Ethicolegal framework for the regulation of human faecal microbiota transplants in South Africa: Progress, challenges and recommendations

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This article examines the ethicolegal challenges in regulating faecal microbiota transplantation (FMT) in South Africa (SA), where a regulatory vacuum under the National Health Act 61 of 2003 (NHA) and Medicines and Related Substances Act 101 of 1965 (MRSA) hinders the implementation of FMT. FMT effectively treats recurrent *Clostridioides difficile* infection by restoring gut microbiome balance, with potential for broader applications, but lacks clear classification as human tissue, biological material, or a medicine under the existing framework. The article suggests regulatory classifications for the different types of human stool under both the NHA and the MRSA. Drawing on relevant guidelines issued by the Food and Drug Administration in the USA and the European Medicines Agency, including the 2024 European Union's Substances of Human Origin (SoHO) Regulation, which standardises microbiota safety and traceability, the article concludes with recommendations aimed at closing the existing regulatory vacuum concerning FMT in SA.

Keywords: faecal microbiota transplantation, regulation, ethicolegal framework, South Africa, microbiome regulation, SoHO Regulation

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The human body consists of a dynamic and diverse microbial community termed the microbiome, which encompasses bacteria, archaea, viruses and eukaryotes. This microbiome exerts a profound influence on health and disease, modulating conditions such as diabetes, multiple sclerosis, autism, cancer and inflammatory bowel disease.[1] In recent years, the gastrointestinal tract microbiome has become the focus of intensive research owing to its critical roles in immunology, nutrition, and overall physiological wellbeing.

Microbial populations within the human body collectively comprise up to 100 trillion cells, exceeding the number of human cells by a factor of 10, while the aggregate microbial genome encodes approximately 500 times more genes than the human genome.[2] The microbiome encompasses all microbiota and their genetic products, including proteins, metabolites and RNA.[3,4] A healthy human microbiome is characterised by high alpha diversity, representing the variety and relative abundance of microbial taxa within an ecosystem.[5] Dysbiosis, defined as a disturbance of this equilibrium, is associated, among other conditions, with pathologies such as obesity,[6] inflammatory bowel disease, autoimmune disorders, allergies and diabetes.[7] Variables shaping diversity of the human microbiome include mode of delivery (vaginal v. caesarean),[8] gestational age,[8] infant feeding practices,[9] antibiotic exposure,[10] and maternal health and dietary patterns.[11] By the age of three, the composition of a child's microbiome becomes similar to an adult's.[12]

Persistent influences on the microbiome encompass the genetics of the individual (albeit to a limited degree), age, sex, geography, chronic illness, diet, medications (particularly antibiotics), and environmental factors.[13] Gut-derived molecules, such as lipopolysaccharides and short-chain fatty acids, affect organs, metabolism and the immune system. The microbiome-gut-brain connection illustrates these extensive effects.[14] Therapeutic interventions targeting the microbiome include probiotics, dietary modifications, phage therapy, antibiotics, and faecal microbiota transplantation (FMT). FMT entails the transfer of gut microbiota from a healthy donor to a recipient to re-establish a balanced microbial ecosystem.[15] It has demonstrated exceptional efficacy in treating recurrent *Clostridioides difficile* infection (CDI) and is incorporated into standard guidelines in the USA and Europe.[16] CDI, attributable to the spore-forming bacterium *C. difficile*, manifests as diarrhoea and potentially fatal colitis, predominantly precipitated by antibiotic-induced dysbiosis.[17] FMT restores helpful microbes that fight harmful ones and produce beneficial substances.[18] Internationally, stool banks such as OpenBiome in the USA have facilitated treatment for thousands of patients and supported clinical trials in this context.[19] OpenBiome, for example, implements stringent donor screening protocols, mitigating challenges such as cost, ethical concerns, and coercion inherent in patient-selected donors.[19]

In South Africa (SA), the implementation of FMT remains constrained and is confined to research applications for recurrent CDI or experimental therapeutic contexts. The current 2015 clinical practice guidelines for FMT by the South African Gastroenterology Society (SAGES)[20] are limited by their narrow scope, lack of regulatory clarity, and outdated clinical framing (see also Nana *et al.*[21]). Some of the gaps in the guidelines include that donor screening protocols are not standardised or detailed, leaving room for variability and risk. There is also no guidance on long-term follow-up, adverse

event tracking, or microbiome monitoring after FMT. Finally, the guidelines do not address quality control, storage or transport of donor material, which are critical for safety and reproducibility. The field of FMT applications has advanced considerably since publication of the guidelines, resulting in persistent regulatory ambiguity, as FMT does not align seamlessly with extant frameworks for human tissue, medicines or medical devices.[22-24]

Clinical practice and safety considerations

FMT is delivered through modalities including colonoscopy, enema, nasogastric tube, or capsules enclosing frozen or lyophilised donor microbiota.[25] Capsular administration has demonstrated 96% efficacy for CDI, comparable to colonoscopy, while offering benefits such as non-invasiveness and absence of sedation-related risks.[26] Recipients of the capsules typically consume 10 - 40 capsules in a single session.[26] Donor screening is paramount: prospective donors undergo comprehensive clinical evaluations, excluding individuals with infectious risks or histories of microbiome-associated disorders (e.g. autoimmune, allergic, neuropsychiatric or neoplastic conditions).[27] Serological and faecal assays screen for pathogens, with periodic reassessments every 2 months.[28] Stool is preserved in cryopreservation at –80°C, with aliquots retained for adverse event investigations.[19] Long-term registries, such as the registry maintained by the American Gastroenterological Association, monitor recipients for up to 10 years after FMT.[29]

Current regulatory challenges in SA

In SA, the regulatory classification of FMT remains unclear.[22-24] FMT may incorporate aspects of tissue transplantation, pharmaceutical registration, or medical practice. The categorisation of medicines in SA typically hinges on origin and extent of manipulation. For human stool, varying degrees of processing are feasible: minimal manipulation (e.g. frozen slurry) or extensive processing (e.g. capsules with defined microbial consortia).[30] Minimal manipulation entails homogenisation of faeces in saline or glycerol without modifying biological attributes of the faeces.[30] Advanced manipulation includes concentrated microbiota in capsules or cultured bacterial assemblages (e.g. groups or communities of bacteria that coexist in a specific environment, interacting with each other).[30]

As noted, SA lacks dedicated regulations for FMT, engendering a regulatory lacuna. The National Health Act 61 of 2003 (NHA)[31] regulates, *inter alia*, the utilisation, extraction and transplantation of human tissue and biological material, whereas the Medicines and Related Substances Act 101 of 1965[32] (MRSA) governs medicines, biological products and medical devices. The classification of FMT and human stool persists as ambiguous in SA. Human stool, unmentioned in NHA definitions, is unlikely to constitute human tissue per section 1, which defines tissue as 'flesh, bone, a gland, an organ, skin, bone marrow or body fluid', excluding blood or gametes, but more aptly fits 'human biological material' as defined in the Regulations Relating to the Use of Human Biological Material,[33] encompassing '*material from a human being* including DNA, RNA, blastomeres, polar bodies, cultured cells, embryos, gametes, progenitor stem cells, small tissue biopsies and growth factors from the same' (emphasis added). The reason for the definition of stool fitting more appropriately under the definition of 'human biological material' in the regulations is that faecal material not only derives from the human body, but may incorporate human-derived cells, DNA and microbiota, and is employed in therapeutic and research settings.

Although earlier publications advocated regulating stool banks as tissue banks under the NHA Regulations Relating to Tissue Banks,[34] mandating quality management, safety protocols, traceability, standard operating procedures, donor records and distribution tracking,[22-24] designating human stool as 'human biological material' appears more congruent with the operational and regulatory paradigm of blood banks (the latter not classified as tissue banks in SA). Notably, Cockeran *et al*.[35] observe that global trends position stool banks within existing blood services, supporting the proposition that, with legal clarity absent in SA, the South African National Blood Service serves as a suitable interim locus for human stool banks. Blood banks possess established mechanisms for donation acquisition, product processing, testing, storage, release, quality assurance and donor traceability.[35] The NHA explicitly excludes human blood from its definition of human tissue, and since 2019, human blood has been designated a biological product or medicine by the South African Health Products Regulatory Authority (SAHPRA).[36] Although it is stated on SAHPRA's website that its Biological Medicines Unit regulates whole blood and plasma, only fractionation products are regulated as medicines. Whole blood and plasma for transfusion purposes are regulated in terms of section 53 of the NHA (and regulations) by the South African National Blood Service and the Western Cape Blood Service.

Distinct regulatory standards and licensing requisites apply to tissue and blood banks, with variances in storage, traceability and donor screening protocols. Both retain safety aliquots and conduct long-term outcome tracking, yet blood banks prioritise immediate transfusion safety, infectious disease screening, and donor eligibility.

In the absence of regulatory clarity in SA, if FMT is deemed experimental medical treatment, it necessitates, per section 11 of the NHA, written informed consent from the patient, the healthcare professional and the head of the health establishment, alongside health research ethics committee approval and adherence to research regulations, including the 2024 Ethics in Health Research Guidelines issued by the National Department of Health.[37]

SA's regulatory void jeopardises patient safety and impedes FMT adoption. To expedite FMT integration without undue delay, this article posits that human stool be classified as human biological material under the NHA. Consequently, stool donation requires prescribed informed consent per the Regulations Relating to the Use of Human Biological Material, mandating written donor consent, including provisions for proxy consent in the case of minors (clause 3). Utilisation is confined to specified purposes, including therapeutic applications (clauses 2 and 5). Stool collection must be done in authorised institutions by authorised persons, as stipulated by the NHA and clause 2 of the Regulations Relating to the Use of Human Biological Material. Given the adaptable nature of these regulations, this article advocates their revision and expansion to accommodate the procurement, utilisation and processing of human stool for therapeutic and research objectives. Should this prove impracticable, a separate set of dedicated regulations for faecal material should be formulated.

For processed FMT (e.g. capsules), regulation should transition to the MRSA, classifying such products as medicines or biological entities based on context, development methodology, and final composition.

In SA, biological medicines, derived from living organisms, encompass vaccines, blood components, and biotherapeutics. Processed stool would qualify as a biological medicine, particularly when manipulated beyond minimal thresholds.[36] SAHPRA registration is requisite prior to marketing and distribution.

Stool manipulation degree dictates faecal material classification and regulatory trajectory. Fresh, frozen (from stool banks) or filtered stool represents minimal manipulation and should be designated 'human biological material'. Stool comprising purified microbial consortia or specific bacterial strains represents substantial manipulation, warranting classification as a biological medicine or a biological product. This classification will similarly apply to oral pills of cultured bacterial mixtures. Ambiguity may arise, however, with concentrated stool microbiota in capsules, akin to faecal slurry administered via colonoscopy or nasogastric tube, as these, although in capsule form, consist of minimally manipulated stool. This dilemma underscores the imperative for meticulous deliberation in revising or developing regulations governing FMT use and administration in SA. Recent advancements in Europe and the USA offer comparative insights beneficial to SA and broader African legislators.

Regulatory approaches in Europe and the USA

In the USA, the Food and Drug Administration (FDA) categorises FMT as a biological product under the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act.[38] This framework designates FMT as an investigational new drug (IND), necessitating rigorous premarket approval for safety and efficacy. Historically, the FDA exercised enforcement discretion for FMT in refractory recurrent CDI, permitting procedures without IND if donor screening complied with guidelines.[38]

By 2024 and 2025, however, this discretion had substantially waned, favouring regulated products to attenuate risks such as pathogen transmission. A pivotal development transpired in November 2022 with the approval of Rebyota, a *single-dose enema* from Ferring Pharmaceuticals for preventing recurrent CDI in adults.[39] This was succeeded in April 2023 by Vowst, an oral capsule from Seres Therapeutics, constituting the *inaugural orally administered* FMT therapy.[40] These approvals, confined to recurrent CDI, compelled manufacturers to substantiate the controlled production, pathogen-free sourcing, and clinical efficacy of faecal material via randomised trials.[41] For alternative indications, such as inflammatory bowel disease or metabolic disorders, IND status remains obligatory, with FDA emphasis on post-market surveillance through registries.[41]

In 2025, the FDA issued a warning letter to an entity for unauthorised FMT distribution, reinforcing stringent enforcement against unapproved applications.[42] Stool banks such as OpenBiome have curtailed operations amid these shifts, pivoting to research-orientated paradigms.[19] This product-focused approach balances innovation and safety, but raises concerns about reduced access to non-commercial FMT, especially in underserved regions.[19] The imperative for standardised microbiota replacement therapies persists, with further investigations required to ascertain long-term safety and adverse outcomes.[43]

Conversely, Europe's regulatory landscape remains fragmented, devoid of a cohesive European Union (EU)-wide framework as of 2025, albeit with ongoing harmonisation initiatives.[44] The European Medicines Agency (EMA) supervises advanced therapy medicinal products (ATMPs), yet FMT eludes a neat categorisation akin to gene therapies or tissue-engineered products.[45] Classifications across member states are varied: most regulate FMT as a medicinal product under Directive 2001/83/EC, mandating good manufacturing practice (GMP) compliance and clinical trial authorisation for non-standard uses.[46] For example, Germany and France designate FMT as a pharmaceutical, requiring pharmaceutical-grade preparation and national agency authorisation.[47] Finland considers it a therapeutic procedure analogous to medical interventions, whereas Italy classifies it as human tissue under blood and tissue directives.[47] In the UK, FMT eschews medicinal product regulation but falls under clinical governance and advisory supervision. It is not regulated by the UK Human Tissue Authority, with establishments advised to consult the Medicines and Healthcare Products Regulatory Agency for borderline determinations. FMT application in the UK is currently limited to antibiotic-refractory CDI and ulcerative colitis.[48]

The EMA horizon scanning report underscores the paucity of specific EU guidance, acknowledging FMT's promise as a microbiome-based therapy while advocating regulatory elucidation to mitigate safety and ethical quandaries.[47] The European Consensus Conference endorses standardised donor screening and traceability, although implementation varies, yielding disparities in access.[49] For research, the Clinical Trials Regulation (EU) 536/2014 applies, necessitating ethics approval and risk-based monitoring.[50] This decentralised paradigm fosters adaptability but invites inconsistencies, such as divergent pathogen testing protocols, potentially impeding transnational collaboration. Recent evolutions in microbiome therapy regulations seek to classify highly manipulated FMT (e.g. defined consortia) as ATMPs,[51] advancing innovation beyond CDI.

Recent regulatory developments

The Substances of Human Origin (SoHO) Regulation (EU) 2024/1938 establishes harmonised standards for the quality and safety of human-derived substances in medical therapies, including blood, tissues, cells and microbiota.[52] Superseding prior directives, it will come into operation on 7 August 2027, proffering a model for standardising safety and quality, although its FMT application remains intricate and emergent. Traditional FMT for therapeutic purposes will be subsumed under the SoHO framework. Defined consortia and manipulated microbiota may qualify as ATMPs under Regulation (EC) 1394/2007 of the European Parliament and of the Council on Advanced Therapy Medicinal Products (amending Directive 2001/83/EC and Regulation (EC) No 726/2004),[53] particularly when substantially altered, while clinical trials involving SoHO products must conform to Clinical Trials Regulation (EU) 536/2014, encompassing ethics approval and monitoring. The SoHO Regulation's core aims include upholding elevated safety and quality benchmarks, facilitating innovation, bolstering crisis preparedness, and promoting harmonisation across EU member states. For FMT implementation, the regulation will redress long-standing classificatory inconsistencies, thereby alleviating cross-border collaboration impediments.

The SoHO Regulation explicitly encompasses faecal microbiota as SoHO, imposing standardised requisites for donor registration, history evaluation, examination, testing, processing, storage, quality control, release, distribution, application, and clinical outcome registration.

When FMT material serves in medicinal product manufacture (e.g. capsules or defined bacterial consortia), the regulation governs initial phases up to manufacturer distribution, whereupon pharmaceutical frameworks will prevail. It regulates donor-centric and upstream activities, with pharmaceutical standards (e.g. ATMP or GMP) applying from manufacturing onwards.[52]

Can SA and the rest of Africa benefit from the SoHO Regulation?

Africa manifests the most underdeveloped regulatory milieu for FMT, with scant dedicated guidelines across its 54 nations. SA, as elaborated, navigates a legal void under the NHA and MRSA. No approved FMT products exist, and stool banks remain unregulated, dependent on *ad hoc* ethics approvals. In other African countries, FMT uptake is negligible owing to resource limitations, infectious disease prevalence, and infrastructural deficits. Deficiencies in cold-chain logistics, donor registries and regulatory clarity exacerbate these challenges.

For instance, Nigeria and Kenya lack bespoke regulations, subsuming FMT under general pharmaceutical or transplant statutes. Neither the Africa Centres for Disease Control and Prevention (Africa CDC) nor the African Medicines Agency (AMA) has evidently addressed microbiome therapies. Challenges encompass elevated antibiotic resistance rates, yet regulatory barriers and ethical issues, such as donor equity in heterogeneous populations, obstruct advancement.[54] Unlike the USA and Europe, Africa's current priorities centre on infectious diseases such as HIV and tuberculosis, diverting resources from nascent therapies.

The SoHO Regulation furnishes a paradigm for SA by illustrating the integration of human-derived substances into a unified framework that prioritises donor and recipient safeguards while promoting equitable access. SA's extant, albeit circumscribed, FMT regulatory elements mirror SoHO's focus on traceability and standardised screening, informed consent, prohibition of remuneration beyond reimbursement, and ethics committee oversight for experimental applications. Moreover, the SoHO model could guide the AMA's endeavours to harmonise continental guidelines, leveraging global biologics standards. Although the AMA is not yet fully operational and has not issued any guidelines yet, it is hoped that the AMA will in the future provide important opportunities for continental harmonisation, and over time perhaps centralised regulatory approval. Notwithstanding its promise, the SoHO approach will not wholly ameliorate SA's resource constraints, necessitating tailored, context-specific guidelines to assure equitable access.

Prospectively, establishing a multidisciplinary working group, comprising specialists in microbiology, gastroenterology, law and ethics, would consolidate protocols for donor recruitment, laboratory processing, and clinical application. It is essential that SA's FMT regulatory model accounts for the nation's diverse populace, incorporating equity-orientated donor criteria to avert biases, alongside sustainable funding mechanisms.

Conclusion and recommendations

FMT constitutes a safe and efficacious intervention for recurrent CDI, with prospective utility in other disorders, yet SA's legal void hampers advancement. Human stool conforms to the NHA's human biological material definition, necessitating stool bank regulation, whereas processed stool aligns with the MRSA's stipulations for biological products or medicines. This article recommends: (*i*) classifying fresh or minimally manipulated stool as human biological material under the NHA; (*ii*) regulating stool banks analogously to, or within the ambit of, blood banks in SA; (*iii*) registering processed FMT products as biological products or medicines under SAHPRA and MRSA oversight; (*iv*) refining and updating the SAGES current FMT clinical guidelines to encompass, *inter alia*, rigorous donor screening, selection and traceability; stringent processing, quality control and storage standards; and pharmacovigilance, post-authorisation activities and long-term monitoring, informed by the EU SoHO Regulation; and (*v*) implementing health research and clinical ethics committee oversight for FMT research. Ultimately, sustained advocacy for legislative revisions is imperative to accommodate future microbiome therapy advancements.

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