Where Stool is a Drug: International Approaches to Regulating the use of Fecal Microbiota for Transplantation

Alexandra Scheeler

Introduction

The human gut microbiome consists of the diverse community of bacteria and other organisms that live in the gastrointestinal tract. While the precise composition and abundance of bacteria varies across individuals, evidence suggests they play an important physiological role in human health. Clinical research has linked gut microbiota with gastrointestinal diseases, including Crohn's disease and ulcerative colitis, and indications with less clear linkages to the gut, including metabolic syndrome, graft-versus-host disease, liver disease, and psychiatric conditions.[1] These associations, coupled with the fact that gut microbiota outnumber human cells in the body, has captured both public and scientific imaginations.[2] Journalists, clinicians, and researchers are re-examining long-held assumptions and definitions about what constitutes the human body, suggesting humans may be better understood as ecosystems or superorganisms rather than discrete individuals.[3]

The physiological importance of a robust, diverse gut microbiota ecosystem is most clearly demonstrated in the treatment of recurrent *Clostridium difficile* infection (rCDI). *C. difficile* produces toxins that cause a broad spectrum of clinical disease, ranging from asymptomatic carriage to diarrhea, colitis, and death.[4] Recent antibiotic use, which disrupts the microbiota ecosystem, is a major risk factor in CDI.[5] While most *C. difficile* cases resolve with antibiotic treatment, recurrence following a primary episode occurs in 10-20% of patients. Following the first recurrence, subsequent rates of recurrence rise to 40-65%.[6] This patient population poses a major therapeutic challenge.

The failure of standard antibiotic treatments to prevent disease recurrence has led to research into novel treatment options, including fecal microbiota transplantation (FMT). FMT involves administration of stool from a healthy, screened donor into the gastrointestinal tract of an ill patient. Numerous case reports, retrospective case series, and randomized controlled trials have demonstrated the benefit of FMT in patients with severe or rCDI, with mean cure rates of 87% to 90%.[7] Despite the demonstrated high efficacy and favorable safety profile for treatment of rCDI, national health authorities vary widely in their

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interpretation of FMT, resulting in variable and unsettled regulatory classifications across the globe.

While the position of the U.S Food and Drug Administration (FDA) and that of regulatory bodies in a number of other countries is that stool product for FMT should be regulated as a drug, this paper concurs with others in holding that the human cell and tissue product (HCT/P) classification is the best available paradigm for FMT regulation. HCT/P classification right-sizes regulatory oversight of FMT by allowing for robust oversight of the critical process elements of donor selection and stool preparation, while permitting flexibility in indication of use. This article assumes that FMT's efficacy is best demonstrated in the treatment of rCDI, and is therefore particularly focused on how current or proposed regulatory schemes allow FMT access for rCDI patients. The HCT/P classification adapts oversight to maximize safety while acknowledging that human-derived products are not produced in a lab, and therefore defy some typical drug requirements like batch uniformity.

Despite HCT/P's apparent fit for stool products, few regulatory bodies choose to regulate FMT this way. As we shall see, many authorities' primary objection is definitional: since the presumed active ingredient is bacteria, it is inappropriate to classify FMT as a *human* cell and tissue product. This article reports on a global survey of national regulations and collates existing FMT classification statuses for reference by researchers and physicians. It also examines several of the debates behind product classification decisions, and in so doing offers a potential path forward for regulators whose objection to the HCT/P classification of FMT is definitional.

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Fecal Microbiota Transplantation for Recurrent CDI: Evidence and Impact

C. difficile is a Gram-positive, spore-forming bacterium usually spread by the fecal-oral route. *Clostridium difficile* infection (CDI) is defined as the acute onset of diarrhea with documented toxigenic *C. difficile* or its toxin and no other documented cause for diarrhea.[8] Risk factors for CDI include advanced age, recent antibiotic exposure, proton pump inhibitor use, extended healthcare setting residency, serious underlying illness, and immunocompromised conditions.[9] The U.S. Centers for Disease Control and Prevention (CDC) identify *Clostridium difficile* as an "urgent threat" to public health, the highest possible threat categorization, due to its virulence and prevalence.[10] Researchers project that there are 453,000 cases of primary CDI annually in the U.S, with 29,300 deaths within 30 days of diagnosis.[11]

Recurrent *C. difficile* infection (rCDI) is defined as an episode of CDI that occurs eight weeks after the onset of a previous episode, provided the symptoms from the previous episode had resolved while on standard of care antibiotics. Recurrence of CDI following a primary episode occurs in approximately 10-20% of patients. Following the first recurrence of CDI, the rates of a subsequent recurrence increase to 40-65%.[12]

rCDI clinically manifests in many of the same ways as the primary episode of CDI: that is, acute onset diarrhea, confirmed by a positive stool test for toxigenic *C. difficile* or its toxin, and rCDI poses an especially grave threat.[13] Inpatients with rCDI have a higher 6-month mortality rate than patients with non-recurrent CDI (36% vs. 26%).[14] Patients with rCDI also serve as vectors for transmission of the disease to other vulnerable populations, particularly in healthcare associated settings.[15] Spores can persist in the environment on high-touch surfaces for weeks, and transmission can occur when patients share bathrooms or other communal living spaces. Transmission can also occur when asymptomatic CDI-colonized health-care professionals working with multiple patients transmit the spores between a sick patient and others.[16]

The limited pharmaceutical options to treat rCDI has led to further research into alternative treatment options, including FMT. Although not fully elucidated, the anticipated mechanism for prevention of CDI recurrence via FMT is that normal colonic microbiota outcompete and thereby competitively exclude exogenous *C. difficile,* providing colonization resistance.[17] The goal of FMT is to restore the phylogenetic diversity and composition typical of a healthy person,

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Table 1

FMT in rCDI Efficacy Evidence

Study	Design	Pop.	FMT Delivery	Efficacy
Randomized Trials				
Kelly et al. 2016[113]	Multicenter, double-blind, randomized, placebo-controlled trial	46 patients with ≥ 3 CDI occurrences	Colonoscopy	Primary cure rate • Donor FMT: 91% • Autologous FMT (placebo): 63% • p=.024
Lee et al. 2016[114]	Double-blind, randomized, non-inferiority trial between frozen-and-thawed FMT and fresh FMT	178 patients with recurrent or refractory CDI	Enema	Primary cure rate • Frozen FMT: 62.7% • Fresh FMT: 62.1% Secondary cure rate • Frozen FMT: 83.5% • Fresh FMT: 85.1% • p=0.01 (non-inferiority)
Kao et al. 2016[115]	Randomized, non-inferiority trial between colonoscopic and capsule FMT administration	105 patients with ≥ 3 cases of CDI	Colonoscopy and capsules	Primary cure rate • Capsule: 96.2% • Colonoscopic: 96.2% • p<0.001 (non-inferiority)
Cammarota et al. 2015[116]	Open-label, randomized trial between vancomycin and FMT	39 patients who had CDI recurrence after ≥1 antibiotic course	Colonoscopy	Primary cure rate • FMT: 90% • Vancomycin (control): 26% • p<.0001; 99.9% CI
Youngster et al. 2014[117]	Randomized, open-label trial between colonoscopic and nasogastric FMT administration	20 patients with a median of 4 CDI recurrences	Colonoscopy and nasogastric tube	Primary cure rate • Colonoscopic: 80% • Nasogastric: 60% Secondary cure rate • Colonoscopic 100% • Nasogastric 80% • p=0.53
van Nood et al. 2013[118]	Open-label, randomized, controlled trial between FMT with bowel lavage; vancomycin only; and vancomycin with bowel lavage	41 patients who had CDI recurrence after ≥1 antibiotic course	Naso-duodenal	Primary cure rate • FMT with bowel lavage: 81% • Vancomycin (control): 31% • Vancomycin with bowel lavage: 23% • p<.001; 99.9% CI
Systematic Reviews & Meta-Analyses				
Quraishi et al. 2017[119]	Statistical analyses of 37 studies: 7 randomized controlled trials and 30 case-series studies	1973 patients with recurrent or refractory CDI: 428 in randomized controlled trials; 1545 in case-series	Various	• Overall cure rate: 92% • Lower delivery: 95% • Upper delivery: 88% • p=0.02; 95% CI
Moayyedi et al. 2017[120]	Statistical analysis of 10 randomized controlled trials	657 CDI patients	Various	• FMT was statistically significantly more effective than either placebo or vancomycin • RR, 0.41; 95% CI, 0.22-0.74

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Study	Design	Pop.	FMT Delivery	Efficacy
Drekonja et al. 2015[121]	Statistical analyses of 35 studies: 2 randomized controlled trials; 28 case-series studies; 5 case reports	516 CDI patients treated with FMT	Various	• Overall cure rate: 85%
Cammarota et al. 2014[122]	Statistical analysis of 36 studies: 20 case-series, 15 case reports, 1 randomized controlled study	536 patients, almost all with recurrent CDI	Various	• Overall cure rate: 87%
Kassam et al. 2013[123]	Statistical analyses of 11 case-series studies	273 CDI patients treated with FMT	Various	• Overall cure rate: 89.7%
Cohort Studies				
Youngster et al. 2016[124]	Open-label cohort study	180 patients with recurrent or refractory CDI	Capsules	Primary cure rate • 82% Secondary cure rate • 91%
Hirsch et al. 2015[125]	Open-label cohort study	19 patients with recurrent CDI	Capsules	Primary cure rate • 68% Secondary cure rate • 89%
Youngster et al. 2014[126]	Open-label cohort study	20 patients with recurrent CDI	Capsules	Primary cure rate • 70% Secondary cure rate • 90%

thus restoring their colonization resistance against *C. difficile* and preventing recurrence of rCDI.[18]

Numerous case reports, retrospective case series, and randomized controlled trials have demonstrated the benefit of FMT in patients with severe or rCDI, with mean cure rates of 87% to 90% for the >500 cases reported in current literature.[19] A recent study found colonoscopic administration of FMT to be the most cost-effective treatment strategy for rCDI compared with vancomycin or fidaxomicin.[20] A double-blind noninferiority clinical trial, comparing the use of frozen FMT compared with fresh FMT for the treatment of recurrent or refractory CDI, found both modalities similar in efficacy and safety.[21]

Regulatory Paradigms and Impact on Patient Access

Regulatory oversight of stool for FMT is clearly indicated. Though FMT has demonstrated an overall favorable safety profile to date, there is a risk of both known and unknown infectious pathogen transfer from donor to patient.[22] Researchers also theorize that microbiome-mediated diseases could be communicated via FMT.[23]

No uniform perspective on FMT classification has emerged. Regulatory agencies have largely chosen to classify FMT into one of four categories. From most restrictive to least restrictive, these categories are: biologic drug, human cell or tissue-based product, medicinal product, or practice of medicine. The classification made by national agencies significantly impacts permissiveness and use of this emerging therapeutic option.

Biologic Drug: Highly Regulated and Restricted Use

The main benefit of the biologic regulatory paradigm is that the end result is a standardized product with proven demonstration of safety and efficacy in a given disease. Nevertheless, classifying stool as a biologic presents significant technical challenges and severely restricts patient access until market approval is granted.[24]

In contrast to chemically synthesized drugs with well-defined structures, biologics are complex and

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often poorly characterized mixtures derived or isolated from living organisms. Because of this, biologics are often more sensitive to environmental factors during their manufacturing (*e.g.* light, heat, contamination), and regulatory agencies accordingly monitor biologics process manufacturing with particular stringency, taking into account not just the biologic product but also the living organism from which the biologic is derived. This presents several challenges in regulating stool. As Edelstein et al. argue, given the high variability of stool composition and without a clear understanding of the active pharmaceutical ingredient, authorities must place somewhat arbitrary parameters around which timepoints in a donor's life history are relevant to the "manufacturing process."[25] Purity and potency are likewise universal characteristics in regulatory authorities' assessment of a biologic drug product, but again, the heterogeneity of stool composition across individuals, individuals' lifecycles, and cultures challenge any definition of "purity," and "potency" is difficult to assess when researchers do not fully understand the mechanism of action.[26]

Additionally, regulating stool as a biologic drug mandates that manufacturers must put their stool product through a pre-market approval process that requires robust demonstration of the safety and efficacy of the biologic drug with clinical outcome data. Until the approval process is complete, the biologic is not available outside clinical trials barring an explicit exception. As this article will discuss in detail, explicit exceptions, or expanded access schemes, currently play a large role in FMT's availability, particularly in the U.S. Once approved, developers price the biologic in order to recuperate their investment in market authorization and use regulatory schemas to exclude competitors to capture additional profit. This is problematic in the domain of stool therapeutics, where much of the research has been developed in the public domain and where rCDI patients are already being served by existing providers.[27]

Due to unusual properties of stool, there are uncommon negative consequences of interim access limitation and long-term expensive pricing.[28] While rigorously screened, technically manufactured stool is a scarce good, stool itself is abundant. Desperate patients have acquired friends and neighbors' stool to conduct "do-it-yourself" medical treatments involving blenders and enemas. This practice, clearly riskier than a fecal transplant performed by a medical professional, often involves little to no donor screening, and material processing occurs in a far from sterile environment.[29] If stool is unavailable until market approval, or if medically-approved stool proves too expensive for portions of the patient population, it stands to reason that unscreened, unsupervised DIY attempts may proliferate.[30]

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Human Cell and Tissue-Based Products: Process-Focused Regulation

Human cell and tissue-based products (HCT/Ps) are a sub-category of biologics. HCT/Ps are regulated in a tiered approach, with the level of regulation corresponding to patient risk. All HCT/Ps must follow certain manufacturing processes, but whether market authorization is required, and whether clinical outcome data demonstrating safety and efficacy is required as part of that market authorization applica-

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tion, depends on the risk assessment of the particular HCT/P by the regulatory authority.

This approach permits robust oversight of donor screening, preparation, storage, and handling of stool treatments, while also allowing for collection of comprehensive safety data and flexibility in indication use. The HCT/P paradigm allows for the toggling of use permissions based on the degree of relation of the donor and the patient, *e.g.* stool donated from a sibling could be used to treat a wider variety of indications than that from a universal stool bank. The end result would be a network of stool banks, some private and some public, operating much like blood banks. Proponents of this regulatory categorization argue that this approach would result in cheaper, safer, more accessible stool material for fecal transplantation, and would reduce risky DIY attempts.[31]

Opponents of this classification main contention is that stool simply does not fit the definition of an HCT/P. For example, in the United States, this is defined as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient;" HCT/Ps are explicitly not "secreted or extracted human products, such as milk, collagen, and cell factors."[32] For opponents, the secretion of stool and the fact that its hypothesized active pharmaceutical ingredient is *bacteria*, not human cells and tissues, disqualifies it from HCT/P classification.[33]

Medicinal Products: Claiming Oversight, Variable Access

The medicinal product classification reflects the common regulatory agency perspective that any product, when intended to treat or prevent a disease, falls within their regulatory jurisdiction. This is often a provisional classification, as agencies seek to establish their authority to regulate FMT use but have not yet decided its final classification, or are awaiting a market application from a specific FMT product to trigger that decision-making.

This classification has highly variable requirements based on the jurisdiction. In Australia, for example, unapproved therapeutic goods (the medicinal product equivalent) are widely accessible to patients under several schemes.[34] Under this paradigm, Australia has become home to one of the world's highest-throughput private stool banks, which treats rCDI and a host of other gastrointestinal indications.[35] Conversely, while Switzerland also classifies FMT as an investigational medicinal product, that classification subjects its use to stringent limitations: for any disease, it may only be used in the context of an approved clinical trial.[36] In sum, the medicinal product classification represents a claim of regulatory authority, but the exercise of that authority and its impact on patient access is inconstant country-to-country.

Practice of Medicine: Devolved Oversight, Unpredictable Access

Regulatory authorities may also choose to not regulate stool for fecal microbiota transplantation, instead considering its use practice of medicine. Under this approach, all decisions relating to donor screening, and material processing, and potentially decisions related to indication usage, are delegated to each patient's doctor and their doctor's supervisory institution.

This nominally permissive approach devolves regulatory oversight with unpredictable consequences for safety and patient access. Doctors who are enthusiastic about FMT, and who make persuasive arguments to their supervisory institution, will be able to offer FMT to patients with a variety of diseases. Donor screening and manufacturing could be based on medical association guidelines, but without oversight, adherence would be self-regulated. Safety information could be collected in adverse event databases, but reporting would be either voluntary or heterogeneously required by sub-national public health or medical boards, and therefore less comprehensive.

Alternatively, doctors who are skeptical about FMT, or doctors whose institutional supervising bodies are circumspect or resource-limited, may not be able to offer FMT for any indication. While treatment guidelines promulgated by medical associations would broadly shape FMT's availability in a given jurisdiction, logistical issues and administrative dynamics would play an outsized role in access.

Methods

As fecal microbiota transplantation is still an emerging treatment option, many national health regulatory agencies have yet to categorize stool. In determining which countries' regulatory agencies to contact, as stated above, this article makes the assumption that FMT's efficacy is best demonstrated in the treatment of rCDI. Historically, CDI was believed to be more prevalent in Western countries with advanced economies, but that assertion has recently been challenged by multiple researchers, who argue the burden is widepsread.[37]

Accordingly, in order to capture a broad swath of the potential rCDI patient population, the author contacted the health regulatory agencies of the fifty most populous countries, as well as the countries that

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Table 2
FMT Regulatory Classification Summary

Country	FMT Regulatory Classification	rCDI Exception	Known stool banks	Notes
North America				
United States	Investigational biologic drug; clinical trial required for use	Yes, with conditions	Yes, non-profit and hospital	
Canada	Investigational biologic drug; clinical trial required for use	Yes, with conditions	No	
Europe				
Austria	None; considered neither a drug, tissue, nor organ	n/a	No	Under reevaluation by regulators
Belgium	Human cell or tissue product; clinical trial required	Yes, with conditions	No	
Denmark	Unlicensed medicinal product	n/a	No	Regulators state tissue regulations are best fit for FMT, but no formal classification
Estonia	None	n/a	No	Determined it is not a HCT/P, but final decision would require specific product information
Finland	Unlicensed drug product	No	No	All use decisions are made on a case-by-case basis; usually permitted in hospital setting
France	Experimental drug; clinical trial required for use	No	No	Hospital and pharmacy preparations acceptable
Germany	No federal-level guidance; case-by-case decision by state authorities	n/a	No	
Ireland	None, considered practice of medicine	n/a	No	
Italy	Human cell and tissue product; clinical trial required	Yes, with conditions	Yes, under development with government support	
Malta	None	n/a	No	
The Netherlands	Unclassified treatment	Yes, with conditions	Yes, non-profit	
Norway	Unlicensed medicinal product	No	No	
Portugal	None	n/a	No	Regulators state there is non-binding precedent to treat as unapproved biologic
Slovenia	None	n/a	No	
Spain	None; considered neither a pharmaceutical product nor a tissue	n/a	No	
Switzerland	Investigational medicinal product	No	No	
United Kingdom	Unlicensed medicinal product; clinical trial required for use	No	Yes, hospital and private	Magistral, officinal, and Specials preparations acceptable

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Country	FMT Regulatory Classification	rCDI Exception	Known stool banks	Notes
Oceania				
Australia	Unapproved therapeutic good	No	Yes, hospital, non-profit, and private	Available subject to regulatory approval under 4 schemes: special access, authorized prescriber, personal use importation, clinical trial. Under re-evaluation by regulators.
New Zealand	Unapproved medicine	No	No	Importation by clinician or pharmaceutical preparation acceptable
Asia				
Hong Kong Special Administrative Region	Refused comment	No	Yes, private	Continuing operation of private stool bank providing FMT for rCDI and IBD implies permissive regulatory structure
Israel	Unapproved medical treatment; clinical trials required	Yes, with conditions	Yes, hospital	
Singapore	Under review	No	No	

the International Monetary Fund identifies as having advanced economies. These combined lists yield 75 countries and three Special Administrative Regions.

Of these, six countries' drug regulatory authorities have issued clear guidance on the regulatory status of FMT; their classifications are discussed below, but the regulatory authorities were not contacted. The Democratic Republic of the Congo was not contacted due to the ongoing civil war, which has disrupted government operations. All other countries health regulatory authorities were contacted. Where available, the opinions of the major gastrointestinal and infectious disease medical societies of each country are also discussed.

North America

United States

The Food and Drug Administration (FDA) classifies FMT as an unapproved biologic drug. While this is ordinarily the most restrictive classification, the FDA has carved out an exception for the treatment of rCDI, provided the physician obtains informed consent.[38]

This unusual enforcement discretion policy speaks to the challenges regulatory agencies face as they balance classification with patient access. Until 2013, FMT was unregulated in the United States, as few physicians sought to treat patients using this method. Interest in the treatment surged after Dutch researchers published the results of the first randomized controlled trial in the *New England Journal of Medicine*.[39] In May 2013, in order to discuss the regulatory and scientific issues associated with FMT, the FDA held a public workshop. At the workshop, the FDA announced FMT would be regulated as an unapproved biologic drug. Investigators who wished to use FMT to treat patients with any indication would be required to submit an Investigational New Drug (IND) application and provide treatment only in a clinical trial setting or emergency use situation.[40]

Physicians, patient advocate groups, scientists, and medical societies expressed concern that the IND regulations would prevent many patients with rCDI from accessing FMT, and that an alternative regulatory approach was warranted for these patients. In response, in July 2013, the FDA issued the enforcement discretion policy. In the issuance, the FDA notes that this is a temporary policy while they further consider the matter.[41]

The FDA has continued to iterate on FMT regulation in a series of draft guidances. These draft guidances were released to solicit public input; neither has been implemented. In March 2014, the FDA pro-

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posed revising the enforcement discretion policy to require that the stool donor be "known" to either the patient or the physician, and to require that all donor and stool screening be conducted with oversight from the physician performing the FMT.[42] This proposal would have effectively shut down public freestanding stool banks, such as OpenBiome, a Cambridge, MA-based provider of FMT material, while permitting hospital-run stool banks and direct donations from friends and family members. Again, a coalition of patient advocates and medical professional societies raised concerns about the draft policy's potential impact on patient access.

In March 2016, the FDA released another draft guidance, which superseded the March 2014 proposal and was still for public comment only. In this draft guidance, the Agency proposed that physicians using material from public stool banks to treat rCDI must do so under an IND. The FDA actively sought feedback on how to implement this proposal so that it would not be excessively burdensome for physicians.[43] The public comment period for that proposal ended in May 2016, and there has been no further draft guidance or finalized guidance released.

Various health care providers and advocates have argued that a reclassification of FMT to a HCT/P would best solve the challenge of balancing patient safety and access with which the FDA continues to struggle.[44] While the biological drug product classification requires an awkward carve-out for rCDI patient access, the HCT/P paradigm permits different treatment uses to be regulated differently. However, the FDA's Tissue Reference Group has stated that FMT does not meet the legal definition of a HCT/P, which is defined as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient;" HCT/Ps are also explicitly not "secreted or extracted human products, such as milk, collagen, and cell factors."[45] As Sachs and Edelstein note, the Tissue Reference Group may object to FMT's classification as an HCT/P for one or both reasons: that as bacteria is presumed an active ingredient, FMT cannot be called a *human* cell or tissue, or that FMT could be considered an HCT/P but is excluded because it is "secreted or extracted."[46] While Sachs and Edelstein identify administrative mechanisms to overcome either definitional barrier, the FDA has so far proven unwilling to entertain reclassification.[47] Despite the FDA's evident discomfort with the existing regulatory structure, for now, FMT remains classified as an investigational biologic drug with an exception for the treatment of rCDI.[48]

Sidestepping the classification debate to provide practical advice, the leading infectious disease and gastroenterological American medical associations have provided recommendations on the matter to their member physicians. The 2013 American College of Gastroenterology (ACG) *C. difficile* infection treatment guidelines conditionally recommends FMT for the treatment of 3 CDI recurrence (fourth episode) to prevent rCDI recurrence.[49] The American Gastroenterological Association (AGA) Gut Microbiome Center Scientific Advisory Board suggests treating 3 CDI episodes of mild-to-moderate CDI with FMT, but also included the recommendation that FMT may be used for patients with at least two episodes of CDI resulting in hospitalization and associated with significant morbidity.[50] Similarly, FMT leaders in the Infectious Diseases Society of America (IDSA) recommend considering FMT following third recurrence (fourth episode) of CDI, or after two CDI episodes requiring hospitalization.[51]

With this "yellow light" from the FDA and support from medical societies, rCDI patient access to FMT has significantly expanded. At the outset of enforcement discretion in November 2013, researchers conducting a geospatial analysis found 6.51% of the U.S. population was within a one-hour drive of an FMT provider, and 10.83% was within a 2-hour drive. By 2017, access dramatically increased: 87.54% of the U.S. population was within a 1-hour drive of an FMT provider, and 97.74% was within a two-hour drive. The greatest percentage increase occurred between 2013-2014, with a 714% increase of the population within a one-hour drive of an FMT provider. Between July 2013 and October 2018, the non-profit stool bank OpenBiome shipped over 40,000 FMT treatments to physicians for the treatment of rCDI.[53] As of April 2019, there are 28 active or enrolling studies in the U.S. for potential therapeutic applications of FMT outside of rCDI.[54] Still, FMT's investigational status and the release of multiple draft guidances have led to some confusion in the medical community as to under what conditions it may be offered to rCDI patients.[55]

Canada

Health Canada considers FMT to be an investigational new biologic drug, the study of which must be done under an authorized clinical trial as part of a Clinical Trial Application (CTA). Like the FDA, Health Canada has also issued an interim policy permitting the use of FMT for rCDI patients, provided certain conditions are met. Health Canada has far more specificity and restrictions than their American counterparts in the conditions for use. Health Canada requires that physicians obtain informed consent, specifies record-

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keeping requirements, and provides a list of infectious and potentially microbiome-mediated diseases that donors must be negative for, and mandates that the donor be "known to either the patient or to a health care practitioner treating the patient." If these requirements are not met, the rCDI patient may only be treated with FMT under a CTA.[56]

Medical societies in Canada have weighed in with their recommendations. The Canadian Association of Gastroenterology (CAG) recommend FMT in patients with 2 recurrences, provided the patient was treated with two different antibiotics.[57] The Association of Medical Microbiology and Infectious Disease Canada (AMMI) also recommends considering FMT in patients with 2 recurrences who have recurred after a vancomycin taper.[58]

The "known donor" restriction has limited Canadian rCDI patients' access to FMT relative to U.S. patients. Sheitoyan-Pesant et al. report that physicians "rarely" resort to FMT when managing rCDI patients.[59] Edelstein et al. note that the time required to identify, screen, and process fecal matter from a direct donor delays patient care.[60] While the procedure is relatively simple, it requires considerable time and effort to prepare one-off treatments, which leads to FMT only being offered in a small proportion of mostly urban hospitals.[61]

Europe

European Union

The European Medicines Agency (EMA) has left decision-making in the hands of its member-states. The Competent Authorities on Substances of Human Origin Expert Group reached this conclusion in 2012, when they determined that feces is not covered by the European Human Tissue Directive 2004/23/EC and would not be considered an HCT/P at the European Union level.[62] As in the United States, this reasoning hinged on a strict definitional interpretation of the Directive guidelines. While the Group acknowledged that FMT contains human and bacterial cells, because the presumed active ingredient of FMT is its bacterial components, they decided it falls outside the scope of the Directive. Accordingly, member states are permitted to regulate FMT as they see fit.[63]

Pan-European medical associations have issued recommendations. The European Society of Clinical Microbiology and Infection Diseases (ESCMID) guidelines "strongly supports a recommendation" of FMT for multiple rCDI, which it defines as 2 recurrences of CDI.[64] United European Gastroenterology (UEG) convened the European FMT Working Group, consisting of 28 experts from 10 countries. This working group recommends FMT as a treatment option for both mild and severe rCDI, with high quality of evidence and strong strength of recommendation.[65] Pediatric doctors offered specialized recommendations for children: a joint North American Society of Pediatric Gastroenterology Hepatology, Nutrition (NASPGHAN) and European Society for Pediatric Gastroenterology Hepatology, Nutrition (ESPGHAN) position paper recommends the consideration of FMT for treatment in children with episodes of mild-to-moderate CDI including a 6-8 week vancomycin taper failure, or for episodes of severe CDI resulting in hospitalization.[66]

Austria

The Austrian Federal Office for Safety in Health Care considers FMT to be a therapeutic intervention, but does not consider it a pharmaceutical drug, a medical device, or a transplant.[67] In correspondence, the Office stated that they are currently reevaluating this position.[68]

In the absence of regulation, a working group of doctors from the Austrian Society of Gastroenterology and Hepatology (ÖGGH), the Austrian Society of Infectious Disease and Tropical Medicine (ÖGIT), and the Austrian Agency for Health and Food Safety (AGES) developed guidelines for FMT use, including appropriate indications, donor screening methodology, and clinical administration. They recommend the use of FMT for rCDI and severe CDI, and advise that all other indications be treated in a clinical trial setting.[69]

Belgium

The Superior Health Council (SHC), the lead scientific advisory board for the Federal Agency for Medicines and Health Products (FAMHP), was asked to provide guidance to the Agency regarding the classification of FMT. In March 2015, they released a report recommending that stool product used for FMT be classified as human body material, the equivalent of a human cell or tissue-based product. They noted that this recommendation would require revision of the 2008 law defining human body material, which specifically excludes stool. Citing public health considerations, they urged the Agency to adjust the regulations to remove the stool exclusion and regulate FMT as an HCT/P.[70] The SHC recommended that FMT be permitted for use in rCDI, citing significant evidence of its efficacy for that indication. It considers treatment for all other indications to be experimental and advised they be conducted as part of a clinical trial.[71]

The FAMHP adopted the SHC recommendations in October 2018, after Belgian legislators amended

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December 2008 legislation so that stool could be classified as an HCT/P.[72]

Denmark
The Danish Medicines Agency (DMA) states that FMT may be considered an unapproved medicinal product, but has issued no formal classification. The DMA further states that tissue regulation best fits the FMT product, but that no official determination has been made.[73]

Estonia
The State Agency of Medicines (SAM) notes that FMT is neither produced nor marketed in Estonia, and therefore no formal determination has yet been made. SAM states that they have concluded that FMT does not belong under the tissue and cell legislation, because the mechanism of action of the product is not related to the tissues and the cells of human origin. The regulator suggested that products that are indicated to contain disease and contain live bacteria are generally considered to be drugs, but that a final decision would require more information about a specific product.[74]

Finland
The Finnish Medicines Agency (Fimea) notes that stool itself is not a medical substance, but, according to the Medicines Act, is considered a drug when intended for use to cure, alleviate, or prevent a disease or its symptoms. Regarding treatment of patients, Fimea states that decisions are made on a case-by-case basis, but that FMT use is usually permitted in a hospital setting.[75]

Finnish clinicians conducting an FMT study queried Fimea and found that their study did not require Fimea's approval. These researchers recommend Finnish physicians follow European FMT Working Group guidelines for FMT use in rCDI, and to investigate all other potential applications in a clinical trial setting.[76]

France
L'Agence National de Securite du Medicament et des Produits (ANSM) classifies FMT as an experimental drug. FMT may be used in the context of an approved clinical trial, or when prepared by a hospital or pharmacy in accordance with Article L.5121-1 of the French Code of Public Health. In its guidance document, the ANSM cautions against wide-spread hospital or pharmacy preparation, noting that in the absence of a clearly established risk/benefit ratio, FMT should be a last resort, reserved for serious or rare situations, after the patient has failed conventional treatments and in the absence of available alternative treatments. When FMT is used, the guidance also requires informed consent, product traceability, and specifies donor screening protocols.[77]

Following the ANSM's guidance, the French Group of Faecal Microbiota Transplantation (FGTF) convened in 2014. The FGTG consisted of a panel of physicians, pharmacists, and microbiologists, and was supported by the French National Society of Gastroenterology (SNFGE), the French Infectious Disease Society (SPILF), and the National Academy of Pharmacy. The recommendations they issued are in line with those of the ESCMID, which finds FMT indicated in multiple recurrent CDI (1 recurrence) after the failure of standard therapies.[78]

Germany
The Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) has issued no formal guidance on FMT classification. In correspondence, BfArM stated that classification is made on a case-by-case basis not by BfArM, but by the competent authority of the German state in which the product will be used.

While re-emphasizing that decision-making authority rests at the state level, BfARM did indicate that FMT fulfills the standard definition of a drug according to the Medicinal Products Act. They further noted that market authorization would not be required, because the product is manufactured from a substance of human origin.[79]

Ireland
The Health Products Regulatory Authority (HPRA) does not regulate FMT, considering its use in the practice of medicine. In correspondence, HPRA pointed to tissue and cell regulation as a good practice standard, though emphasized it is not legally applicable to FMT.[80]

Irish researchers found that despite a permissive regulatory structure, FMT remains underutilized due to logistical issues such as the lack of frozen prescreened stool, donor selection challenges, and absence of a national protocol. Clinicians expressed a desire to use FMT in the treatment of rCDI patients, but cited stool availability as the major hurdle.[81]

Italy
In Italy, FMT is regulated by the Italian National Transplant Centre (CNT) using the safety and quality standards of cells and tissues. In April 2018, the *ad acta* Commissioner released a document outlining the regulatory, clinical, and organizational aspects of a national FMT program. The document specifies inclusion and exclusion criteria for patients and donors, including screening tests, stool processing and stor-

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age practices, and patient follow-up. For a duration of at least two years, the CNT will provide logistical support and expert guidance in the establishment of FMT centers, and will also facilitate the collection of patient outcome and adverse event data. In a clinical setting, clinicians may only use FMT for the treatment of rCDI, with a preference for colonoscopic or enema administration. All other indications must be treated in the context of a clinical trial.[82]

Malta
The Medicines Authority does not currently regulate FMT, though the issue is under discussion.[83]

The Netherlands
When used as a treatment in a medical setting, the The Dutch Healthcare and Youth Inspectorate states that FMT is subject to national legal regulations concerning quality of care.[84] Dutch researchers report in practice that FMT is permitted for use in patients with rCDI, but that other indications must be treated in the context of an approved clinical trial.[85]

In 2015, the non-profit Netherland Donor Feces Bank (NDFB) was founded to provide a standard FMT product for Dutch rCDI patients. In its first nine months offering FMT, NDFB sent 31 FMTs to 18 hospitals and reported a cure rate of 84%.[86]

Norway
The Norwegian Medicines Agency (NoMA) provisionally classifies FMT as a medicinal product. In correspondence, they write that no products have yet been formally evaluated.[87]

Poland
When contacted, the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products Body disclaimed jurisdiction over FMT regulation and referred the author to the National Centre of Tissue and Cell Banking, stating that that office has the responsibility for determinations of medical products with human origins.[88] The National Centre of Tissue and Cell Banking did not respond to inquiry.

Portugal
The National Authority of Medicines and Health Products (INFARMED) has no formal position on the classification of FMT. However, in correspondence, INFARMED states there is non-binding precedent to treat it as a biological medicinal product.[89]

Slovenia
In correspondence, a representative from the Agency for Medicinal Products and Medical Devices (JAZMP) commented that JAZMP has no formal regulatory position on this product.[90]

Spain
The Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) does not consider FMT a pharmaceutical product. The Spanish National Transplant Organization (ONT) likewise disclaims regulatory authority, believing FMT to be neither a tissue nor an organ transplant. Accordingly, there is no national-level regulation of FMT in Spain.[91]

The Asociación Española de Gastroenterología (AEG) recommends FMT for adult patients with 3 episodes of CDI after failure of standard therapies, or for adults with refractory CDI. Citing a lack of evidence, the AEG does not recommend FMT for children, pregnant women, or patients with a life expectancy of less than 3 months.[92]

Switzerland
SwissMedic regulates FMT as an investigational medicinal product, and requires all uses to be conducted under an approved clinical trial protocol.[93] As of April 2019, there was one enrolling clinical trial investigating FMT for the eradication of antibiotic-resistant bacteria colonization.[94]

United Kingdom
The Medicines & Healthcare Products Regulatory Agency (MHRA) regulates FMT as an unlicensed medicinal product. In their June 2015 position paper, MHRA emphasizes several ways patients may access FMT. FMT may be prepared by a pharmacy for patient use when it is either in accordance with a prescription for an individual patient (the "magistral option"), when it is intended for the direct use of that pharmacy's patients (the "officinal formula"), or when it is prepared for use in an approved clinical trial. FMT may also be provided under the "Specials" framework, where it is formulated in accordance with the specifications of a physician for use by an individual patient under his or her direct care.[95]

MHRA made this determination immediately following the Human Tissues Authority (HTA) disclaimer of regulatory authority over the product. In June 2014, the HTA was asked to consider whether FMT met the definition of a human tissue, and therefore should be regulated under their authority. After deliberation, the HTA concluded that FMT regulation does not fall within their purview, though they recommended that organizations formulating FMT consider the HTA's quality and safety assurance guidelines as a matter of good practice.[96]

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The National Institute for Health and Care Excellence (NICE), responsible for developing evidence-based guidance and quality standards for health and social care within the United Kingdom (UK), recommends the use of FMT for rCDI patients. In their guidance document, they urge that the usual patient safeguards of informed consent, audit, and clinical governance must be in place, record-keeping must be robust, and the patient must have failed traditional antibiotic therapies.[97] Public Health England likewise recommends consideration of FMT for patients who experience multiple CDI recurrences.[98]

Medical societies in the UK concur with the NICE recommendations. A joint FMT working group composed of members of the British Society of Gastroenterology (BSG) and the Healthcare Infection Society (HIS) issued guidelines strongly recommending FMT for patients with 3 episodes of CDI or 2 episodes of CDI with risk factors for further episodes, including severe or severe-complicated CDI. Caution is recommended for rCDI patients with certain comorbidities, including decompensated chronic liver disease, immunosuppression, allergies, and inflammatory bowel disease.[99]

Despite this reasonably permissive regulatory structure and positive guidance from NICE and medical societies, FMT access in the UK is regionally variable. A 2015 survey of 130 sites found that only 28% had performed FMT for rCDI, and only seven of those sites had treated 10 patients. Sites that did not offer FMT and referred patients elsewhere primarily referred them to Glasgow, Birmingham, and Exeter. 70% of the sites that did not offer FMT services expressed interest in doing so, but cited logistical hurdles and the fact they "did not know where to start" as the primary barriers to provision of the treatment. The researchers recommended the adoption of national donor screening and stool preparation guidelines to facilitate more widespread adoption.[100]

Oceania

Australia

The Therapeutic Goods Administration (TGA) currently considers FMT to be an unapproved therapeutic good, accessible to patients under four schemes. Under the Special Access Scheme, patients may access FMT under exceptional clinical circumstances, as indicated by their prescribing doctor. Under the Authorized Prescriber Scheme, clinicians may apply to the TGA for blanket authorization to provide FMT to all patients in their immediate care with a given indication. Patients may also import, with TGA approval, therapeutic goods for their personal use, or access FMT as part of a clinical trial.[101]

The TGA is actively considering revising the regulations around FMT. In October 2018, they hosted a stakeholder forum with the aim of opening a dialogue about modifying FMT regulation in a way that is safe and clinically appropriate, while ensuring its continued supply. In January 2019, they released a consultation paper soliciting input on future regulation. In the paper, they identified four possible regulatory frameworks, ranging from strict regulation as an investigational biologic drug, to practice of medicine, to industry self-regulation. The comment period for this document closed in March 2019, and the TGA has not communicated a timeline for issuing revised guidance.[102]

The Gastroenterological Society of Australia (GESA) supports the use of FMT as a treatment option for all Australian rCDI patients, and advocates that there be at least one public hospital in each state or territory that offers FMT. GESA recommends that FMT for all other indications should be conducted in a clinical trial setting. GESA also takes a position on the classification of FMT, arguing that "faeces for FMT would be better classified as a bodily tissue donation in a similar way that blood and blood donation is regarded."[103] The Australasian Society of Infectious Diseases (ASID) likewise recommends FMT for 2 recurrences, provided

In the U.S., adjusting the definition of an HCT/P to allow for the inclusion of stool, and specifically the bacteria within stool, does represent a shift in thinking. This proposed shift is grounded in changing societal and scientific understandings of human-to-other boundaries. While amending legal definitions can be burdensome, the Belgian example demonstrates that it can be done when scientists, clinicians, and policymakers are willing to challenge the status quo and privilege positive public health outcomes over calcified definitions.

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standard antibiotics have failed and there are no contraindications. ASID is more cautious in its pediatric recommendation, advising FMT on a case-by-case basis in severe, refractory or relapsing CDI with >3 episodes of disease.[104]

Australia is a locus of FMT research, led by Dr. Thomas Borody of the Centre for Digestive Diseases (CDD). The Sydney-based CDD treats patients with rCDI along with a host of other indications, including irritable bowel disease and parasitic infections. Borody reports he has overseen over 12,000 FMT administrations.[105] While the Sydney clinic serves an expansive patient population, access throughout the rest of the Australian continent is variable. GESA calls for stool banks to be established in at least one public hospital in each Australian state or territory, recognizing that Australia's vast geography necessitates regional distribution of stool banks to adequately meet patients' needs.[106]

New Zealand

The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) considers FMT an unapproved medicine, and notes that clinicians may import or procure through a pharmacy unapproved medicines for use in a patient under their direct care.[107]

Asia

Hong Kong SAR

The Department of Health (DOH) of the Special Administrative Region of Hong Kong would not comment on the classification of FMT.[108] However, Hong Kong is the site of AsiaBioBank, a stool bank that provides processed, frozen FMT for the treatment of rCDI and irritable bowel diseases. The continued operation of this bank implies a permissive regulatory structure.[109]

Israel

In Israel, the Medical Directorate considers FMT an unapproved medicinal product. FMT may be used in a hospital setting for the treatment rCDI. All other indications must be treated under an approved clinical trial protocol.[110]

Singapore

The Therapeutic Products Branch of the Health Sciences Authority (HSA) stated in correspondence that the classification of FMT is currently under review, and that they are unable to provide advice at this time.[111]

Conclusion

Definitions shift over time to meet evolving needs, norms, and understandings. Recent research suggests human cells' gene expression is deeply entangled with their microbiome, to such an extent that philosophers, medical professionals, and journalists have begun reconceptualizing the demarcation between the human and the non-human.[112]

In the U.S., adjusting the definition of an HCT/P to allow for the inclusion of stool, and specifically the bacteria within stool, does represent a shift in thinking. This proposed shift is grounded in changing societal and scientific understandings of human-to-other boundaries. While amending legal definitions can be burdensome, the Belgian example demonstrates that it can be done when scientists, clinicians, and policymakers are willing to challenge the status quo and privilege positive public health outcomes over calcified definitions.

Note

Ms. Scheeler reports personal fees from OpenBiome and Finch Therapeutics Group outside the submitted work.

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