OPTIONS FOR THE REGULATION OF FMT MATERIALS (FMTM)

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BACKGROUND

Faecal microbiota transplantation (FMT), the infusion of FMT material/s (FMTM) from a healthy individual into a recipient, has been employed sporadically in modern medicine since 1958[1-3] and used in Australia clinically since 1988[42]. Originally employed as a treatment of last-resort for life-threatening fulminant *Clostridioides difficile* infection (CDI),[1-3] it emerged as an effective treatment during the CDI epidemic, where it consistently achieved cure rates >90% in patients who had previously failed antibiotics.[4-6] Since then, owing to its unique mechanism/s of action, it is increasingly being investigated for the treatment of various conditions in which the gut microbiome (GM) is hypothesized to play a role and where a high unmet need exists (e.g. Inflammatory Bowel Disease, Parkinson's disease, multiple sclerosis, autism, ulcerative colitis, diabetes etc).[7] Given the increasing use of FMT and its perception as a therapeutic product, it was perceived that regulatory oversight is required as is required for drugs.

Although *clinical practice,* which may include FMT, does not technically fall under the governance of the Therapeutic Goods Administration (TGA), the production and supply of FMTM can be perceived as supplying a 'substance' which resembles a therapeutic product. With increasing use of FMT in Australia, regulation of FMTM has been placed under the microscope, and it is now crucial that appropriate regulation be developed. In order to do so, it is instructive to learn from the US experience. In May of 2013, the US Food and Drug Administration (FDA) announced that FMT would be regulated as a 'drug' (requiring an investigational new drug [IND] application),[8] a move that was widely criticized by physicians and patients alike due to concerns that it would impede access to this therapy and stifle research. Following these concerns, the FDA revised its decision and advised that it would "exercise enforcement discretion" regarding IND requirements.[8] However, the FDA has maintained that the enforcement discretion policy does not apply to other uses of FMT, including research or treatment of conditions other than recurrent CDI(rCDI), and these require an IND.

The FDA guidance or rules have inadvertently slipped into the minds of a number of Australian FMT stakeholders, to the extent that some have fallen into the trap of thinking that the FDA

rules apply in Australia. A number of patients in Australia were refused to have an FMT treatment for CDI until they had failed 2 antibiotic therapies and therefore they had a prolonged wait for FMT. Such a delay has caused patients to travel from other states to Sydney for their FMT. It is well known that this FDA rule of initially using antibiotics is not evidence-based. There is no scientific reason why we cannot treat with FMT on the first diagnosis of CDI. Delaying treatment has potentially caused a number of deaths in the US.

There is a current rethinking of the FDA position in the US and the FMT stakeholders have called for reconsideration of the FDA classification of FMT as a drug (fmt working group **[REDACTED]**).

On the 10th of October, 2018, an FMT stakeholder meeting was convened in Melbourne, Australia to gather views from key opinion leaders delivering FMT in Australia. The purpose of this meeting was to determine a suitable regulatory framework that allows safe access to FMTM in Australia without inhibiting current clinical use of FMT by overburdening clinicians with unrealistic regulations. The key message from this stakeholder meeting was that FMT may fall outside the current regulatory 'boxes' (Discussion Paper: Regulation of FMT 2018).

SAFETY: SHORT AND LONG-TERM ADVERSE EFFECTS OF FMT

This topic is relevant under "Options' discussion because oversight, regulation, GMP – all refer to safety and express some concern about adverse events.

Despite an estimated number of >70,000 FMT procedures carried out worldwide to date, there has **not been a single documented case of infection transmission from FMTM** itself. In a systematic review examining adverse events with FMT from 50 publications comprising 1089 patients, an adverse event rate of 28.5% was reported, with most being mild-to-moderate in nature. However, closer inspection revealed these to either be as a *result of the delivery method itself or as a result of the underlying gastrointestinal condition/illness*.[9] This was confirmed in a subsequent review of the literature, which included 109 publications comprising 1555 individuals.[10] The authors noted that adverse events were uncommon, often mild and self-limiting and primarily gastrointestinal in nature. Importantly, they concluded that a "credible association could not be established" between FMT and the AEs due to the lack of controlled data. Results of recent randomized studies, which have a control group, have shown similar rates of minor adverse events between treatment and control groups, confirming this view.[11] The *lack of adverse events attributed to the FMT material itself* in the literature is an encouraging signal that current screening measures are effective.

In contrast, rare but at times fatal adverse events have been reported with probiotic/yoghurt preparations. For example, a case of fatal gastrointestinal mucormycosis has been reported in

an infant following ingestion of a contaminated, GMP-certified probiotic supplement (Solgar ABC Dophilus powder).[12] In 2013, a foodborne fungal pathogen outbreak also occurred with the commercial probiotic yoghurt brand Chobani® after 200 people reported becoming ill with nausea, vomiting, and diarrhoea, with investigation by the FDA identifying *mucor circinelloides* as the contaminant.[13] Outbreaks of foodborne botulism have also been reported in the literature, with an early report describing 27 people who became ill, one of whom died, as a result of hazelnut yoghurt contaminated with *Clostridium botulinum* type B toxin.[14] In a comprehensive review, Enache-Angoulvant et al. (2005) identified 92 cases of invasive *Saccharomyces* infections reported in the literature with probiotic preparations.[15] *S. boulardii* accounted for 51.3% of fungaemias, however, *S. cerevisiae* was associated with poorer prognosis.[15] These cases highlight the challenges associated with contamination control during mass production in spite of GMP.

Short-term adverse effects are minor and transient and are no longer of major issue among FMT users across the world. But there are repetitious calls for studying long-term adverse effects of FMT, exposing the authors perceptions of FMTM being parallel to a drug or a biologic, such as azathioprine or infliximab. These are drugs which enter human tissues, and are not comparable to FMTM which remains outside the body and behaves differently. So in this situation we need to "unlearn and re-learn" that FMTM in its numerous presentations (eg liquid infusate or lyophilised powder) probably falls under numerous classes of therapeutic agents but particularly not under the class of a drug. It is more analogous to studying long-term adverse effects of transplanting hair, bone marrow a heart or liver. The gut microbiome could be seen as a series of tissues ('groups of cells that have a similar structure and act together to perform a specific function') and it has been argued convincingly to be an organ. Looking back, hair transplantation has not been met with obsessive calls for long-term adverse effects on the recipient of the transplanted hair. They are into-tissue transplants but not microbiota, so there is a whole new classification that has to be considered for microbiome transplantation, though likely to show positive rather than adverse long term effects. One of the more powerful arguments for the lack of adverse effects is the origin of FMTM from eg a 30y old healthy donor, where this mass of faecal cells has resided for decades in a 'test bed' for adverse events and none have developed. There are no drugs nor biologics tested for decades before marketing. On the other hand *cultured microbiota consortia* do demand observation because we do not have a model carrying cultured microbiota for decades. To monitor long-term adverse effects of cultured consortia one really needs compare prospectively donor source consortia and recipients of the consortia over many years. For full spectrum FMTM we could retrospectively check what happened to *the recipient and the donor* to answer the question of whether donated stool works differently in the recipient. In our own experience at the Centre for Digestive Diseases(CDD) in Sydney with over 17,000 FMTs, on review, there were no outstanding

symptoms with long-term follow up for up to 25 years. Nevertheless, it would be worthwhile in Australia setting up donor/recipient comparative follow-up prospective study.

IMPORTANT IMPROVEMENTS FOR TGA REGULATIONS

AVOID USE OF ANTIBIOTICS AFTER DIAGNOSING CDI

Approximately 30% of patients fail first-line treatment of CDI using vancomycin or metronidazole.[16, 17] Following a second recurrence (RCDI), approximately 40-60% of patients fail to eradicate their rCDI with further antibiotics.[17] Given that the initial CDI epidemic was driven in part by our widespread use of antibiotics and subsequent antibiotic-induced damage to the GI microbiota, it is not unsurprising that further antibiotic use is incapable of restoring the underlying microbiota deficiencies which are needed, required to prevent the cycle of recurrence. Studies have shown that vancomycin drastically depletes most intestinal microbiota genera and operational taxonomic units, including those from the phylum *Bacteroidetes*, which are recognized as being necessary to prevent CDI recurrence.[18, 19] Metronidazole has similarly been shown to significantly reduce bacterial diversity in the gut[20] and dramatically alter the ileal and caecal microbiota.[21] Despite the higher rate of failure with antibiotic agents and the involvement of these agents in the perpetuation of CDI recurrence[22], we continue to rely on antibiotics for first- and second-line therapy for CDI.[22]

The Centers for Disease Control and Prevention has recognised *C. difficile* as one of three organisms that pose an urgent threat in the US.[23] It is responsible for 453,000 infections each year and results in ~30,000 deaths annually.[24] Current US mortality (~ 30,000/y) rises often due to delay to FMT and is estimated as being 5% or 1500 deaths yearly could be attributed to FDA regulation requiring initial treatment/s to be antibiotics. FMT is currently recommended by the IDSA as second-line therapy in rCDI in the US,[25] where is achieves a ~90% cure rate.[4-6] So use of any antibiotics, including metronidazole or vancomycin, further disturbs the gut microbiome composition and is counterintuitive for the treatment of CDI which in the first place is facilitated by the use of antibiotics. TGA regulations should be evidence-based and avoid pre-FMT trials of metronidazole or vancomycin as in the US. The latter should be used only in the context of pre-FMT workup.

FMT SHOULD BE FIRST-LINE THERAPY FOR *CLOSTRIDIOIDES DIFFICILE* INFECTION

Recent evidence suggests that cure rates of ~100% can be achieved if FMT is employed as a first-line therapy in CDI.[26] Given that antibiotics have a significantly higher failure rate than FMT, **there is a lack of evidence-based reasoning to support current guidelines in delaying FMT to second or third-line** therapy. Delaying safe and effective treatment puts the patient at substantially increased risk of morbidity (i.e. colectomy) and death, and places an economic burden on our healthcare system. In a recent economic evaluation examining the cost effectiveness of FMT compared with vancomycin for rCDI, treatment with vancomycin resulted

in an increased cost of AU$4094 (95% CI: AU$26, AU$8161) compared with nasoduodenal delivery of FMT and AU$4045 (95% CI: -AU$33, AU$8124) compared with colorectal delivery.[27] The incremental effectiveness of either FMT delivery compared with vancomycin was 1.2 (95% CI: 0.1, 2.3) quality-adjusted life years, or 1.4 (95% CI: 0.4, 2.4) life years saved. They conservatively estimated that "if FMT, rather than vancomycin, became standard care for recurrent CDI in Australia, the estimated national healthcare savings would be over AU$4000 per treated person". As there are no currently available medical therapies for rCDI which rival the near-100% cure rates achieved by FMT, every effort should be made to minimize unnecessary antibiotic damage to the GI microbiota, prevent patient suffering, morbidity and mortality, and alleviate the economic burden of rCDI on our healthcare system. **We propose that the Australian TGA work towards FMT as first-line therapy for CDI.**

REGULATORY OPTIONS

Therapeutic Category Definition

The therapeutic category/ies assigned to FMTM is of primary importance as it underpins the development of all subsequent regulations. The Therapeutic Goods Act of 1989 (the Act),[28] Therapeutic Goods Regulations 1990 (the TG Regulations),[29] and previous Acts were not designed with FMTM in mind. As such, FMTM does not fit within a clear category of the Acts and Regulations. Given the absence of a TGA category for FMTM, it has been suggested that FMTM may meet the definition of a biological as per subsection 32A(1),[28] based on the assumption that human cells, or colonocytes, are present in the rectal (donor) stool and are therapeutically active. In order to address this, we must first look to published work relating to colonocyte research, which has largely been aimed at detection of premalignant and malignant colon cells from stool. Although premalignant/malignant colonocytes are shown to readily exfoliate/shed from polyps and cancer, in contrast, several studies have shown that exfoliated colonocytes in the normal colon are not lost in the faecal contents, but are rather retained in the matrix or mucocellular layer.[30] In their review, Loktionov et al. (2007) summarised that "cell exfoliation from colonic epithelium appears to be a relatively rare event in normal conditions (*such as in donor conditions*) but its rate dramatically increases in neoplasia when cell removal by apoptosis in situ does not function properly.[30] The authors further add that although high proliferation and constant flow of colonocytes from crypts to lumen is "generally correct for the colonic epithelium of rodents…there are good reasons for doubts about its applicability to humans" where exfoliation occurs at a much lower rate than previously believed.[30] Iyengar added that "colonic epithelial cells terminally differentiated and are devoid of proliferative activity" indicating that they would not be therapeutically active. [41] Hence in normal donors one would expect very few colonocytes, mostly trapped in the mucocellular layer and inactive. Based on these findings, it is extremely unlikely that normal donor colonocytes that survive bacterial digestion are present in stool in significant numbers. The European commission

shared this same view in their 2014 legal opinion, that the cells found in the FMTM are not the active component and therefore "not intended for human application" within the meaning of the EU tissue and Cell the directive (2004/23/EC).[31, 32] Hence **from this evidence-based data we can safely conclude that FMTM does not meet the *current* definition of a biological under the Act 32A(1).[28]**

FMTM is emerging not as a single therapeutic product but as a group of different products, including a liquid enema, frozen enema, frozen capsules, lyophilised capsules, and even flavoured liquid for ingestion. Hence, the Regulatory Scheme may need to consider defining several differing categories for FMTM as Therapeutic Goods. Similarly various 'Options' may *need to co-exist* to deliver the various clinical therapeutic functions.

Option 1: REGULATION UNDER THE BIOLOGICALS FRAMEWORK

There as some advantage to define material from human faeces as biologicals under this Option. However, the listed Options have *closely overlapping features*, so several may need to be combined yet achieve the same outcome. We need to accept the lack of definite direction due to the old definition, which included the terminology "derived from human cells or tissue". Moving to the new definition of biologic would need to include:

a) Microbiome – bacteria, virus and fungus (gut, lung, oral or other microbiomes to be included for the future). Cells may be dead or alive.

b) The biologic may also contain the surrounding fluids e.g. water, bile, mucus, saliva and food residues among them. Lung and nasal secretions would need to be included in greater detail, as this needs to cover microbiomes from the skin, eyes, sinuses, vagina and other areas.

c) Human derived cells may be present in the gut microbiome as mucosal living or dead cells, oral cells, nasal cells and oesophageal squamous cells. Given the argument above, these are likely to be mostly dead and non-functioning.

d) In the 'minimally modified' concept practically there will be much compositional variation.

The Australian code of GMP for biologicals should be required only for commercial product development and will need to:

a) Be modified for FMT materials. Comparing with a biological such as Infliximab, its molecular mass is so unlike faecal material that the GMP code for Infliximab will not fit FMTM, with all its numerous and different types of components as mentioned above.

b) For commercial FMT products development of process for manufacturing GMP products to cover FMT will need to be worked out.

c) It should not be carried out in any GMP facility due to contamination. So the cost to set up committed GMP are would be far too expensive and an onerous burden for an Approved Medical Clinic or Approved Hospital.

d) GMP should only apply to products for sale or supply. The use of the FMT by the physician in his own patients and clinic will need to be exempt of GMP under 'clinical practice'.

e) When taken from appropriate donors, non-commercial FMTMs have a unique class of biologicals where there should be self-governance [see Option 4] because of the minimal manipulation and because they are going to be used by a physician as part of his clinical practice. In this way, these will be:

1. Excluded from regulation.
2. There will be no formal GMP.
3. However, FMT should be carried out in Approved Medical Clinics and Approved Hospitals, but not requiring approval of physicians.
4. The FMTM cannot achieve the requirements necessary to submit a dossier for registration on the ARTG for lack of consistency and absence of onerous costs for analysis at species and subspecies level of bioinformatics.

Commercial FMT production/supply should be:

1. TGA regulated
2. GMP should apply
3. Facilities and production should be FDA-regulated

Unless major modifications are made as outlined above **the impact** of this Option would cause failure to deliver appropriate regulation of FMT. The current patient demand for FMT could not be met if we were to follow this Option. If we do not have an Option which permits the clinician to treat with FMT in an unobstructed fashion in his clinical practice, clinicians are likely to close down their FMT practices, patients will seek treatment elsewhere, and some will self-treat at home.

Option 2: REGULATE UNDER THE BIOLOGICALS FRAMEWORK – CLASS 1 CAT.

This Option has in part already been described in Option 1, including the minimally manipulated FMTM, i.e. mixing with saline filtration, additional glycerol, freezing or cryopreservation from appropriately screened donors. The product would best be produced in an Approved Medical Clinic or Approved Hospital and in addition be administered under supervision of an FMT-

experienced. No TGA oversight would be required to achieve safety for patients as this has already been achieved without TGA oversight through self-regulation.

The impact under option 2 of requiring the FMTM to have the product included in the Register is onerous. This in itself will close down FMT clinics. Expansion of donor-screening criteria under '88' should be implemented, but this is a simple step and easily achieved across all Approved Clinics and Hospitals.

CDD does not support a recommendation regulating FMT under Option 2.

Option 3: REGULATE UNDER THE BIOLOGICALS FRAMEWORK, INTRODUCING EXCLUSIONS AND/OR EXEMPTIONS FOR SOME FMT MATERIALS

We see this as more acceptable than Option 2 regulation – to be used in an Approved Hospital or Approved Medical Clinic, under supervision of an FMT-experienced practitioner, but also in a graduated, or slowly-adapting environment. External governance will need not to be overwhelming but understanding working with Clinics and Hospitals.

It is advantageous that GMP is excluded and only applicable to more commercial ventures seeking to supply. Most FMT stakeholders would like to see rCDI and IBD therapy access available with ability to progressively research expanding applications without the restrictions overseas, which have compromised research. It is crucial that the regulatory structure permit ongoing expansion of applications of FMT into conditions where the gut microbiome appears to have some evidence of pathogenic role.

In non-Approved institutions treatment of rCDI should remain available. In FMT Research Institutions with research track record and FMT programs, early evidence, even from prospective or collected case reports in publications, should be followed progressively by evidence-based established methods of research to generate appropriate evidence of FMT applications in specific disorders. Simply being a hospital or a medical clinic should not automatically give license to develop new FMT applications until research Approval is obtained. At this stage there is no Approval body, and this remains to be developed.

The impact of this Option is that it will be particularly advantageous to those practitioners currently practicing FMT. Separating those with full Research capabilities from those with FMT practice for CDI only could promote greater safety and maintain public health quality.

CDD supports Option 3 which also opens the door to incremental modification of FMT practice as improvements eg in delivery methods, become known and published.

The exempt/excluded status should apply to both rCDI as well as other disease applications where bona fide research is being undertaken in that field – regardless of condition – since the gut microbiome involvement in various diseases has brought many surprises and more, even

unpredictable indications may require research trials. Mechanisms for treatment of appropriate conditions could be determined by a Human Research Ethics Committee (HREC).

Option 4: SELF-REGULATION OPTIONS

Components of the self–regulation options do give further flexibility in standards and manufacturing controls. There is however to date no ready expert supervisory body to accredit, supervise and ensure industry standards are adhered to. This aspect alone will take considerable time to achieve. Furthermore, FMTM regulation with composition, quality, and efficacy may not be adequate under this Option.

Self-regulation even today shows some evidence of FMT use in low-evidence applications without stimulating research to be undertaken to generate greater evidence for such applications. Features of Option 4 would still require some aspects found in Option 3.

The impact of going with Option 4 may open the door to greater use of FMT in questionable diseases without HREC approval and trial design. Alternative non-TGA body to develop a supervisory role and examine FMT centres for Approval – requires further consultation and is unavailable at present. For greater public health safety features of Option 3 are more attractive.

CDD therefore does not recommend Option 4.

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