Clostridium difficile* infection with fecal microbiota transplantation. *Clin Gastroenterol Hepatol.* 9: 1044-1049 (2011); van Nood E, et al. 2013. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med.* 368: 407-415 (2013); Relman D, et al. Current consensus guidance on donor screening and stool testing for FMT. Bethesda: American Gastroenterological Association (2013); Paramsothy S, et al. Donor recruitment for fecal microbiota transplantation. *Inflamm Bowel Dis.* 21: 1600-1606 (2015); Kelly CR, et al. Update on fecal microbiota transplantation 2015: indications, methodologies, mechanisms, and outlook. *Gastroenterology* 149: 223-237 (2015); OpenBiome website: www.openbiome.org
[12] Guide to the quality and safety of tissues and cells for human application (4th ed.). Strasbourg: European Directorate for the Quality of Medicines (EDQM) (2019).

Demonstrating compliance

Compliance with these standards will need to be shown for all providers of FMT products:

- For facilities that classify as supplying FMT products that are Class 1 biologicals, **a declaration** would need to be made that they comply with all of the requirements in these standards.
- For facilities that classify as supplying FMT products that are Class 2 biologicals (or greater), they would need to submit **a dossier** demonstrating compliance with the requirements, and TGA would review and approve this supporting information. Further guidance will be provided in 2020 on the data requirements for a Class 2 dossier for an FMT product.

Consultation

Appendix 1 provides detailed guidance and justification on the requirements outlined in the draft *Therapeutic Goods Order: Standards for Faecal Microbiota Transplant Products*. A copy of the draft TGO is also included as Appendix 2.

Please review the appendices carefully to ensure that you understand the impact of the proposed standards on your FMT operations. We value your input on the specific questions raised in this paper, as well as specific feedback on any other aspects raised.

Your views are sought

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

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.

Appendix 1: Guidance on draft Therapeutic Goods (Standard for FMT Products) Order

Please note that the section and subsection numbering in Appendix 1 reflects those associated with requirements outlined in the draft TGO as shown in Appendix 2. Guidance is not provided against every requirement, only where the intent may not be clear. All requirements are mandatory.

Part 2 – General requirements

Section 7 General requirements for FMT products

The requirements are purposely general and designed to capture the principles that ensure quality and safety of FMT products. Generally, compliance with the applicable specific sections in the draft TGO ensure these requirements would be met. The requirements are largely duplicated from the requirements contained in *TGO 88*.

Subsections (2) and (4) are new and are designed to contain principles for the minimal facility requirements for manufacturers of FMT products. These principles are intentionally broad, with more specific details being provided below.

Subsection 1 Collection and manufacture

Section 7 General requirements for all faecal microbiota transplant products that are biologicals

- *In relation to the collection and manufacture of FMT products that are biologicals, a person collecting or manufacturing such products must have procedures in place that demonstrate:*
  - *(a) Steps taken to mitigate the risk of transmission of infectious agents during collection and manufacture; and*
  - *(b) Processes for notifying persons / organisations of a donor test result that is positive for, or reactive to, an infectious agent; and*
  - (c) *Criteria for acceptance and release of FMT products, based on microbial specifications.*

For subsection 1(b), a documented process must be in place to demonstrate that results of infectious disease test results are reported back to donors, where necessary.

Subsection 2 Manufacturing facilities

Section 7 General requirements for all faecal microbiota transplant products that are biologicals

(1) The manufacturing facility must ensure:

a. All manufacturing processes are clearly defined by policies and standard operating procedures, are systematically reviewed in the light of experience, and are shown to be capable of consistently manufacturing products of the required quality that comply with their specifications.

b. Qualification of equipment and reagents.

c. Validation of processes and methods.

d. All necessary resources are provided including appropriately qualified and trained personnel, adequate premises, suitable equipment, appropriate critical materials, approved procedures and instructions, suitable storage and transport.

e. Traceability of the stool from collection to recipient in order to facilitate a recall or hazard alert, if necessary, of any product suspected of not conforming to specifications, and there is also a system to handle complaints from the patient or treating physician.

f. A system is in place to ensure process and quality improvement functions and activities.

This subsection has been introduced to ensure that facilities processing and supplying FMT products that are otherwise exempt from Good Manufacturing Practice (GMP) licensing (i.e. Class 1 biologicals) still apply minimal principles to their facility. The design and construction of the facility should be suitable to the type of processing conducted, with separation of areas for minimising mix-ups / contamination.

Despite the fact that the manufacture of an FMT product takes place in a hospital, the facility and procedures should be designed and developed in a way that takes account of the requirements of Good Laboratory Practice (GLP).

Where a facility holds a TGA manufacturing licence, compliance with this subsection is achieved through complying with the requirements of the Australian cGMP. Guidance will be published in early 2020 to assist facilities on how the Australian cGMP would apply to a manufacturer of FMT products.

Subsection (2)(a)

The facility should have established working protocols that cover all aspect of the manufacturing process. This should include written procedures for handling of starting materials (stool), such as receipt and quarantine, processing, sampling, labelling, storage and release.

Subsection (2)(b)

All materials, that may affect product quality and safety, should be controlled and meet defined written specification. The level of control of each material should reflect its use and potential risk to the product.

The requirements in place at both hospitals and day care centres to use materials sourced through clinic suppliers or pharmacies are likely to meet this requirement, e.g. containers and reagents that are sterile and within expiry.

Subsection (2)(c)

Facilities, systems, equipment and processes should be tested and qualified to verify that they are operating in a valid manner. In addition, periodic evaluation should be in place to ensure ongoing effectiveness. If there are requirements to sterilise any re-usable parts, central sterile services department may be used but is required to comply with the public health requirements.

Subsection (2)(d)

The facilities must allow for the safe processing of stool (including for operators and staff), such as at least biosafety level 2, but the suitable environment for manufacture will depend on the location of the facility whether it is hospital, day care clinics, or a purpose-built manufacturing facility. A designated area for processing and storage should be used to avoid mix-ups and adding to the existing bioburden.

The premises should be adequately adapted and of sufficient size including a potential mobile unit (clean trolley) and should not be located in high traffic areas, understanding that environment design and operating practices cannot prevent the shedding of microorganisms into the environment by human operators. The trolley should also not be located under any air vents. The area should be designed and maintained to suit the operation(s) to be performed.

Pest control is a requirement by the hospitals or the clinics, and there should be records including ensuring that chemicals in use are not affecting the quality of the product.

Where appropriate, contingency plans for breakdowns in critical services should be in place, for example, hospital generators. For smaller hospitals, there may be other contingency plans in place as all processes would be affected if there is a power outage. The process in place, must be documented. If there are no generators, etcetera, it is acceptable to state that manufacturing will not occur, where considered and documented.

In hospitals there is already a requirement to ensure adequate cleaning to reduce infectious disease, and would be suitable for compliance with the minimal requirements.

Where controlled temperature conditions are required (including during transport and storage of final product), there should be temperature recording devices and records kept and reviewed. This is already a requirement in certain sections of hospitals.

The correct manufacture of FMT product relies upon well-trained people. For this reason, there should be competent personnel to carry out all the tasks in accordance with documented procedures.

Training should be given to all personnel, and the need for ongoing training should be reflected in procedures and training records.

Subsection (2)(e)

Compliance with *Therapeutic Goods Order No. 87: General requirements for the labelling of biologicals* is required, and ensures traceability of the FMT product from the point of stool collection to supply. A system must also be in place to facilitate efficient and rapid traceability of the FMT product from donation to the released product.

There also needs to be a system in place to handle any complaints or customer feedback, especially from patients or treating clinician. This concept is already a requirement for working in a hospital.

Subsection (2)(f)

Ensuring the safety of patients and personnel and improving quality have become important objectives for hospitals. Healthcare organisations are increasingly expected by governments, medical practitioners and patients and they all have introduced quality control systems and outcome improvement strategies.

As with any quality management system, there must be a review process in place. Processes that are already implemented in hospitals, including actions to address risks and opportunities, would ensure that the delivery of service is in compliance with this requirement. These include examples of the following:

- Clinical supervision and leadership
- Medical records and documentation
- Risk Management systems
- Materials Management
- Monitoring and measuring resources
  - Suppliers contracts, bio-medical testing, linen, catering, cleaning, security etc.
- Compliments and complaints handling
- Management and staff meetings
- Compliance with International Organisation for Standardisation (ISO) and NSQHS (National Safety and Quality Health Service)
  - Change management
  - Non conformances
  - Internal and external audits
  - Potential improvement to processes
- Infection Control Management plan
- Compliance to AS 4187

Your views are sought

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?

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.

Subsection 4 Critical materials

Section 7 General requirements for all faecal microbiota transplant products that are biologicals

(2) Critical materials used in collection and manufacture of FMT product must be of a design and quality that will not adversely affect the quality and safety of the FMT product.

The term 'critical material' is used for all supplies and reagents that come into **direct contact** with the stool during any stage of manufacture; this includes primary containers and collection kits. Equipment that is used in the manufacturing process of FMT products, but do not come into direct contact with stool is not a critical material, e.g. centrifuges.

Selection and evaluation of a critical material is usually via documents provided by the material manufacturer, or of testing performed by the manufacturer, to demonstrate suitability. If these documents do not provide sufficient evidence, a manufacturer may need to perform testing on critical materials to ensure they are not contaminated with or likely to introduce bacterial or other infectious agents.

Justification of the selection and evaluation of critical material should be included in any submitted dossier. Section 13 of *TGO 88* provides additional direction on the level of evidence that may need to be provided to demonstrate suitability of solutions, human- and animal-derived materials, and containers.[13]

If the solution is included in the ARTG, the manufacturer can cross reference the ARTG entry number and does not need to resubmit validation data for reassessment. The information provided should include a statement justifying that it is being used for the same purpose for which it is registered and that it meets the sterility requirements.

Where equipment and containers are in direct contact with stool, they should be either sterile single-use only, or if reusable, subject to validated and monitored cleaning and sterilisation processes to minimise risk of cross-contamination.

Part 3 – Specific requirements

Section 8 Medical and social history of prospective stool donors

This section specifies the minimum standards for assessing the suitability of a stool donor. The medical and social history is the first tier of risk minimisation in terms of stool quality and safety (including infectious disease transmission).

[13] For further guidance on adventitious agent safety of criterial materials containing or manufactured using materials of animal or human origin, please refer to ARGPM Guidance 10.

Subsection 1 Donor interview

Section 8 Requirements in relation to the medical and social history of prospective stool donors

(1) Human stool must only be collected from a donor with whom an interview to obtain the donor's medical and social history has been conducted and recorded in accordance with the following requirements:

(a) The interview must be conducted with the donor by a trained interviewer and should be a face-to-face interview; and

(b) The interview must be conducted no more than 1 month prior to the first donation, and for banked stool within 1 month after the last donation (in a donation window of no more than 2 months)

(c) An abridged medical and social history (based on a risk assessment) must be collected at the time of each donation; and

(d) For repeat donors, the interview must be repeated at least every 3 months.

This clause is adapted from *TGO 88*.[14] The Australian CWG mentions screening of donors with a careful history or personal history.[15] The EU consensus group outlines the need for a medical interview at the beginning of donor selection,[16] along with a further interview on the same day of the stool donation in order to check for any recent onset potentially harmful issue.[17] The International consensus statement talks about a clinical questionnaire examining the risk of infectious diseases, the history of disorders potentially associated with perturbation of the gut microbiota and the use of treatments that can affect the gut microbiota.[18]

It is preferred that a face-to-face interview occur with prospective donors. However, it is recognised that this may not always be possible or practicable. The use of an interview that is not face-to-face needs to be justified.

Importantly, there still needs to be a face-to-face aspect to the initial donor recruitment to meet the minimal requirements for a physical assessment of the patient. This allows a general health assessment prior to, or at the time of, stool donation. This is a key risk mitigation step in screening and monitoring the health of a potential / ongoing donor, as required by Section 10 of the draft TGO.

Obtaining preliminary information without an interviewer prior to the formal interview may be acceptable, but confirmation of information / currency of donor history must be in the presence of an interviewer. The interviewer must be familiar with, or trained in, the screening of donors of stool for the preparation of FMT products.

It is recognised that often the donor interview process is broken up into several parts when screening new potential donors. This is acceptable, but all of the criteria outlined in subsection 8(3) and 8(4) must have been covered no more than 1 month prior to a donation.

[14] Clause 9(1): *TGO 88*.
[15] Statements 1 and 2: Haifer C, et al. Consensus Guidelines for the Production and Use of Fecal Microbiota Transplantation in Clinical Practice. Manuscript submitted for publication (2019).
[16] Box 1: Cammarota G, et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 66: 569-580 (2017).
[17] Box 2: Cammarota G, et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 66: 569-580 (2017).
[18] Box 1: Cammarota G, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* (28 Sep 2019), pii: gutjnl-2019-319548, doi: 10.1136/gutjnl-2019-319548.

For returning stool donors (either for processing of fresh stool or banked stool), all of the criteria asked in the initial interview will need to be repeated with a frequency that would ensure the information has been collected within 3 months of any donation.

A proportion of the questions that relate to infectious disease risks that can change acutely must be asked of the donor and recorded at the time of each donation. It is up to the sponsor to determine and justify which questions are asked at the time of each donation. For example, questions may be directed towards symptoms suggestive of a new gastrointestinal infection (diarrhoea, nausea, vomiting, abdominal pain), an acute infection (fever, swollen lymph nodes), use of new medications, and travel to high risk locations. Cammarota et al. (2017) provides some additional guidance on the type of questions that should be regularly asked of potential stool donors.[19]

Under Subsections 9(2) and (3) of this guidance, a diagram is provided that show examples of donor workup requirements for fresh and banked stool donors.

Your views are sought

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.

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.

Subsection 3 Ineligibility criteria

Section 8 Requirements in relation to the medical and social history of prospective stool donors

(4) A donor of stool for allogeneic use who meets any of the criteria listed in Table 1 Column 1 is subject to the corresponding period of ineligibility prior to donation as set out in Table 1 Column 2

This clause and the criteria outlined in Table 1 are adapted from *TGO 88*,[20] where applicable. Additional criteria were considered from the consensus statements.

The donor interview must include questions that capture information from potential donors that relate to each of the criteria listed in Table 1. The criteria outlined in Table 1 reflect those where there is general consensus by international experts and consensus statements that these risks could impact on the quality or safety of the stool. These medical and social criteria are those that are **minimally required by TGA** to determine donor suitability. Guidance and the support for each criterion required in Table 1 are expanded on below.

[19] Box 2: Cammarota G, et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 66: 569-580 (2017).
[20] Subsection 9(4): *TGO 88*.

Table 1: Minimal medical and social criteria required to determine donor suitability

(a) A *donor known to be infected with any of the following:*

(1) HCV
(2) HBV
(3) HAV
(4) HIV-1 / HIV-2
(5) HTLV-1 / HTLV-2
(6) Syphilis

– *Permanently ineligible. For HAV and HCV, ineligible until an uninfected state can be established.*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
Yes	Yes	Yes	Yes	Yes

This clause is adapted from *TGO 88*.[21] Both the Australian and EU consensus statements note screening for the first five virus infections listed. The US review notes that HCV, HBV, HCV and HIV blood screening is recommended by all six protocols, with HTLV-1/HTLV-2 also recommended by two protocols. The UK working group recommended a questionnaire asking about known prior exposure to HIV and/or viral hepatitis. Syphilis has been added, as noted in the EU consensus statement and International consensus statement.

Guidance

The ability to allow donors to be accepted after a period of ineligibility is dependent on an uninfected state of the donor being demonstrated.

For HCV, this would mean that an individual had undergone successful anti-viral treatment and shown to be viral negative by polymerase chain reaction (PCR).

For HAV, clinical illness in some persons can be prolonged or even relapse for up to 6 months. Virus is also excreted for months following clinical recovery. To demonstrate an uninfected state a donor the sponsor should consider the most appropriate criteria, for example, the donor should initially be deferred for > 6 months, and be anti-HAV IgM negative and/or negative for NAT testing for HAV RNA.

Your views are sought

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.

[21] Table 1(a): *TGO 88*.

(b) A recipient of viable, non-human (i.e. animal) cell or tissue transplant

– *Permanently ineligible*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
No	No	No	No	No

Guidance

This clause is adapted from *TGO 88*.[22] This criterion is not listed in the Australian or EU consensus statements. It is also not listed by any of the six protocols reviewed by the US group, and is not in the UK working group statement or International consensus statement.

For recipients of viable animal cells or tissue products there is a risk of xenogeneic infections, so donors receiving such transplants should not be accepted. At the time when *TGO 88* was drafted, xenotransplant products were actively under development and clinical trials underway in several countries, but progress has been slow. In addition, for any product approved by a comparable regulatory authority, the risk of xenogeneic infections would have been considered and minimised. Therefore, although this requirement is included in the draft TGO, we believe it could be removed. Alternatively, retaining this requirement potentially future-proofs the standard should the development of xenotransplant products be reinvigorated.

Your views are sought

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?

(c) A donor with a risk of prion disease

– *Permanently ineligible*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
No	Yes	No	Yes	No

[22] Table 1(e): *TGO 88*.

This clause is adapted from *TGO 88*.[23] This criterion is not listed in the Australian CWG statement, US review or International consensus statement. However, it is listed in the EU consensus statement and by the UK working group.

This risk of transmission of prion disease is considered to be low, but the risk has not significantly changed since *TGO 88* was first drafted in 2013, and the risk of transmission through stool is possible. The guidance below clearly outlines the specific circumstances when donors should be deferred based on this risk of exposure.

Guidance

The term 'risk of prion disease' means where a donor has been exposed to the putative causative agent(s) of any one of the family of pathogenic transmissible spongiform encephalopathies through the following means:

- genetic (familial), or
- environmental, which includes donors who have lived in or visited England, Scotland, Wales, Northern Ireland or the Isle of Man for a cumulative period of six months or more, between 1 January 1980 and 31 December 1996 inclusive, or
- iatrogenic, which includes donors who have received a transfusion or injection of blood or blood components while in England, Scotland, Wales, Northern Ireland or the Isle of Man at any time since 1 January 1980 onwards.

Other situations where permanent deferral of a donor may need to be considered due to risk of prion disease include where patients have symptoms of progressive neurological disease consistent with prion disease, and where activities that could iatrogenically transfer prion disease have occurred.

(d) A donor who has ever injected, or been injected with, any drug for a non-medical reason

- *Ineligible for 5 years from last injection*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
Yes	Yes	Yes	Yes	Yes

This clause is adapted from *TGO 88*.[24] This criterion is listed in the Australian and EU consensus statements and also in the US review, UK working group statement, and International consensus statement.

Guidance

The term 'non-medical reason' refers to procedures such as recreational drug use or cosmetic procedures that are not undertaken by a registered healthcare provider. This deferral criterion is not intended to apply to individuals that have participated in clinical trials.

[23] Table 1(f): *TGO 88*.
[24] Table 1(d): *TGO 88*.

(e) A donor whose sexual practices put them at increased risk of acquiring infectious diseases that can be transmitted through stool

- *Ineligible for 12 months from last contact*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
Yes	Yes	Yes	Yes	Yes

This clause is adapted from *TGO 88*.[25] This criterion is listed in the Australian and EU consensus statements and also in the US review, UK working group statement, and International consensus statement.

Guidance

Sexual practices that are considered to increase the risk of acquiring infectious diseases that can be transmitted in stool include, but are not limited to: sexual activity with a sex-worker, sexual activity with someone who uses intravenous drugs, having a partner who lives or lived in a high HIV risk country. The donor information that informs this deferral should be determined based on risk as relevant to the nature of the product and its use.

(f) A donor with exposure to any of the following risks of acquiring a blood borne transmissible infection:

(a) mucosal splash with blood
(b) needle stick injury
(c) tattoo
(d) body piercing (including earring)
(e) acupuncture, unless performed using sterile, single-use needles

- *Ineligible for 6 months from the time of exposure, or for 4 months provided the NAT for HCV is negative*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
Yes	Yes	Yes	Yes	Yes

This clause is adapted from *TGO 88*,[26] with all criteria deemed to be equally applicable to determining suitability of a stool donor. All these criteria are listed in the EU consensus statement, UK working group statement, and International consensus statement. All these criteria are also listed in the Australian CWG statement, with the exception of acupuncture. The US review also lists these criteria, with the exception of body piercing and acupuncture.

[25] Table 1(k): *TGO 88*.
[26] Table 1(h): *TGO 88*.

Guidance

A donor with exposure to the risk of acquiring a blood borne transmissible infection must be deferred for a period that allows determination of disease development, and that they test negative for the HIV, HBV and HCV.

(g) A recipient of human pituitary derived hormone

- *Permanently ineligible*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
No	No	No	No	No

This clause is adapted from *TGO 88*.[27] This criterion is not listed in the Australian or EU consensus statements. It is also not listed in the US review, UK working group statement, or International consensus statement.

Between 1967 and 1985, cadaver derived pituitary hormones were supplied in Australia to a total of 2,163 people.[28] Supply was ceased after overseas reports of deaths from Creutzfeldt-Jakob disease (CJD) in people who received treatment. The first case of CJD in a pituitary hormone recipient in Australia was in 1988, with a total of 5 cases being diagnosed, and all 5 individuals dying between 1988 and 1991. With a symptom-free incubation period of this form of CJD ranging from 4 to 30 years, and an average of 15 years based on international experience, it is now considered that there is minimal risk associated with recipients for human pituitary hormones to justify deferral. Therefore, although this requirement is included in the draft TGO, it could potentially be removed in the Australian setting. However, for donors that received the material overseas or where donors are from overseas (e.g. importation of FMT products) the demarcation of the risk may not be so clear.

Guidance

It is recognised that human derived pituitary hormone is currently not available in Australia and that synthetically-derived product is currently used. The ineligibility does not apply to potential donors that have received synthetically-derived product.

Your views are sought

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?

[27] Table 1(g): *TGO 88*.
[28] Australian Government Department of Health, Pituitary hormones initiatives [website accessed 6 Nov 2019].

(h) A donor with an active infection, unexplained fever or unexplained infectious illness that would render the stool unsuitable for manufacture

– *Ineligible for at least 2 weeks following the date of full recovery*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
No	Yes	Yes	No	Yes

This clause is adapted from *TGO 88*.[29] This criterion is not listed in the Australian CWG statement or UK working group statement. It is listed in the EU consensus statement. The US review lists the broad criterion of a 'general medical illness or use of medication that could be excreted into feces that might pose a risk to recipients'. The International consensus statement lists an 'enteric pathogen infection'.

Guidance

Clinical judgement should be used to determine the relevance of the infection, fever or illness to the suitability of the stool. This may include a list of enteric infections. Determination of a disease free-state should be established before a donor can be allowed to donate. This may include an algorithm and testing or specified parameters to demonstrate that an infection has cleared.

(i) History of functional gastrointestinal disorders

– *Permanently ineligible*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
Yes	Yes	Yes	Yes	Yes

This clause is not in *TGO 88*, but is listed in both the Australian and EU consensus statements. It is also listed in the US review, UK working group statement, and International consensus statement.

Guidance

'Gastrointestinal disorders' refer to any condition or disease that occurs within the gastrointestinal tract. A list of disorders should be maintained and justified.

(j) History of gastrointestinal malignancy or known genetic polyp condition

– *Permanently ineligible*

[29] Table 1(m): *TGO 88*.

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
Yes	Yes	Yes	Yes	Yes

This clause is new and not in *TGO 88*, but is listed in both the Australian and EU consensus statements. It is also listed in the US review, UK working group statement, and International consensus statement.

Guidance

Careful consideration should be given to the types of malignancy and polyp conditions that should result in permanent ineligibility, or where it must be clinically assessed as to the suitability of the donor. Such a list must be maintained and justified. Transmission of cancers through stool donation is generally considered low.

Examples of malignancy history that would result in a donor not being accepted may include:

- Upper digestive tract malignancies, such as oesophageal, stomach, pancreatic, liver, and gallbladder cancers, mucosa-associated lymphoid tissue (MALT) lymphoma, gastrointestinal stromal tumours cancers of the biliary tree including cholangiocarcinoma;
- Lower digestive tract malignancies, such as colorectal, and anal cancers and carcinoid tumours;
- Genetic polyps such as hereditary mixed polyposis syndrome (HMPS), familial adenomatous polyposis (FAP); Peutz-Jeghers syndrome, and juvenile polyposis syndrome (JPS).

(k) History of major gastrointestinal surgery

– *Permanently ineligible*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
Yes	No	Yes	Yes	No

This clause is not in *TGO 88*. This criterion is listed by the Australian and US review, but is not in the EU consensus statement or International consensus statement. The UK working group statement mentions 'bariatric surgery'. A number of criteria in the consensus statements may capture deferral of individuals that have undergone significant gastrointestinal surgery, for example a history of gastrointestinal malignancy or disorder.

Guidance

Clinical judgement should be used to determine the relevance of the surgery to the suitability of stool from a potential donor. This may include surgeries such as abdominal surgery, adrenalectomy, anoplasty, appendectomy, colectomy, colon resection, colostomy, haemorrhoidectomy, ileostomy, Nissen fundoplication, polypectomy, Roux-en-Y anastomosis, strictureplasty, and Whipple procedures. In addition, it is likely to include colorectal surgical disorders and a range of surgeries to treat gastrointestinal problems and diseases.

(l) Antibiotics or immunosuppressive agent use

– *Ineligible for at least 3 months following cessation of treatment*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
Yes	Yes	Yes	Yes	Yes

This clause is new and not in *TGO 88*. This criterion is listed in both the Australian and EU consensus statements. It is also listed in the US review, the UK working group statement (as 'antimicrobials'), and International consensus statement (as 'antimicrobial drugs').

Guidance

A list of antibiotics and immunosuppressive agents that should result in deferral or ineligibility of a potential donor must be maintained and justified.

Some antibiotics have a more substantial and prolonged impact on gut dysposis, so donor deferral may need to be for up to 6 months.

The list of medications may include:

· Antibiotic classes including penicillins, tetracyclines, cephalosporins, quinolones, lincomycins, macrolides, sulphonamides, glycopeptides, aminoglycosides, and carbapenems;

· Immunosuppressive drugs including glucocorticoids, cytostatics, antibodies, drugs acting on immunophilins, interferons, opioids, and TNF binding proteins;

· Antiprotozoals including antimalarial drugs, drugs for amebiasis, and miscellaneous antiprotozoals.

(m) Symptoms of a gastrointestinal illness (e.g. diarrhoea, vomiting, haematochezia, gastroenteritis) OR household contact with gastrointestinal illness

– *Ineligible for at least 1 month following exposure*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
Yes	Yes	Yes	Yes	Yes

This clause is new and not in *TGO 88*. This criterion is listed in both the Australian and EU consensus statements. It is also listed in the US review, UK working group statement, and International consensus statement.

Guidance

Where a donor is allowed to resume following recovery or exposure to a gastrointestinal illness, careful consideration should be given to the risk of transmission through donated stool. Where

the actual agent is identified, active testing for the presence may be appropriate prior to allowing the individual to be a suitable donor.

Household contacts generally refers to other individuals living in the same single residence. It is recognised that the degree of transmission that occurs between members in the household will depend on the characteristics of the household members, the degree of contact between them, and the household environment.

(n) History of any autoimmune disease

- *Permanently ineligible*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
Yes	Yes	Yes	Yes	Yes

This clause is new and not in *TGO 88*. This criterion is listed in both the Australian and EU consensus statements. It is also listed in the US review, UK working group statement, and International consensus statement.

Guidance

Microbiota dysbiosis has been shown in a number of autoimmune disorders,[30] and there has been a possible case of transmission, or autoimmune disease development following FMT transplant. Further, a recent study has found that bacteria found in the small intestines of humans can travel to other organs and trigger autoimmune responses.[31]

A list must be maintained and justified of autoimmune diseases that impact the quality of the stool and should thereby result in permanent ineligibility, or where it must be clinically assessed as to the suitability of the donor. This may include a list of autoimmune diseases with known gastrointestinal manifestations such as systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren's syndrome, Behçet's disease, progressive systemic sclerosis, polyarteritis nodosa, Kawasaki disease, inflammatory muscle disorders, giant cell arteritis, Henoch-Schönlein purpura, Takayasu arthritis, Cogan's syndrome, Churg-Strauss syndrome, Wegener granulomatosis, antiphospholipid antibody syndrome, and spondyloarthropathies.

(o) Metabolic syndrome, diabetes, or BMI > 30 kg / m^2

- *Permanently ineligible*

[30] De Luca F, Shoenfeld Y. The microbiome in autoimmune diseases. *Clin Exp Immunol.* 195: 74-85 (2019).
[31] Manfredo Vieira S, et al. Translocation of a gut pathobiont drives autoimmunity in mice and humans. *Science* 359: 1156-1161 (2018).

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
Yes	Yes	Yes	Yes	Yes

This clause is not in *TGO 88*. This metabolic criterion is listed in both the Australian (as BMI > 30 kg/m^2) and EU consensus statements (as BMI > 25 kg/m^2). The US review, UK working group statement, and International consensus statement all list a comparable criterion (as BMI > 30 kg/m^2). Most studies of people with BMI >30 show microbiota dysbiosis that could impact quality and efficacy.[32]

Guidance

A cluster of risk factors for cardiovascular disease and type 2 diabetes mellitus, which occur together more often than by chance alone, have become known as the 'metabolic syndrome'. The risk factors include raised blood pressure, dyslipidemia (raised triglycerides and lowered high-density lipoprotein cholesterol), raised fasting glucose, and central obesity.

(p) A donor with exposure to particular epidemiological situations, e.g. travel to high endemic risk areas of travellers' diarrhoea or multi-drug resistant bacteria

- *Ineligible until at least 3 months following the return from travel*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
Yes	Yes	Yes	Yes	Yes

The general requirement for deferral of donors exposed to epidemiological situations is specified in *TGO 88*, but not any of the consensus and working groups.

However, deferral of donor at high risk of travellers' diarrhoea or multi-drug resistant organism (MDRO) exposure are listed in both the Australian and EU consensus statements. The US review and UK working group statement both mention travel to tropical countries. The International consensus statement lists 'high-risk travel'.

Guidance

This deferral is intentionally broad to encompass unforeseen infectious disease risks, e.g. an epidemic or other emerging or re-emerging infectious disease outbreak. It is the responsibility of the sponsor to demonstrate that a process is in place to satisfactorily monitor, assess and action epidemiological situations relevant to their products.

For travel based-deferrals, documented procedures must be in place to record the countries where crucial infectious diseases are endemic or where there is an outbreak. The deferral may be based on a country of travel, or where the endemic agent may be localised to a local area within that country. World Health Organization (WHO) maintains and publishes a list of

[32] Ley RE, et al. Obesity alters gut microbial ecology. *PNAS* 102: 11070-5 (2005); Aron-Wisnewsky J, et al. Major microbiota dysbiosis in severe obesity: fate after bariatric surgery. *Gut* 68: 70-82 (2019).

countries where specific diseases (e.g. malaria, Zika virus, dengue fever, Ebola virus disease, West Nile Virus [WNV]) are present.

(q) A donor with any of the high risk factors for multi-drug resistant organisms (MDROs):

(4) Healthcare workers with exposure to patients in hospitals or long-term care facilities
(5) Persons who have recently been hospitalised or discharged from long-term care facilities
(6) Persons who regularly attend outpatient medical or surgical clinics
(7) Persons who have recently engaged in medical tourism

– *Deferral until carrier-free state has been demonstrated*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
Yes	Yes	Yes	No	Yes

This clause is not in *TGO 88*. This criterion is listed in both the Australian and EU consensus statements. It also follows on from the recent safety alert by the US FDA of the potential risk of serious or life-threatening bacterial infections caused by MDROs through the use of FMT products. The details of these clinical cases were published online on 30 October 2019.[33] The UK working group does not list this criterion, while the US review lists 'employment in clinical work'. The International consensus statement lists 'recent hospitalisation or discharge from long-term care facilities' and 'engaged in medical tourism'.

Guidance

These questions were recently identified as key questions that should be asked of potential donors, to exclude those at risk of being carriers of MDROs. Where a donor meets one of these criteria from an active or recent exposure, they should be deferred or deemed ineligible. However, where the exposure is no longer relevant the individual stool must still be tested and a carrier-free status determined to allow then to be a stool donor.

(r) A donor who has been vaccinated with a live vaccine, where there is a risk of transmission

– *Consistent with defined criteria for the particular vaccine used*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
No	No	No	Yes	Yes

This clause is adapted from *TGO 88*.[34] This criterion is not listed in Australian and EU consensus statements, and is not in the US review. It is listed in the UK working group statement and International consensus statement. There is evidence that a number of live vaccine strains are

[33] DeFilipp Z, et al. Drug-Resistant *E. coli* Bacteremia Transmitted by Fecal Microbiota Transplant. *N Engl J Med.* (30 Oct 2019). doi: 10.1056/NEJMoa1910437.
[34] Subsection 9(10): *TGO 88*.

shed for long periods of time following vaccination.[35] For some vaccines, e.g. oral polio vaccine, there is also evidence the strain could cause pathogenic infections in immunocompromised individuals.[36]

Guidance

This clause has been limited to deferral of a potential donor exposed to live vaccines. The length of deferral should be based on knowledge of the length of persistence of the vaccine agent, testing of the donor, or based on the assessment of the risk to use of stool for transplantation.

For example, with the rotavirus vaccine there is evidence the virus is shed for up to 14 weeks following vaccination and transmission can cause gastroenteritis, so a deferral of 4-6 months may be appropriate.

(s) A donor with known exposure to any of the following:

(i) HCV
(ii) HIV-1 / HIV-2
(iii) HTLV-1 / HTLV-2
(iv) Syphilis

– *Ineligible until an uninfected state can be established*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
No	Yes	Yes	Yes	No

This clause is adapted from *TGO 88*.[37] Donors with a history or, or known exposure to these organisms are not listed in the Australian or International consensus statements. They are listed in the US review, UK working group statement, and the EU consensus statement. This is an important 'catch-all' provision to identify donors that have been exposed to these organisms, but have not been tested to confirm whether transmission occurred to them or not.

(t) A donor with known exposure to HBV

– *Permanently ineligible, except for HBsAg negative persons who are demonstrated to be immune or demonstrated to have never been exposed.*

– *For HBsAg negative persons who are demonstrated to be immune or never exposed, no ineligibility period applies provided the NAT for HBV is negative.*

[35] Yen C, et al. Detection of fecal shedding of rotavirus vaccine in infants following their first dose of pentavalent rotavirus vaccine. *Vaccine* 29: 4151-5 (2011).
[36] Kotton CN. Vaccination and immunization against travel-related diseases in immunocompromised hosts. *Expert Rev Vaccines* 7: 663-72 (2008).
[37] Table 1(b): *TGO 88*.

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
No	Yes	Yes	Yes	No

This clause is adapted from *TGO 88*.[38] Donors with a history or, or known exposure to HBV is not listed in the Australian or International consensus statements. It is listed in the US review, UK working group statement, and the EU consensus statement. This is an important 'catch-all' requirement to identify donors that have been exposed to these organisms, but have not been tested to confirm whether transmission occurred to them or not.

Guidance

Demonstration of immunity to HBV would be determined by a testing algorithm that is informed from evidence in scientific literature or other reliable sources.

Donors suspected of being infected with HBV who are HBsAg negative are considered to be 'immune' if both of the following are true:

- They have an antibody titre to HBsAg at a level greater than or equal to 100 IU/L (or 100 mIU/mL); and
- HBV NAT is negative.

Donors suspected of being infected with HBV who are HBsAg negative are considered to be 'not exposed' if they test negative for antibodies to HBsAg and test negative by HBV NAT.

For HBsAg negative persons who are demonstrated to be immune or never exposed, no ineligibility period applies.

(u) A recipient of allogeneic blood, blood components or human derived clotting factors, organs, cells or tissues that are not in accordance with the requirements of Therapeutic Goods Order No. 88: Standards for donor selection, testing and minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products (TGO 88)

- *Ineligible for 6 months from the time of exposure, or for 4 months provided the NAT for HCV is negative*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
No	No	No	No	No

This clause is adapted from *TGO 88*.[39] This criterion is not listed in the Australian or EU consensus statements. It is also not listed in the US review, UK working group statement, or

[38] Table 1(c): *TGO 88*.
[39] Table 1(j): *TGO 88*.

International consensus statement. *TGO 88* is only applicable in Australia, and ensures the quality and safety of transplants after the date it came into operation.

Guidance

If a potential donor has received allogeneic blood, blood components or human derived clotting factors, cells or tissues, the sponsor must ensure that the product the donor received is compliant with *TGO 88*. Where the patient received these products in Australia after 31 May 2014, it can be assumed that they comply with the TGO.

(v) An inmate of a prison

- *Ineligible for 12 months from date of release (when imprisoned for a consecutive period of 72 hours or more)*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
Yes	No	No	No	No

This clause is adapted from *TGO 88*.[40] This criterion is listed in the Australian CWG statement but is not in the EU consensus statement. It is also not specifically listed in the US review, UK working group statement, or International consensus statement. However, all of the international positions include reference to donors at 'risk of transmissible diseases', 'known exposure to HIV and/or viral hepatitis' and 'high risk sexual behaviour', all which might include exclusion of an individual that was an inmate of a prison.

There is a known close relationship between imprisonment, drug use, and sexually-transmitted and blood-borne virus infections, such as hepatitis B and C.

(w) A donor working with animals as an occupation (where transmission of zoonotic infections is likely)

- *Deferral until 3 months following exposure*

Summary of position in FMT consensus statements:

Australia	EU	US	UK	International
No	Yes	No	No	No

This clause is not in *TGO 88*. This criterion is not listed by the Australian CWG, the US review, UK working group statement, or International consensus statement. However, it is in the EU consensus statement. Such a donor risk is considered to be a professional hazard equivalent to donors at high risk of MDROs.

In Australia, the prevalence of zoonotic infections may be asymptomatic (e.g. 20-80% for Q fever). In some patients, infection can result in a self-limiting influenza-like illness, pneumonia,

[40] Table 1(l): *TGO 88*.

hepatitis, endocarditis, and osteomyelitis, or patients may experience a protracted post-Q fever fatigue syndrome. The occupations most at risk of zoonotic infections include those having regular contact with sheep, cattle or goats, abattoir work, and those assisting with animal births. However, prevalence is generally low in urban areas, with vaccination available for people in high risk groups. An alternative to deferring donors may be to test for the presence of potential zoonotic agent if the donor works with animals as a vocation.

Guidance

A list of professions where such exposure may occur should be determined. This would include high level exposure to large animal herds.

Your views are sought

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?

Other criteria

The various FMT consensus statements listed a large number of possible other donor screening ineligibility criteria. These are listed below, but the level of evidence to defer donors was determined to be too weak or not relevant in the Australian context to support inclusion in the draft TGO at this time. For example, an individual being treated for chronic therapy with proton pump inhibitors (PPIs) is likely to not be eligible as a donor due to a history of functional gastrointestinal disorders, captured by Table 1(i). In addition, an established link between disease and microbiota composition has not been sufficiently established at this time for individuals with a history of neurological, psychiatric, or pain conditions.

All of the criteria below should be considered by your facility and may be implemented in addition to the mandatory requirement outlined in this subsection.

Criterion	Australia	EU	US	UK	International
Malaria	No	Yes	No	No	No
Trypanosomiasis	No	Yes	No	No	No
Tuberculosis	No	Yes	No	Yes	No
Chronic therapy with proton pump inhibitors	No	Yes	No	Yes	Yes
History of receiving growth hormone	No	No	No	No	Yes
History of receiving insulin from cows	No	No	No	No	Yes
History of receiving growth hormone	No	No	No	No	Yes
Family history of colon cancer	No	No	No	No	Yes

Criterion	Australia	EU	US	UK	International
History of neurological / psychiatric / pain conditions	No	Yes	Yes	Yes	Yes

Your views are sought

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.

Subsection 4 Autologous use

Section 8 Requirements in relation to the medical and social history of prospective stool donors

(5) Where stool is collected from a donor for autologous use, the manufacturer and sponsor must determine, based on a risk assessment and considering the nature and intended use of the stool, which if any of the medical and social history criteria set out in Table 1 Column 1 will apply.

We understand that stool may be collected from a donor and frozen for a period of time prior to certain treatments, for re-infusion to that patient at a later time. This subsection outlines a provision that allows treating physicians to determine the extent of the medical and social history to be recorded for when stool is collected in such circumstances for autologous use. There is an expectation that a risk-assessment has been performed and a decision recorded to justify the level of donor medical and social history taken.

Your views are sought

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

Subsection 5 Changing donor criteria for banked FMT products

Section 8 Requirements in relation to the medical and social history of prospective stool donors

Ø *When the criteria for donor medical and social history change during the life of any FMT product; and when that product has been banked, the suitability of the donation must be reassessed against the new criteria prior to release of the product.*

A policy should be in place that reviews the suitability of banked stool in instances where the donor interview criteria change during the storage period.

Subsection 6 Exemptions of donor criteria

Section 8 Requirements in relation to the medical and social history of prospective stool donors

(3) FMT product must not be manufactured from a donor who is known to have a disease or condition that may compromise the quality, safety or efficacy of the FMT product for the intended therapeutic purpose, unless:

(i) Criteria for donor acceptance and periods of donor ineligibility, as justified by the sponsor or manufacturer, in that it supports the quality, safety, and efficacy of the product for its intended therapeutic purpose, are applied for donors with the specified disease or condition; or

(ii) Where the disease or condition has not been specifically identified in the donor acceptance and deferral criteria, and where individual donors are subject to review and subsequent acceptance by the sponsor or manufacturer's medical officer. The rationale for such acceptance must be recorded.

In addition to the ineligibility criteria outlined in subsection 8(3), this subsection outlines a general requirement that requires sponsors to consider clinical presentations, quality of the stool, general donor health status, and conditions that have been associated with gut dysbiosis that may compromise the quality, safety or efficacy of the FMT product for the intended therapeutic purpose. This subsection provides flexibility to implement additional criteria that may result in rejection of a donor group based on emerging evidence.

A sponsor must have a list of criteria and the relevance of this list must be actively monitored. This is crucial in what is a rapidly evolving environment around the quality and safety of FMT products.

Where there is evidence of a condition or disease that may be transmissible, donor exclusion must occur. However, there is a wide range of conditions where an association with gut dysbiosis has been suggested or demonstrated, but the current level of evidence to defer donor is low. This includes the following:

- Atopic disease
- Chronic pain conditions
- Medicated psychiatric disease
- Neurological disease
- Non-GI malignant disease
- Developmental disorder
- Chronic fatigue
- Autism spectrum disorder
- Attention deficit hyperactivity disorder (ADHD)

For most of these conditions, a clinical judgement is also required to determine the suitability of an individual donor.

This list of conditions (and others) for deferral of donors was considered by numerous FMT consensus groups worldwide. The Australian CWG judged that the grade of evidence as 'very low' and the strength of recommendation as 'weak'.[41] The concern was the lack of a clear causative link for transmission of these conditions through FMT, as opposed to the only potential impact being on the quality of the FMT product. By contrast, the EU consensus statement lists a 'history of neurological/neurodegenerative disorders' and 'history of psychiatric conditions' as being key issues (i.e. screening requirements).[42] The US review lists 'history of chronic pain syndromes (fibromyalgia, chronic fatigue) or neurologic or neurodevelopmental disorders' in five of the six protocols, and 'history of psychiatric conditions' in one of the six protocols.[43] The UK working group lists 'history of chronic pain syndromes, including chronic fatigue syndrome and fibromyalgia' and 'any neurological or psychiatric conditions'.[44] The International consensus statement lists a 'personal history of neurological / neurodegenerative disorders' and of 'psychiatric / neurodevelopmental conditions' as disorders potentially associated with perturbation of the gut microbiota.[45]

Other examples of criteria that may be applied by sponsors to defer donors includes a visual assessment of their stool against the Bristol stool scale,[46] or where the results of general blood tests could be suggestive of an underlying metabolic disease.

If TGA become aware of a new safety or quality aspect that should be considered in the donor interview, then we may contact sponsors directly. An example of this would be the recent safety alert from the US FDA in June 2019 to providers of FMT products of the need to add additional questions and testing to address the risk of transmission of MDROs.[47]

Your views are sought

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?

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.

[41] Statement 4: Haifer C, et al. Consensus Guidelines for the Production and Use of Fecal Microbiota Transplantation in Clinical Practice. Manuscript submitted for publication (2019).
[42] Box 1: Cammarota G, et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 66: 569-580 (2017).
[43] Table 1: Woodworth MH, et al. Laboratory Testing of Donors and Stool Samples for Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection. *J Clin Microbiol.* 55: 1002-1010 (2017).
[44] Box 1: Mullish BH, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *Gut* 67: 1920-1941 (2018).
[45] Box 1: Cammarota G, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* (28 Sep 2019), pii: gutjnl-2019-319548, doi: 10.1136/gutjnl-2019-319548.
[46] Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol.* 32: 920-924 (1997).
[47] DeFilipp Z, et al. Drug-Resistant *E. coli* Bacteremia Transmitted by Fecal Microbiota Transplant. *N Engl J Med.* (30 Oct 2019). doi: 10.1056/NEJMoa1910437.

Subsection 7 Age limits

Section 8 Requirements in relation to the medical and social history of prospective stool donors

(4) There must be criteria for upper and lower age limits for stool donors to ensure that the donor age is appropriate and would not compromise the safety and efficacy of the intended therapeutic application for the donated stool.

The Australian CWG state that donors should be age 16-60.[48] The EU consensus statement is that 'individuals aged <60 years' should be preferred. However, this indication cannot be mandatory in order not to foreclose the use of healthy partners merely because of age'.[49] The UK working group suggest that 'people should only be considered as potential FMT donors if they are ≥18 and ≤60 years old'.[50] The US review is for donors to be 'age > 18 years' in five of six protocols.[51] The International consensus statement states that 'since increasing age has been associated with altered gut microbiota composition, young individuals (aged <50 years or <60 if they have completed appropriate bowel cancer screening) are preferred as potential donors'.[52]

Guidance

Age limits must be set based on the potential to compromise the safety and efficacy of the FMT product. Generally, donors should be aged between 16-60, as per the Australian CWG. For donors over the age of 50, appropriate bowel cancer screening should be completed. For donors over the age of 60, additional justification should be provided as to why quality, safety and efficacy of the stool is still appropriate.

Section 9 Donor blood and stool testing

This section specifies the minimum requirements for samples and test methods used for testing blood and stool samples of potential donors. The quality of the samples collected and validation of the methods used in donor testing is critical for determining donor suitability.

Subsection 1 Collection and testing: general

Section 9 Requirements in relation to donor blood and stool testing

(6) To determine the suitability of a person for stool donation, samples of the person's blood must be collected using aseptic procedures, and samples of stool must also be collected. These samples must be tested in accordance with this section for the purpose of donor screening.

[48] Statement 2: Haifer C, et al. Consensus Guidelines for the Production and Use of Fecal Microbiota Transplantation in Clinical Practice. Manuscript submitted for publication (2019).
[49] Cammarota G, et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 66: 569-580 (2017).
[50] Mullish BH, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *Gut* 67: 1920-1941 (2018).
[51] Table 1: Woodworth MH, et al. Laboratory Testing of Donors and Stool Samples for Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection. *J Clin Microbiol.* 55: 1002-1010 (2017).
[52] Cammarota G, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* (28 Sep 2019), pii: gutjnl-2019-319548, doi: 10.1136/gutjnl-2019-319548.

No direct demonstration of compliance with this requirement is required.

Subsections 2 and 3 Collection and testing of blood and stool samples

Section 9 Requirements in relation to donor blood and stool testing

(7) A blood sample from a stool donor must be collected and tested:

a. For fresh stool donation:

i. No more than 1 month prior to the first donation; and

ii. Every 3 months for repeat donors.

b. For banked stool donation:

i. No more than 1 month prior to the first donation and 1 month after the last donation (no less than 2 months apart), in a donation window of no more than 2 months; and

ii. Every 3 months for repeat donors.

(8) A stool sample from a stool donor must be collected and tested for quality and infectious diseases:

c. For fresh stool donation:

i. No more than 1 month prior to the first donation; and

ii. Every 3 months for repeat donors.

d. For banked stool donation:

i. No more than 1 month prior to the first donation and 1 month after the last donation (no less than 2 months apart), in a donation window of no more than 2 months; and

ii. Every 3 months for repeat donors.

These subsections aim to set out the frequency of blood and stool samples to be collected and tested from donors of FMT material. The testing to be performed on blood and stool is outlined below.

TGO 88 specifies that blood sampling for testing must take place no more than 7 days prior to or 7 days after collection of the biological. This TGO does not specify the frequency of re-testing; historically, this has not been an issue given that most tissue donation is either a single episode or infrequent. An exception is apheresis plasma donors who may have material collected every few weeks; for these donors, blood testing is repeated at every donation.

By contrast to the donor interview, there is less international consensus on the frequency and timing of donor testing, with frequency ranging from 28 to 72 days prior to donation.

The Australian CWG states that donors should have their initial screen (questionnaire, blood and stool testing) no more than 30 days prior to donation.[53] For stool banks, the Australian CWG states that a second donor screen should be completed 8 weeks after the donation.[54]

[53] Statement 5b: Haifer C, et al. Consensus Guidelines for the Production and Use of Fecal Microbiota Transplantation in Clinical Practice. Manuscript submitted for publication (2019).
[54] Statement 5a: Haifer C, et al. Consensus Guidelines for the Production and Use of Fecal Microbiota Transplantation in Clinical Practice. Manuscript submitted for publication (2019).

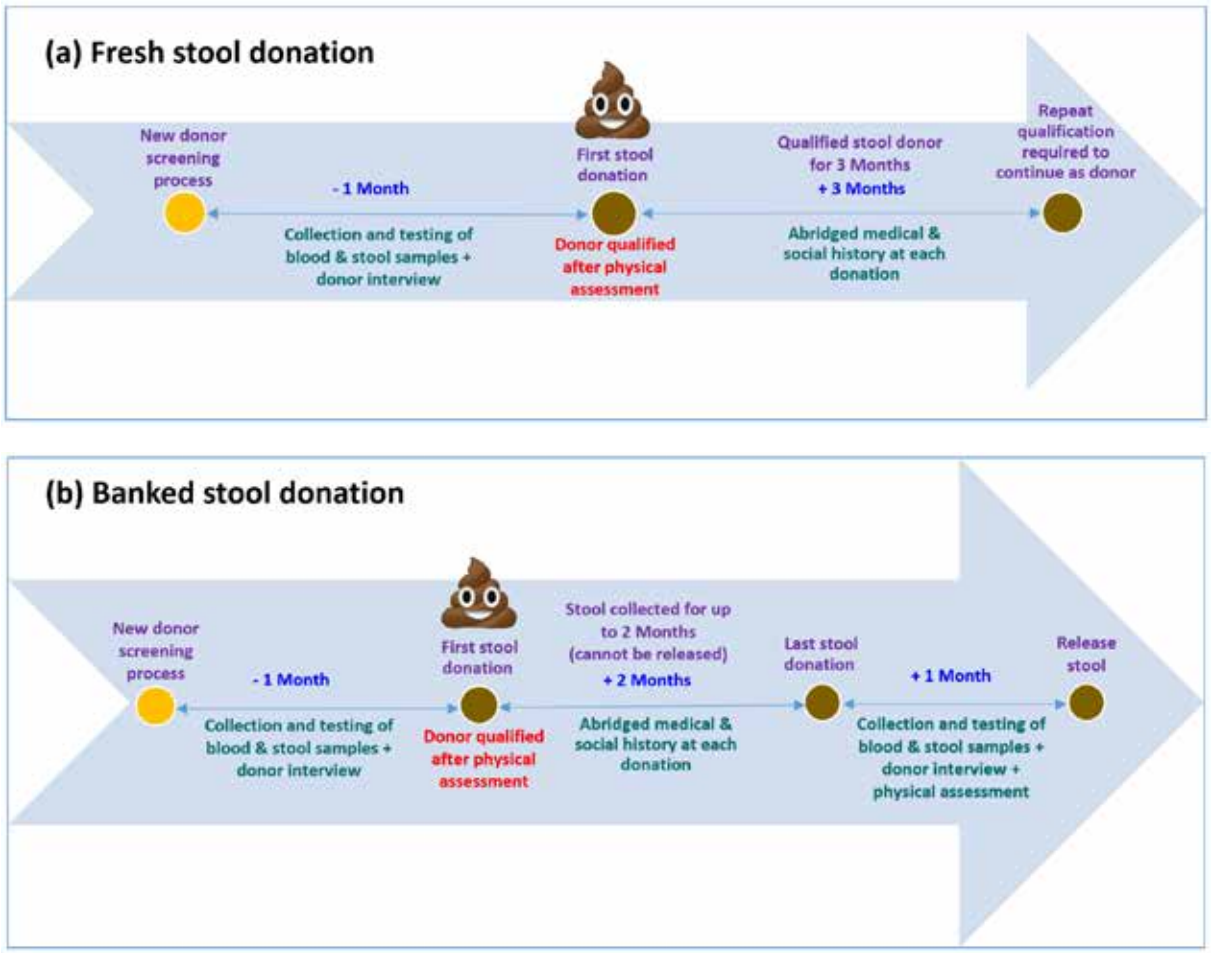
In other jurisdictions:

- The US review notes differing protocols which require sampling and testing to occur 28 to 72 days prior to donation.[55] For banked product that is placed in quarantine, there was consensus that the blood and stool samples be re-tested at the end of a 60-day collection period. US FDA seems to also encourage a third blood screen more than 2 weeks after that last donation to detect window period donations.
- The UK working group states that for fresh donors, repeat screening at least every 4 weeks and 'bookend testing' for quarantined product is acceptable.[56]
- The EU Consensus paper also agreed that sampling and testing should occur 4 weeks prior to donation, and repeated every 8 weeks if there are no changes to medical donor history.[57] This frequency is based on the excellent safety profile in several randomised controlled trials (RCTs) of FMT material.
- The International consensus statement notes that stool 'can theoretically be donated daily, and repeating a complete blood and stool screening at each donation would be unreasonable. The panel proposed several measures to guarantee the safety of donor [stool]. After initial testing, each donated [stool] aliquot should be either (1) directly tested with a rapid molecular assay for stool pathogens or (2) remain in quarantine until that donor has passed a further donor screening at the end of a period of donation (even if the donor does not wish to provide [stool] any more), and be available for administration to patients only after this further check'.[58]

The following diagrams show examples of how the donor work-up requirements are envisaged for

- fresh stool donation, and
- banked stool donation.

[55] Woodworth MH, et al. Laboratory Testing of Donors and Stool Samples for Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection. *J Clin Microbiol.* 55: 1002-1010 (2017).
[56] Mullish BH, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *Gut* 67: 1920-1941 (2018).
[57] Cammarota G, et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 66: 569-580 (2017), p. 572.
[58] Cammarota G, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* (28 Sep 2019), pii: gutjnl-2019-319548, doi: 10.1136/gutjnl-2019-319548.



For initial blood and stool sampling and testing, this must occur no more than 1 month prior to donation. For banked stool, repeat sampling and testing for blood and stool must be performed within 1 month after the last donation.

A limit of a 2-month collection window is required for banked stool, to highlight the need for repeat donor workup and testing to be performed, to ensure the infectious disease status of the donor has not changed. This is consistent with the requirement for repeat testing of returning donors every 3 months.

For all FMT donors, it is important to ensure the ongoing safety of a donor following the initial screening and testing. For this reason, all repeat stool donors, blood and stool samples must be collected and tested at least every 3 months. The need for re-testing donors more frequently should be considered if any changes are noted to a donor's medical and social history.

Note that where nucleic acid testing (NAT) is not performed on a potential donor of fresh stool, a second blood sample would need to be performed for infectious disease serology testing before any collection from that donor. Alternatively, it is possible that stool from such a donor could be frozen and quarantined for a few days, awaiting the results of the repeat serology.

For returning donors it is recognised that more frequent testing for some blood or stool infectious agents may be implemented, but at minimum all testing outlined in Section 10 must be repeated within the 3-month period. This does not place any restriction on a facility imposing a stricter testing regime, such as daily testing for certain infectious disease agents.

Your views are sought

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.

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.

Subsection 4 Collection and testing: timing

Section 9 Requirements in relation to donor blood and stool testing

(9) Donor blood and stool samples must be tested as soon as practicable after collection of the sample, and within the timeframes stipulated by the manufacturer of the test kits / methodologies being used.

Timeframes for sample testing and the review of results are specified to minimise the risk of introducing an infectious product into the routine processing operations of the manufacturing facility, and to also maximise the suitability of the samples. Generally, the testing laboratory service provider will provide direction as to how samples should be handled and maximal timeframes between sample collection and testing. Sample collection and handling should be conducted in accordance with the test kit instructions. Where sample collection and handling is performed outside the test kit instructions, validation to support the changes must be demonstrated.

Subsection 5 Test kits / methodologies

Section 9 Requirements in relation to donor blood and stool testing

(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.*

Each test kit/methodology used for the mandatory donor screening tests and confirmatory tests (if these support final product release) should be validated for the purpose for which it is to be used (intended use), and used in accordance with the test kit instructions. Where test methods are used beyond the test kit instructions, validation to support the extended use must be demonstrated; for example, where it is only approved for diagnostic purposes rather than

screening purposes (for the purpose of donor eligibility selection). For Australian testing laboratories, this would classify as a Class 4 in-house in vitro diagnostic device (IVD).

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

The most appropriate technology / methodology shall be determined and justified by the sponsor. The infectious diseases test screening protocol could be an 'in-house' test or a commercial kit and may be conducted by the sponsor or a contract laboratory. The sponsor should also consider utilising new test methods, such as more sensitive assays, as they become available.

Subsection (5)(b) Approval of test kits

If the test kit and methodology has current approval by the relevant regulatory authority in the country where the testing is performed, the evidence of this approval should be provided to TGA.

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

Subsection (5)(c) Testing facility

All facilities performing donor testing must be approved by the regulatory authority in the country where the testing is performed. For Class 1 biologicals, the hospital can determine the suitability and suitable accreditation of the facility performing infectious disease testing. For testing on stool to be used in Class 2 biologicals, a TGA licence will generally be required for domestic facilities (NATA accreditation is not sufficient), while the sponsor must hold a TGA clearance demonstrating compliance with GMP requirements for overseas testing facilities. Where confirmatory testing is utilised to decide suitability of a donor, the facility's GMP must include this purpose.

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

Test kits used in Australia for donor screening must meet the requirements of the IVD regulatory framework. For test kits used overseas, sponsors are encouraged to contact TGA to ask about kit acceptability. Sponsors using overseas testing facilities are required to have a TGA clearance for the site.

Under TGA's IVD regulatory framework, an IVD intended to detect the presence of, or exposure to, transmissible agents in blood or tissues (donated faecal material is considered to be a tissue as it contains human cells) to assess suitability for transplantation is regulated as a Class 4 IVD (or Class 4 in-house IVD). This includes both serological and nucleic acid tests (NATs). The exception to this rule is microbial culture media, which is considered a Class 1 IVD. For the majority of donor blood tests being proposed, there are Class 4 IVDs included in the ARTG that are intended for donor screening (except for Hepatitis A IgM and strongyloides). However, there are currently no Class 4 IVDs included in the ARTG for testing of stool specimens, that are intended for donor screening.

Therefore, 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. TGA is aware of the need to work with laboratories to assist them to understand what the requirements would be to fully validate these tests as Class 4 in-house IVDs.

The National Pathology Accreditation Advisory Council (NPAAC) document Requirements for the development and use of in-house in vitro diagnostic medical devices (IVDs) sets out the principles and assessment criteria by which in-house IVDs must be designed, developed, produced, validated and monitored for use by medical laboratories in Australia.

Similarly, 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. Further information is included in the Global Harmonization Task Force (GHTF) guidance document: Clinical Evidence for IVD Medical Devices - Clinical Performance Studies for In Vitro Diagnostic Medical Devices Study.

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.

Your views are sought

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?

Subsection 6 Service agreements with testing labs

Section 9 Requirements in relation to donor blood and stool testing

(11) The test kits / methodologies used for infectious disease testing must be recorded in the procedures and / or a service agreement with the contracted testing laboratory.

It is understood that for most facilities blood and stool samples are currently generally sent to pathology providers for testing, and it is up to the provider to determine the suitable assay method. To meet the requirements of this subsection, it is likely that a contractual arrangement with the pathology provider will need to be established, including stipulation of the test kits to be used, and the need for them to notify sponsors if there are changes introduced.

The reason for this requirement is 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.

Your views are sought

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?

Subsection 9 Blood (serum / plasma) and stool archiving

Section 9 Requirements in relation to donor blood and stool testing

(1) Donor stool and blood (serum / plasma) samples must be placed in long-term storage as below:

a. For blood samples, those taken in accordance with subsection 9(2) must be stored at or below minus 25°C; and

b. For stool samples, those taken in accordance with subsection 9(3), and a sample from each stool donation must be stored at or below minus 80°C; or

c. Alternative storage specifications to those specified in subsection (9)(a) and (9)(b) may be used, where validated by the sponsor or manufacturer in relation to a different temperature, or as recommended by the test kit manufacturer; and

d. Retained for a minimum of two years after the expiry date of the products.

This subsection outlines the need for sample archives to be maintained for both blood (or the serum/plasma isolated from those blood samples) and stool donor samples. The primary role of these retention samples is to allow 'look-back' of donor suitability should a safety issue be identified.

Circumstances that would be considered as a justification for a failure to archive or maintain a sample may include:

- Low sample volume;
- Breakage and loss;
- The sample is used up by relevant testing.

Failure to store a sample or loss of sample is a 'non-conformance' and should follow internal non-conformance procedures. This may be subject to review during GMP inspection, if applicable.

TGO 88 mandates blood samples (or the serum/plasma isolated from those blood samples) to be archived from all donors, and these must be retained under appropriate conditions for a minimum of two years after the expiry date of the products. *TGO 88* does not mandate sample archive of starting material, or finished product, but long-term storage of retention samples of the finished product is often imposed as a condition of ARTG registration on more complex cell therapy products where safety issues may arise.

Samples must be archived for all blood and stool samples required under subsection 9(2) and 9(3). In addition, it is possible that an adverse event requires lookback to the level of a specific stool, so archiving should occur for a sample of each stool collected from a donor.

Where facilities choose not to maintain the archived blood samples on site, arrangements will need to be made to ensure this can occur. Where samples are currently sent to pathology providers for testing it is understood that currently it is up to that provider as to whether your samples are archived, and if so, the conditions and duration. To meet the requirements of this subsection it is therefore likely that a contractual arrangement with the pathology provider will need to be established, including stipulation of the samples that need to be archives, and the storage conditions and duration.

Your views are sought

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?

Subsection 11 Results of tests: recording

Section 9 Requirements in relation to donor blood and stool testing

(9) Records on individual donors of the tests performed, test modifications, test results, analyses and any anomalies in the test results must be maintained.

The retention of records is consistent with the requirements of the cGMP. Retention times must take into account jurisdictional or hospital policies and be consistent with cGMP and clinical trial regulatory guidelines, where applicable.

The application should specify and justify record retention periods and include consideration of product risk, shelf life of product, and timeframe for which the product is expected to have a therapeutic or physiological function in the recipient. Records can be kept in paper or electronic form and be available to inspectors.

Section 10 Donor physical assessment and testing

This section specifies the requirements for the physical assessment of donors and the minimum donor infectious disease testing requirements. In addition to the medical and social history of the donor, assessment of donor blood samples and the physical assessment of the donor are further key determinants of donor acceptability. Assessment and testing of donors are critical tiers of risk mitigation for infectious disease transmission as the outcomes provide evidence of donor and product safety.

Subsection 2 Donor physical assessment

Section 10 Requirements in relation to donor physical assessment and testing

(11) A physical assessment of the potential donor must be conducted by a trained assessor, and must take place at the time of the first collection, unless justified by the sponsor.

International recommendations[59] highlight the need for a general physical examination for any starting material sourced from allogeneic donors.

Physical assessment is defined as a clinical inspection of an individual to determine suitability of the person to be a donor and may include, but is not limited to, assessing the relevance of any abrasion / laceration, bruise / haematoma, fracture, tattoo, piercing, scar, skin lesion, surgical

[59] Cammarota G, et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 66: 569-580 (2017); Woodworth MH, et al. Laboratory Testing of Donors and Stool Samples for Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection. *J Clin Microbiol.* 55: 1002-1010 (2017).

incision or other distinguishing external feature that may be indicative of a behaviour or lifestyle or suggestive of any risk factor in relation to a relevant communicable disease. Donors must be viewed by a trained individual to determine if their general health looks acceptable and that they are not suffering from an acute infection.

The exact nature of the assessment is not prescribed, but it is emphasised that the assessment must be sufficient to 'determine suitability of the person to be a donor'. The process must be appropriately documented.

Subsection 3 Repeat clinical assessment

Section 10 Requirements in relation to donor physical assessment and testing

(12) For repeat donors, the physical assessment must be repeated at least every 3 months.

As per the International consensus statement,[60] donors who repeatedly donate should undergo clinical re-assessment at regular intervals. This has been set at every 3 months, aligning with the requirement for repeat donor workup and testing.

Subsection 4 Donor blood sample testing

Section 10 Requirements in relation to donor physical assessment and testing

(13) Donor blood samples must be tested in accordance with the following requirements:

(a) Serology testing for HIV-1 / HIV-2, HBV, HCV, HTLV-1 / HTLV-2, Strongyloides stercoralis, and syphilis (Treponema pallidum); and

(b) HAV testing; and

(c) NAT for HIV-1, HBV and HCV; or

(d) Where blood is not tested by NAT as per subsection (4)(c), a repeat blood sample must be collected from the donor and repeat tested after a minimum of 3 months by serology, as per subsection (4)(a).

[60] Cammarota G, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* (28 Sep 2019), pii: gutjnl-2019-319548, doi: 10.1136/gutjnl-2019-319548.

Summary of position in FMT consensus statements:

Test	Australia	EU	US	UK	International
HIV-1/HIV-2	Yes	Yes	Yes	Yes	Yes
Hepatitis A	Yes	Yes	Yes	Yes	Yes
Hepatitis B	Yes	Yes	Yes	Yes	Yes
Hepatitis C	Yes	Yes	Yes	Yes	Yes
HTLV-1/HTLV-2	Yes	Yes	Yes	Yes	No
Strongyloides stercoralis	Yes	Yes	Yes	Yes	Yes
Syphilis (Treponema pallidum)	Yes	Yes	Yes	Yes	Yes

This clause is adapted from *TGO 88*.[61] These transmissible diseases are all listed in the Australian CWG statement.[62] The EU consensus statement lists all these transmissible diseases along with numerous others including cytomegalovirus, Epstein-Barr virus (EBV) and *Entamoeba histolytica*.[63] The UK working group lists all these transmissible diseases with the exception of syphilis (Treponema pallidum), along with numerous others including cytomegalovirus, Epstein-Barr virus (EBV) and *Entamoeba histolytica*.[64] The US review lists all these transmissible diseases with the exception of syphilis (Treponema pallidum), along with numerous others including cytomegalovirus, EBV, and *Entamoeba histolytica*.[65] The International consensus statement[66] includes Hepatitis E, which is also included in the EU statement and UK working group.

Guidance

The requirement to perform NAT is to significantly shorten the window period for detection of HIV, HBV and HCV infections. If NAT and serology testing are both performed during the donor work-up for on a potential fresh stool donor, then this is sufficient. However, if NAT is not to be performed, then a repeat blood collection and repeat serology must be performed at a minimum of 3 months apart before the donor can be accepted in to the donor program.

Despite the presence of HAV and strongyloides in stool, serology testing for these agents in the blood is currently considered as being the most sensitive test.

The onus is on the sponsor to determine the most appropriate method for screening a patient for HAV. NAT for HAV RNA is the most sensitive, subject to the lowest rate of false positives and

[61] Table 3: *TGO 88*.
[62] Statement 3B: Haifer C, et al. Consensus Guidelines for the Production and Use of Fecal Microbiota Transplantation in Clinical Practice. Manuscript submitted for publication (2019).
[63] Box 3: Cammarota G, et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 66: 569-580 (2017).
[64] Box 2: Mullish BH, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *Gut* 67: 1920-1941 (2018).
[65] Table 2: Woodworth MH, et al. Laboratory Testing of Donors and Stool Samples for Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection. *J Clin Microbiol.* 55: 1002-1010 (2017).
[66] Box 2: Cammarota G, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* (28 Sep 2019), pii: gutjnl-2019-319548, doi: 10.1136/gutjnl-2019-319548.

with the shortest window period. Otherwise, IgM anti-HAV is considered the most appropriate test method.

Your views are sought

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.

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.

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?

Other criteria

The various FMT consensus statements list a large number of possible other donor blood tests, as below.

Currently, these tests have not been specified into the draft TGO because the Australian CWG did not deem them relevant in the Australian context. For example, the epidemiology for Hepatitis E does not support testing for the organism in Australia at this time, Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) should be considered if treating immunocompromised patients only (captured by subsection 10(10)), and the general blood tests provide limited specific information that can be used to determine the suitability of a donor.

All of the blood tests below should be considered by your facility and may be implemented in addition to the mandatory requirement outlined in this subsection.

Test	Australia	EU	US	UK	International
Hepatitis E	No	Yes	No	Yes	Yes
Cytomegalovirus	No	Yes	Yes	Yes	No
Epstein-Barr virus (EBV)	No	Yes	Yes	Yes	No
Entamoeba histolytica	No	Yes	Yes	Yes	No
Complete blood count with differential	No	Yes	Yes	Yes	Yes
C-reactive protein and erythrocyte sedimentation rate	No	Yes	No	Yes	No
Albumin	No	Yes	No	Yes	No
Creatinine and electrolytes	No	Yes	No	Yes	Yes
Aminotransferases, bilirubin, gamma-glutamyltransferase, alkaline phosphatase	No	Yes	No	Yes	Yes
Complete metabolic panel	No	No	Yes	Yes	No
Liver function panel	No	Yes	Yes	Yes	No
ESR and CRP	No	No	Yes	No	No

Your views are sought

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.

Subsection 5 Test sample results

Section 10 Requirements in relation to donor physical assessment and testing

(14) For all donors except autologous donors, a test indicated in subsection 10(3) must demonstrate that the samples are non-reactive, or confirmatory testing must confirm the result as being a false positive.

The term 'non-reactive' is intended to include other terminology for the same test result such as 'negative' and 'not detected'.

Generally, if any test required by subsection 10(3) is reactive, stool must not be collected from the donor. However, it is possible that confirmatory tests can be performed to determine if a 'reactive' result is true or represents a false positive result. The use of any confirmatory testing in the determination of determining donor suitability must be justified. If any test required by subsection 10(3) is reactive, stool must not be collected from the donor.

The policy for determining the individual infectious disease status based on test results must be documented. For example, HBV testing algorithms may be used to interpret the status of the donor: NAT positive/serology negative or NAT negative/serology positive results.

Subsection 8 Microorganisms in stool

Section 10 Requirements in relation to donor physical assessment and testing

(1) Stool samples from all potential donors must be screened and shown to not contain a list of specified microorganisms that impact the quality and safety of the stool and include:

- *a. Clostridioides difficile*
- *b. Salmonella spp.*
- *c. Shigella spp.*
- *d. Campylobacter spp.*
- *e. Giardia*
- *f. Cryptosporidium spp.*
- *g. Entamoeba histolytica*
- *h. Norovirus*
- *i. Rotavirus*
- *j. Enterovirus*
- *k. MDROs including vancomycin-resistant enterococci (VRE), extended-spectrum β-lactamase (ESBL), and carbapenem-resistant enterobacteriaceae (CRE)*
- *l. Helicobacter pylori, where the FMT product is delivered by upper gastrointestinal route*

Summary of position in FMT consensus statements:

Test	Australia	EU	US	UK	International
Clostridioides difficile	Yes	Yes	Yes	Yes	Yes
Salmonella spp.	Yes	Yes	Yes	Yes	Yes
Shiga-toxin producing Escherichia coli	No	Yes	Yes	Yes	Yes
Shigella spp.	Yes	Yes	Yes	Yes	Yes
Campylobacter spp.	Yes	Yes	Yes	Yes	Yes
Giardia	Yes	Yes	Yes	No	Yes
Cryptosporidium spp.	Yes	No	Yes	No	Yes
Entamoeba histolytica	Yes	No	No	No	No
Norovirus	Yes	Yes	Yes	Yes	Yes
Rotavirus	Yes	Yes	Yes	Yes	Yes
Enterovirus	Yes	No	No	No	No
Multi-drug resistant organisms (MDROs) including vancomycin-resistant enterococci (VRE), extended-spectrum β-lactamase (ESBL), and carbapenem-resistant enterobacteriaceae (CRE)	Yes	Yes	Yes	Yes	Yes
Helicobacter pylori	Yes	Yes	Yes	Yes	Yes

Guidance

This subsection requires that stool samples from all potential donors must be screened and shown not to contain a list of specified microorganisms.

This list does not encompass all microorganisms that might be objectionable. The list generated by the sponsor or service provider should also consider other microorganisms that could be objectionable and which could affect the quality and safety of the stool.

The principles to be applied to determine if the presence of an organism should be actively tested for include whether the organism is transmissible, is there a reasonable association with disease in a recipient and whether there is a carrier state or acute asymptomatic window (i.e. no acute presentation obvious during clinical review or collection of donor medical history).

For some organisms, it may be more appropriate to exclude recipients rather than donors. For example, where the organism is very prevalent in stool, but the presence is only a risk for a specific group of patients or can be readily treated (prophylactic or following onset of symptoms).

The current list outlined is based largely on the organisms determined by the Australian CWG. This is an evolving area and the list needs to be reviewed regularly. The main areas where there is not consensus across the recommendations are around testing for *Entamoeba histolytica,* Shiga-toxin producing *Escherichia coli*, and Enterovirus. The justification for including these in the Australian contest is as follows:

- The prevalence of *Entamoeba histolytica* in Australia is unknown and likely to be rare, although it is known to be present in a percentage of travellers, immigrants, individuals that engage in sexual practices that put them at increased risk of acquiring infectious diseases, and in some indigenous communities. Most of the consensus statements propose testing should be carried out on stool or blood, but not both. 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.

- 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. The prevalence in Australia does not seem to justify varying from the international position.

- Testing for enteroviruses was listed in the Australian CWG statement so has been listed in the draft TGO at this time. Enteroviruses are very common and there are many types, but most infected people do not become sick or present with only mild symptoms. Therefore, it may be more appropriate to not mandate testing for enteroviruses in all donors. Instead, this is a family of viruses that would be captured by the requirement to monitor for epidemiological situations (Table 1(p)), and when there is an outbreak of a strain of enterovirus that causes more severe illness donors should be tested for and not accepted if confirmed positive.

The term 'screened' was deliberately used to cover any methods used to detect the presence of these agents such as microscopy for parasites, mass spectrometry (MS), NAT and culture methods, or other biochemical tests for toxins. As per subsection 9(5), the test kits / methodologies used for the presence of infectious agents must employ the most appropriate technology / methodology for the sample being tested. Any testing performed on these additional objectionable organisms will also qualify as Class 4 or Class 4 in-house IVDs.

This list is based on current knowledge around use in the treatment of recurrent or refractory *Clostridioides difficile* infection (CDI). Additional testing of stool and blood may be required for other clinical indications. These microorganisms are all listed in the Australian CWG statement.[67]

[67] Statement 3B: Haifer C, et al. Consensus Guidelines for the Production and Use of Fecal Microbiota Transplantation in Clinical Practice. Manuscript submitted for publication (2019).

The EU consensus statement,[68] US review,[69] UK working group,[70] and International consensus statement[71] include a comparable list of microorganisms.

Your views are sought

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.

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?

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?

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?

Other criteria

The FMT consensus statements listed a large number of possible other donor stool microorganisms that could be tested for and result in exclusion, as below. Currently, these have not been specified into the draft TGO as the Australian CWG did not deem them relevant in the Australian context, and there appears to be no strong position on whether to include them or not from the other consensus groups.

All of the organisms below should be considered by your facility and may be implemented in addition to the mandatory requirement outlined in this subsection.

[68] Box 3: Cammarota G, et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut* 66: 569-580 (2017).
[69] Table 3: Woodworth MH, et al. Laboratory Testing of Donors and Stool Samples for Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection. *J Clin Microbiol.* 55: 1002-1010 (2017).
[70] Box 3: Mullish BH, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *Gut* 67: 1920-1941 (2018).
[71] Box 2: Cammarota G, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* (28 Sep 2019), pii: gutjnl-2019-319548, doi: 10.1136/gutjnl-2019-319548.

Microorganisms and other test agents	Australia	EU	US	UK	International
Yersinia spp.	No	Yes	No	No	Yes
Methicillin-resistant staphylococcus aureus	No	Yes	No	No	No
Gram-negative multidrug-resistant bacteria	No	Yes	No	No	No
Protozoa (including Blastocystis hominis) and helminths and parasites	No	Yes	No	No	Yes
Faecal occult blood testing	No	Yes	No	No	No
Vibrio cholera	No	Yes	No	No	Yes
Listeria monocytogenes	No	Yes	No	No	No
Isospora and Microsporidia	No	Yes	No	No	Yes
Calprotectin	No	Yes	No	No	No
Adenovirus	No	No	Yes	No	Yes
Ovum and parasite microscopic examination	No	No	Yes	Yes	No
Microsporidia microscopic examination	No	No	Yes	Yes	No
Isospora and Cyclospora microscopic examination	No	No	Yes	Yes	No

Your views are sought

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.

Subsection 9 Conditions for stool rejection

Section 10 Requirements in relation to donor physical assessment and testing

(8) Where the presence of a specified microorganism, as specified in subsection 10(8), is detected, stool from that donor must not be used for the manufacture of FMT products.

Where the presence of specified microorganism screened for in subsection 10(7) is detected, stool from that donor must be rejected for therapeutic use. However, donors may be allowed to re-donate once stool samples are shown to be clear of the specified microorganism.

Generally, where an organism is detected at the end of a donation cycle, the whole batch must not be used for manufacture of FMT product. However, further testing of stool could be performed on earlier donations to determine the suitability of some of the batch of stool from that donor. The donor should also be counselled to identify the potential change in circumstances that led to the organism being present in the stool, and the exposure risk should be considered in determining the suitability of any of the batch of stool.

Subsection 10 Blood and stool testing in specific situations

Section 10 Requirements in relation to donor physical assessment and testing

(9) In specific situations, such as when use is indicated for particular high-risk patients, additional blood and stool testing should be performed.

Additional testing of blood and / or stool may be required for specific high risk patient groups and for specific clinical indications. Where such patient groups may be treated, a list of additional microorganisms must be provided and the choice of organisms to be tested must be justified, for example, CMV and EBV.

Section 11 Microbial control

Subsection 1 Transport and storage of donated stool prior to processing

Section 11 Requirements in relation to microbial control

(9) The stool should be processed as soon as possible following defecation (within 6 hours), and the stool should be cooled to 4 ℃ if there is any delay to the transportation or processing, unless otherwise validated by the manufacturer.

Where the stool donation does not occur at the manufacturing site, it is important that the stool should be cooled during any temporary storage or during transport and delivery to the stool bank. This requirement must be clearly communicated with stool donors, and enforced.

However, allowance has been made for manufacturers to justify and set their own transport and storage temperature requirements.

The requirement for stool to be processed as soon as possible following defecation does not imply that processing must be complete within 6 hours. The freezing of stool, prior to future additional processing steps, is considered a step in processing and would be sufficient to meet this requirement.

The UK working group recommends that stool be transported to the FMT production site as soon as possible post defaecation (and within 6 hours).[72]

The International consensus statement states that stool should be transported to the stool bank as soon as possible after defaecation to ensure that manipulation and storage is done within 6 hours. The final FMT product must be put in a special sterile container, labelled, registered, and stored at -80°C.[73]

Currently, a specified timeframe and condition is not specified for banked stool. Each sponsor must justify that the storage conditions used are appropriate to ensure quality and safety and efficacy of the stool. The addition of specific solutions and preservation agents should be justified and / or validated.

Subsection 2 Validated procedure for processing stool

Section 11 Requirements in relation to microbial control

(10) There must be a validated procedure for processing stool, including:

a. Strategy to minimise proliferation of intrinsic microbial contamination in the stool and prevent extrinsic microbial contamination of the stool, during processing; and

b. Specifications for processing temperature and duration; and

c. For fresh stool, processing and use must occur within 6 hours at ambient temperature (maximum 37°C), or under specifications set and validated by the sponsor.

The UK working group[74] and EDQM guide[75] both recommend that fresh donor stool be processed within 6 hours of defaecation.

It is acknowledged that stool is by definition not sterile. However, during processing, validated processes must be in place to prevent proliferation of the intrinsic microbial contamination of the stool, to prevent extrinsic microbial contamination of the stool and to prevent cross-contamination of between stools.

Each sponsor must justify that the storage conditions used are appropriate to ensure quality and safety and efficacy of the stool. The addition of specific solutions and preservation agents should be justified and / or validated.

[72] Box 4: Mullish BH, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *Gut* 67: 1920-1941 (2018).
[73] Box 4: Cammarota G, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* (28 Sep 2019), pii: gutjnl-2019-319548, doi: 10.1136/gutjnl-2019-319548.
[74] Mullish BH, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *Gut* 67: 1920-1941 (2018).
[75] Guide to the quality and safety of tissues and cells for human application (4th ed.). Strasbourg: European Directorate for the Quality of Medicines (EDQM) (2019), p. 406.

Subsection 4 Post-processing storage of stool and FMT products

Section 11 Requirements in relation to microbial control

(1) During processing or after processing, the storage of stool and FMT products must be:

a. At less than minus 80°C in a suitable cryopreservation agent for a maximum of 12 months; or

b. In accordance with time and temperature specifications set and justified by the sponsor; and

c. In a manner that ensures that during transport time and temperature specifications are maintained.

The EDQM guide recommends that donor stool mixed with a cryoprotectant (e.g. glycerol) could be stored at minus 80°C until required for use. [76] The UK working group recommends that banked donor stool stored at minus 80°C has a maximum shelf life of 6 months,[77] while the EDQM guide states 5-6 months and potentially even longer.[78] However, the International consensus statement states represent the most recent publication and has drawn on accumulating data out of international stool banks, and have made an informed recommendation that frozen samples should be used within 1 year from donation.[79] Some pre-clinical studies has reported loss in product viability after this time, but others have longer term data to support even longer storage conditions. All facilities are encouraged to establish long-term stability studies, potentially including accelerated conditions, to justify any further extension to the shelf-life.

The temperature and conditions used during transportation and delivery must be carefully considered, but may be different from the storage conditions. Validation data should be available to demonstrate that quality and therefore efficacy would not be impacted by any proposed transport conditions.

[76] Guide to the quality and safety of tissues and cells for human application (4th ed.). Strasbourg: European Directorate for the Quality of Medicines (EDQM) (2019), p. 407.
[77] Mullish BH, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *Gut* 67: 1920-1941 (2018).
[78] Guide to the quality and safety of tissues and cells for human application (4th ed.). Strasbourg: European Directorate for the Quality of Medicines (EDQM) (2019), p. 407.
[79] Cammarota G, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* (28 Sep 2019), pii: gutjnl-2019-319548, doi: 10.1136/gutjnl-2019-319548.

Appendix 2: Draft Therapeutic Goods (Standard for FMT Products) Order

The following is an extract from the draft TGO. Some of the initial sections have been removed for the purposes of this consultation, but the section numbering has been maintained.

Part 1 – Preliminary

Section 4 Definitions

Note: A number of expressions used in this instrument are defined in subsection 3(1) of the Act, including the following:

(a) biological;

(b) container;

(c) manufacture (in relation to therapeutic goods that are not medical devices);

(d) Secretary; and

(e) therapeutic goods.

In this instrument:

Act means the *Therapeutic Goods Act 1989*.

allogeneic use means the use of an FMT product that is derived from stool obtained from one person and administered to another person.

autologous use means the use of an FMT product that is derived from stool obtained from the same person.

banked stool means stool collected from a donor that was screened prior to donation, and the stool is stored, frozen, to allow re-testing of the donor prior to use of the donated stool to manufacture an FMT product.

blood means whole blood collected from a single human donor and used for infectious disease testing or processed either for transfusion or further manufacturing.

blood components mean any of the following therapeutic components of blood that can be prepared by centrifugation, filtration or freezing using conventional methodologies in blood establishment:

(a) red cells;

(b) white cells;

(c) platelets;

(d) plasma;

but does not include haematopoietic progenitor cells.

BMI means body mass index.

CRE means carbapenem-resistant enterobacteriaceae.

critical materials means all materials or supplies used in the collection or manufacture of:

(a) therapeutic goods; or

(b) material which is used to manufacture therapeutic goods; and

that may have a direct impact on the safety, quality or function of the goods.

ESBL means extended-spectrum β-lactamase.

faecal microbiota transplant (FMT) product means a thing that:

(a) comprises, contains, or is derived from human stool; and

(b) is for introduction into a person for a therapeutic use.

fresh stool means stool collected from a donor that was screened prior to donation, but is not stored to allow re-testing of the donor prior to use of the donated stool to manufacture an FMT product. The stool may be used on the same day of donation or banked for a few days prior to use.

HBsAg means hepatitis B surface antigen.

HAV means hepatitis A virus.

HBV means hepatitis B virus.

HCV means hepatitis C virus.

HIV-1 means human immunodeficiency virus type 1.

HIV-2 means human immunodeficiency virus type 2.

HTLV-1 means human T-lymphotropic virus type 1.

HTLV-2 means human T-lymphotropic virus type 2.

MDRO means multi-drug resistant organism.

microbial specifications means parameters that are applied to the stool during processing or to the final FMT product to ensure specified microorganisms are excluded, and intrinsic and extrinsic microbial contamination risk is minimised.

NAT means nucleic acid test.

physical assessment means a clinical inspection of a potential donor to determine suitability of the person to be a donor and may include, but is not limited to, assessing the relevance of any abrasion / laceration, bruise / haematoma, fracture, tattoo, piercing, scars, skin lesion, surgical incision or other distinguishing external feature that may be indicative of a behaviour or lifestyle, or suggestive of any risk factor in relation to a relevant communicable disease.

Regulations means the *Therapeutic Goods Regulations 1990*.

risk of prion disease means where a donor has been exposed to the putative causative agent(s) of any one of the family of pathogenic transmissible spongiform encephalopathies through the following means:

(a) genetic (familial), or

(b) environmental, which includes donors who have lived in or visited England, Scotland, Wales, Northern Ireland or the Isle of Man for a cumulative period of six months or more, between 1 January 1980 and 31 December 1996 inclusive, or

(c) iatrogenic, which includes donors who have received a transfusion or injection of blood or blood components while in England, Scotland, Wales, Northern Ireland or the Isle of Man at any time since 1 January 1980 onwards.

specified microorganism means a microorganism of clinical significance which, if isolated from the stool necessitates rejection of the product for therapeutic use.

stool means the mass of matter evacuated at a movement of the bowels; faeces.

VRE means vancomycin-resistant enterococci.

Section 5 Standard

This instrument constitutes a standard for FMT products.

Section 6 Application

(1) Subject to subsection (2), this instrument applies to therapeutic goods that are FMT products.

(2) This instrument does not apply to components of FMT products that have been purified and can be characterised by physiochemical or biological means.

Part 2 – General requirements for FMT products

Section 7 General requirements for all FMT products that are biologicals

(1) In relation to the collection and manufacture of FMT products that are biologicals, a person collecting or manufacturing such products must have procedures in place that demonstrate:

(a) Steps taken to mitigate the risk of transmission of infectious agents during collection and manufacture; and

(b) Processes for notifying persons / organisations of a donor test result that is positive for, or reactive to, an infectious agent; and

(c) Criteria for acceptance and release of FMT products, based on microbial specifications.

(2) The manufacturing facility must ensure:

(a) All manufacturing processes are clearly defined by policies and standard operating procedures, are systematically reviewed in the light of experience, and are shown to be capable of consistently manufacturing products of the required quality that comply with their specifications.

(b) Qualification of equipment and reagents.

(c) Validation of processes and methods.

(d) All necessary resources are provided including appropriately qualified and trained personnel, adequate premises, suitable equipment, appropriate critical materials, approved procedures and instructions, suitable storage and transport.

(e) Traceability of the stool from collection to recipient in order to facilitate a recall or hazard alert, if necessary, of any product suspected of not conforming to specifications, and there is also a system to handle complaints from the patient or treating physician.

(f) A system is in place to ensure process and quality improvement functions and activities.

(3) In all cases, procedures in place as required by subsection 7(1) must be followed.

(4) Critical materials used in collection and manufacture of FMT product must be of a design and quality that will not adversely affect the quality and safety of the FMT product.

Part 3 – Specific requirements for FMT products

Section 8 Requirements in relation to the medical and social history of prospective stool donors

(1) Human stool must only be collected from a donor with whom an interview to obtain the donor's medical and social history has been conducted and recorded in accordance with the following requirements:

(a) The interview must be conducted with the donor by a trained interviewer and should be a face-to-face interview; and

(b) The interview must be conducted no more than 1 month prior to the first donation, and for banked stool within 1 month after the last donation (in a donation window of no more than 2 months)

(c) An abridged medical and social history (based on a risk assessment) must be collected at the time of each donation; and

(d) For repeat donors, the interview must be repeated at least every 3 months.

(2) Donor medical and social history criteria, as required to be obtained by each of subsection 8(1), must be reviewed and evaluated using the minimum donor medical and social history criteria set out in Table 1 Column 1.

(3) A donor of stool for allogeneic use who meets any of the criteria listed in Table 1 Column 1 is subject to the corresponding period of ineligibility prior to donation as set out in Table 1 Column 2.

Table 1: Minimal medical and social criteria required to determine donor suitability

Column 1: Donor medical and social history criteria	Column 2: Period of ineligibility, related testing and notification requirements
(a) A donor known to be infected with any of the following: (i) HCV (ii) HBV (iii) HAV (iv) HIV-1 / HIV-2 (v) HTLV-1 / HTLV-2 (vi) Syphilis	Permanently ineligible. For HAV and HCV, ineligible until an uninfected state can be established.
(b) A recipient of viable, non-human (i.e. animal) cells or tissues	Permanently ineligible
(c) A donor with a risk of prion disease	Permanently ineligible
(d) A donor who has ever injected, or been injected with, any drug for a non-medical reason	Ineligible for 5 years from last injection
(e) A donor whose sexual practices put them at increased risk of acquiring infectious diseases that can be transmitted through stool	Ineligible for 12 months from last contact
(f) A donor with exposure to any of the following risks of acquiring a blood borne transmissible infection: (i) mucosal splash with blood (ii) needle stick injury (iii) tattoo (iv) body piercing (including earring) (v) acupuncture, unless performed using sterile, single-use needles	Ineligible for 6 months from the time of exposure, or for 4 months provided the NAT for HCV is negative
(g) A recipient of human pituitary derived hormone	Permanently ineligible

(h) A donor with an active infection, unexplained fever or unexplained infectious illness that would render the stool unsuitable for manufacture	Ineligible for at least 2 weeks following the date of full recovery
(i) History of functional gastrointestinal disorders	Permanently ineligible
(j) History of gastrointestinal malignancy or known genetic polyp condition	Permanently ineligible
(k) History of major gastrointestinal surgery	Permanently ineligible
(l) Antibiotics or immunosuppressive agent use	Ineligible for at least 3 months following cessation of treatment
(m) Symptoms of a gastrointestinal illness (e.g. diarrhoea, vomiting, haematochezia, gastroenteritis) OR household contact with gastrointestinal illness	Ineligible for at least 1 month following exposure
(n) History of any autoimmune disease	Permanently ineligible
(o) Metabolic syndrome, diabetes, or BMI > 30 kg / m^2	Permanently ineligible
(p) A donor with exposure to particular epidemiological situations, e.g. travel to high endemic risk areas of travellers' diarrhoea or multi-drug resistant bacteria	Ineligible until at least 3 months following the return from travel
(q) A donor with any of the high risk factors for multi-drug resistant organisms (MDROs): (vi) Healthcare workers with exposure to patients in hospitals or long-term care facilities (vii) Persons who have recently been hospitalised or discharged from long-term care facilities (viii) Persons who regularly attend outpatient medical or surgical clinics (ix) Persons who have recently engaged in medical tourism	Deferral until carrier-free state has been demonstrated

(r) A donor who has been vaccinated with a live vaccine, where there is a risk of transmission	Consistent with defined criteria for the particular vaccine used
(s) A donor with known exposure to any of the following: (i) HCV (ii) HIV-1 / HIV-2 (iii) HTLV-1 / HTLV-2 (iv) Syphilis	Ineligible until an uninfected state can be established
(t) A donor with known exposure to HBV	Permanently ineligible, except for HBsAg negative persons who are demonstrated to be immune or demonstrated to have never been exposed. For HBsAg negative persons who are demonstrated to be immune or never exposed, no ineligibility period applies provided the NAT for HBV is negative.
(u) A recipient of allogeneic blood, blood components or human derived clotting factors, organs, cells or tissues that are not in accordance with the requirements of *Therapeutic Goods Order No. 88: Standards for donor selection, testing and minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products (TGO 88)*	Ineligible for 6 months from the time of exposure, or for 4 months provided the NAT for HCV is negative
(v) An inmate of a prison	Ineligible for 12 months from date of release (when imprisoned for a consecutive period of 72 hours or more)
(w) A donor working with animals as an occupation (where transmission of zoonotic infections is likely)	Deferral until 3 months following exposure

(4) Where stool is collected from a donor for autologous use, the manufacturer and sponsor must determine, based on a risk assessment and considering the nature and intended use of the stool, which if any of the medical and social history criteria set out in Table 1 Column 1 will apply.

(5) When the criteria for donor medical and social history change during the life of any FMT product; and when that product has been banked, the suitability of the donation must be reassessed against the new criteria prior to release of the product.

(6) FMT product must not be manufactured from a donor who is known to have a disease or condition that may compromise the quality, safety or efficacy of the FMT product for the intended therapeutic purpose, unless:

(a) Criteria for donor acceptance and periods of donor ineligibility, as justified by the sponsor or manufacturer, in that it supports the quality, safety, and efficacy of the product for its intended therapeutic purpose, are applied for donors with the specified disease or condition; or

(b) Where the disease or condition has not been specifically identified in the donor acceptance and deferral criteria, and where individual donors are subject to review and subsequent acceptance by the sponsor or manufacturer's medical officer. The rationale for such acceptance must be recorded.

(7) There must be criteria for upper and lower age limits for stool donors to ensure that the donor age is appropriate and would not compromise the safety and efficacy of the intended therapeutic application for the donated stool.

Section 9 Requirements in relation to donor blood and stool testing

(1) To determine the suitability of a person for stool donation, samples of the person's blood must be collected using aseptic procedures, and samples of stool must also be collected. These samples must be tested in accordance with this section for the purpose of donor screening.

(2) A blood sample from a stool donor must be collected and tested:

(a) For fresh stool donation:

i. No more than 1 month prior to the first donation; and

ii. Every 3 months for repeat donors.

(b) For banked stool donation:

i. No more than 1 month prior to the first donation and 1 month after the last donation (no less than 2 months apart), in a donation window of no more than 2 months; and

ii. Every 3 months for repeat donors.

(3) A stool sample from a stool donor must be collected and tested for quality and infectious diseases:

(c) For fresh stool donation:

i. No more than 1 month prior to the first donation; and

ii. Every 3 months for repeat donors.

(d) For banked stool donation:

i. No more than 1 month prior to the first donation and 1 month after the last donation (no less than 2 months apart), in a donation window of no more than 2 months; and

ii. Every 3 months for repeat donors.

(4) Donor blood and stool samples must be tested as soon as practicable after collection of the sample, and within the timeframes stipulated by the manufacturer of the test kits / methodologies being used.

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

(e) The most suitable technology / methodology for the sample and agent being tested; and

(f) Approved by the relevant regulatory authority in the country in which the testing is performed; and

(g) Performed in a facility approved by the regulatory authority to perform such testing; and

(h) Considered acceptable by TGA.

(6) The test kits / methodologies used for infectious disease testing must be recorded in the procedures and / or a service agreement with the contracted testing laboratory.

(7) The results of the tests performed in accordance with Section 10 must be evaluated prior to release of the FMT product. If the results of the tests are not available, the product must not be released for supply until the results of testing become available and are evaluated.

(8) Records must be maintained that include the tests performed, test modifications, test results, analyses and any anomalies in the test results of individual donors.

(9) Donor stool and blood (serum / plasma) samples must be placed in long-term storage as below:

(i) For blood samples, those taken in accordance with subsection 9(2) must be stored at or below minus 25°C; and

(j) For stool samples, those taken in accordance with subsection 9(3), and a sample from each stool donation must be stored at or below minus 80°C; or

(k) Alternative storage specifications to those specified in subsection (9)(a) and (9)(b) may be used, where validated by the sponsor or manufacturer in relation to a different temperature, or as recommended by the test kit manufacturer; and

(l) Retained for a minimum of two years after the expiry date of the products.

(10) When the testing requirements mentioned in Section 10 change while a product is in storage, where possible a donor's archived samples must be retested with the new screening test protocol prior to release of the product. The requirement to retest is to be determined by the sponsor or manufacturer based on a risk assessment, and after consultation with TGA.

(11) Records on individual donors of the tests performed, test modifications, test results, analyses and any anomalies in the test results must be maintained.

Section 10 Requirements in relation to donor physical assessment and testing

(1) All potential donors of stool must be tested and evaluated in accordance with this section before the stool is released from that donor for manufacture of an FMT product.

(2) A physical assessment of the potential donor must be conducted by a trained assessor, and must take place at the time of the first collection, unless justified by the sponsor.

(3) For repeat donors, the physical assessment must be repeated at least every 3 months.

(4) Donor blood samples must be tested in accordance with the following requirements:

(a) Serology testing for HIV-1 / HIV-2, HBV, HCV, HTLV-1 / HTLV-2, Strongyloides stercoralis, and syphilis (Treponema pallidum); and

(b) HAV testing; and

(c) NAT for HIV-1, HBV and HCV; or

(d) Where blood is not tested by NAT as per subsection (4)(c), a repeat blood sample must be collected from the donor and repeat tested after a minimum of 3 months by serology, as per subsection (4)(a).

(5) For all donors except autologous donors, a test indicated in subsection 10(3) must demonstrate that the samples are non-reactive, or confirmatory testing must confirm the result as being a false positive.

(6) In cases where stool is manufactured for autologous use from a donor with repeatedly reactive mandatory screening tests as set out in subsection 10(3), segregation and quarantine must be applied to that stool and FMT product, and the rationale for the use of the product must be recorded.

(7) Written specifications for stool must include a list of specified microorganisms, so that where there is evidence in sampled blood or stool of active infection by any of the specified microorganisms, stool from that donor must be rejected for therapeutic use until the specified microorganism has been cleared by follow-up testing.

(8) Stool samples from all potential donors must be screened and shown to not contain a list of specified microorganisms that impact the quality and safety of the stool and include:

(a) Clostridioides difficile

(b) Salmonella spp.

(c) Shigella spp.

(d) Campylobacter spp.

(e) Giardia

(f) Cryptosporidium spp.

(g) Entamoeba histolytica

(h) Norovirus

(i) Rotavirus

(j) Enterovirus

(k) MDROs including vancomycin-resistant enterococci (VRE), extended-spectrum β-lactamase (ESBL), and carbapenem-resistant enterobacteriaceae (CRE)

(l) Helicobacter pylori, where the FMT product is delivered by upper gastrointestinal route

(9) Where the presence of a specified microorganism, as specified in subsection 10(8), is detected, stool from that donor must not be used for the manufacture of FMT products.

(10) In specific situations, such as when use is indicated for particular high-risk patients, additional blood and stool testing should be performed.

(11) This list of microorganisms is non-exhaustive and includes the ability to add new and emerging infectious agents and epidemiological situations where necessary.

Section 11 Requirements in relation to microbial control

(1) The stool should be processed as soon as possible following defecation (within 6 hours), and the stool should be cooled to 4°C if there is any delay to the transportation or processing, unless otherwise validated by the manufacturer.

(2) There must be a validated procedure for processing stool, including:

(a) Strategy to minimise proliferation of intrinsic microbial contamination in the stool and prevent extrinsic microbial contamination of the stool, during processing; and; and

(b) Specifications for processing temperature and duration; and

(c) For fresh stool, processing and use must occur within 6 hours at ambient temperature (maximum 37°C), or under specifications set and validated by the sponsor.

(3) After processing, stool must be sealed within a sterile container as to:

(a) Prevent ingress / egress of the stool; and

(b) Ensure that any breach of integrity of the container will be evident.

(4) During processing or after processing, the storage of stool and FMT products must be:

(a) At less than minus 80°C in a suitable cryopreservation agent for a maximum of 12 months; or

(b) In accordance with time and temperature specifications set and justified by the sponsor; and

(c) In a manner that ensures that during transport time and temperature specifications are maintained.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Biological Sciences Section, Scientific Evaluation Branch	November 2019

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

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