Microb Health Dis 2023; 5: e954

EUROPEAN ACADEMIC FAECAL MICROBIOTA TRANSPLANTATION (EURFMT) NETWORK: IMPROVING THE SAFETY AND QUALITY OF MICROBIOME THERAPIES IN EUROPE

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Abstract – Faecal microbiota transplantation (FMT) has evolved from an anecdotally reported last resort for the critically ill to a well-established first-line treatment for patients with recurrent *Clostridioides difficile* infection (CDI), supported by grade 1a evidence. Given our improved understanding of the intestinal microbiota and how it impacts human health, FMT is now being explored for a range of emerging indications beyond CDI. In light of the rapid emergence of FMT as a novel treatment strategy in medicine, a need for international harmonisation has arisen. Addressing this need, the recently published 5th edition of the Guide to the quality and safety of tissues and cells for human application, issued by the European Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM), harbours complete descriptions of the collection, procurement and application of donor faeces as a substance of human origin (SoHO). The proposed revision of the Blood Tissue and Cell Regulation of the European Union (EU) incorporates stool for FMT as a SoHO. This revised regulation will provide a regulatory framework for the future development of donor-derived microbiome therapies. To implement and underpin the safety and quality requirements for FMT in this newly designed legal context, and to facilitate clinical use, collaboration and research, we established the European Academic FMT Network (EurFMT network). The European FMT Registry plays a pivotal role within this network, facilitating its clinical activities and monitoring safety. In this document, we summarise the basis for using donor faeces-derived microbiome therapies as well as the aim and main scope for the EurFMT network.

Keywords: Fecal microbiota transplantation, Regulation, Microbiome, Therapy, Intestinal diseases.

INTRODUCTION

Faecal microbiota transplantation (FMT), a life-saving therapy primarily used for recurrent *Clostridioides difficile* infection (CDI), is now a well-established therapeutic modality in most European countries[1]. Essentially, FMT is the transfer of a minimally manipulated, complete intestinal microbiota from a healthy donor to a patient. The procedure may, more accurately, be coined 'intestinal microbiota transplantation (IMT)'[2,3], and the terms FMT and IMT may be used interchangeably.

The use of FMT in modern science was first described in a brief report from Colorado published in 1958, where four patients suffering from fulminant pseudomembranous colitis improved following the application of rectal enemas with donor faeces[4]. Nearly five decades later, the Hallmark Study, a small randomised clinical trial published in 2013[5], documented 90% efficacy of the duodenal application. The trial was paralleled by retrospective cohorts[6,7] and subsequent clinical trials showing similar results[8-10]. Effect rates around 90% after a single application have been substantiated in meta-analyses[11-13], providing grade 1a evidence supporting the use of FMT for recurrent CDI. Emerging indications are being explored in clinical trials and include ulcerative colitis[14-18], colonisation with multidrug-resistant bacteria[19-24], graft-versus-host disease[25,26] and chronic liver disease[27].

The use of donor faeces for human application raises complex logistic, ethical and scientific dilemmas[28]. Faeces from a voluntary and unpaid donor is a substance of human origin (SoHO). The technical guide for the safety and quality of tissues and cells for human application, issued by the European Council[29], describes the handling, procurement, and application of donor faeces. Currently, a proposal has been presented to integrate SoHOs into the European Union (EU) regulative framework for blood, tissues and cells[30]. Whereas minimally processed donor faeces may be regarded as a SoHO, manufactured products derived from and potentially dependent on faeces donations may be regarded as medicinal products[31]. Consequently, several regulative domains apply to the use of donor faeces-derived products, whether they exhibit tissue-like or drug-like characteristics (Figure 1).

Establishing harmonised standards for collecting, procuring and using donor faeces aims to improve the quality of care and patients' access to treatment. As documented in a Europe-wide survey, use of FMT is limited and unevenly distributed across Europe[1]. Collaborative international initiatives have proposed clinical frameworks and application principles for FMT to promote the development of best practice and bridge disparities between countries[32-34]. In the ever-evolving landscape of microbiome therapies, which is marked by increasing complexity, expanding indications and progressively refined application methods,

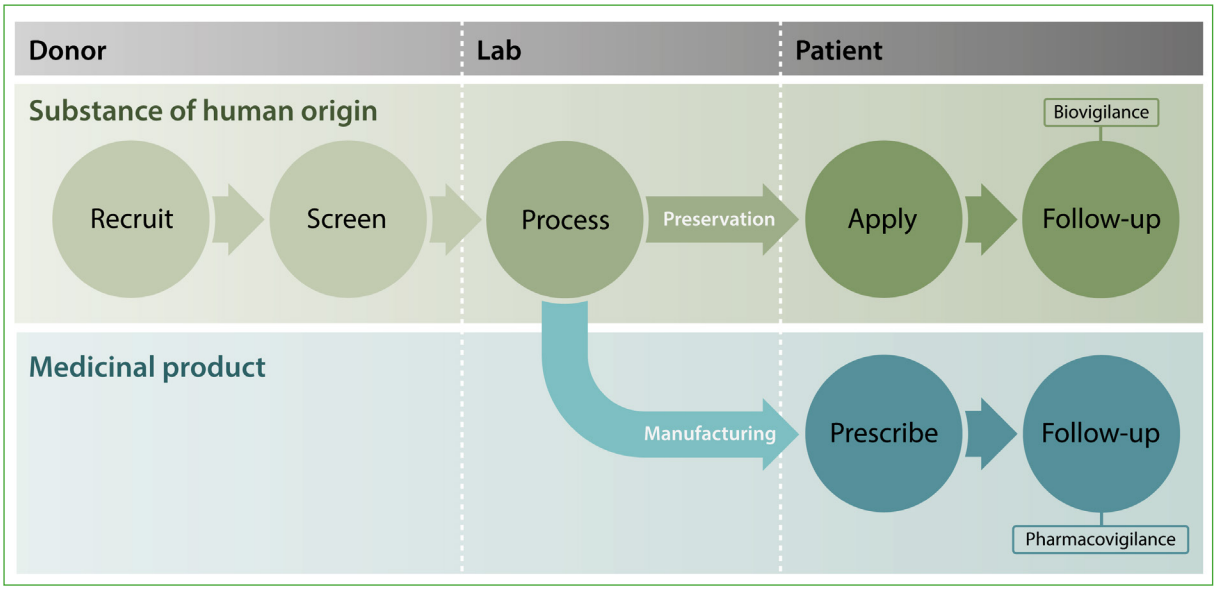

Figure 1. Regulatory domains related to donor faeces-derived products that may be regarded as substances of human origin (SoHOs) or medicinal products.

the demand for knowledge exchange, harmonisation and collaborative efforts in research, manufacturing and clinical application is on the rise. In response to these challenges, we have launched the European Academic FMT Network (EurFMT Network) aiming to unite all non-commercial institutions in Europe involved in the manufacturing and clinical application of donor faeces.

The objective of the present document is to describe the formation, aim, current projects and perspectives of the EurFMT Network.

Aim of the EurFMT Network

The EurFMT Network unites the international collaborative efforts of academics who aim to advance and facilitate the implementation and use of FMT in clinical practice and research.

Establishing the Network: Roots and Dissemination

Rooted in international consensus papers on the use of FMT in clinical practice[32,33,35], a common interest group meeting convened at the United European Gastroenterology (UEG) Week in Barcelona, 2019. The meeting facilitated the development of a standardised model for FMT stool banking[34] and the execution of a Europe-wide survey on the use of FMT, providing a map of its use throughout Europe[1]. During the Covid-19 pandemic, the network grew stronger through collaborative efforts aimed at optimising and harmonising a balanced approach to addressing the infectious risks from novel viral diseases and the need for safe and scalable FMT application[36,37]. Subsequently, after the establishment of network governance and joint discussions at a common interest group meeting of the UEG Week in Vienna in 2022, a general assembly, held virtually on 03 May 2023, marked the formal initiation of the EurFMT Network.

The EurFMT Network invites all active academic institutions in Europe and associated countries to participate. The network currently counts 72 members from a total of 22 countries (Table 1). A visual identity (Figure 2) and a dissemination strategy have been implemented, including a quarterly European FMT newsletter (https://mailchi.mp/ba65bf226f2f/eurfmt-newsletter-12619320) and webpage (http://eurfmt.com). In academic meetings, dedicated academic sessions featured the use of FMT in clinical patient care and research at the European Helico-

TABLE 1. THE EURFMT NETWORK CURRENTLY COUNTS 72 MEMBERS FROM A TOTAL OF 22 COUNTRIES.

Country	Members
Austria	2
Belgium	3
Croatia	2
Czech Republic	1
Denmark	10
Finland	3
France	10
Germany	8
Iceland	1
Israel	1
Italy	3
Lithuania	1
Netherlands	4
Norway	3
Romania	1
Slovakia	1
Spain	2
Sweden	2
Switzerland	2
Turkey	1
Ukraine	1
United Kingdom	10
Total	**72**

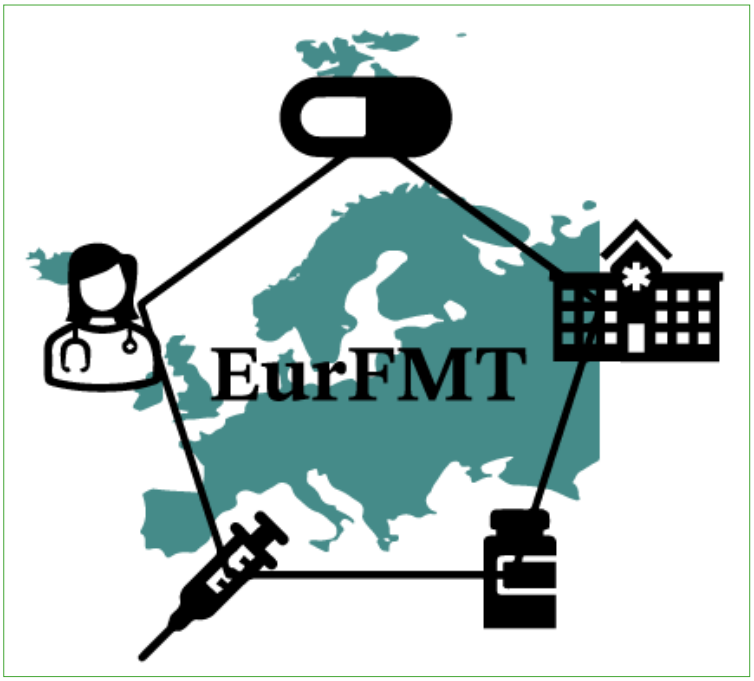

Figure 2. The European Academic Faecal Microbiota Transplantation Network (the EurFMT Network) enables collaboration and knowledge exchange between clinicians, microbiologists and basic science researchers to improve the safety and quality of FMT in Europe.

bacter & Microbiota Study Group (EHMSG) workshops in Glasgow, Scotland, in 2022, and in Antwerp, Belgium, 2023; and during the United European Gastroenterology Week in Copenhagen, 2023.

Expert Groups

Knowledge sharing and collaboration in clinical work and research play a pivotal role in the development of microbiome therapies. The EurFMT Network aims to establish interdisciplinary expert groups under the auspices of UEG and EHMSG. These groups will be affiliated with academic institutions and will collaborate with national scientific societies, relevant authorities, industry, and patient organisations. Bilateral dialogue fora have been established between clinic and research group leaders and relevant national authorities in Germany, Italy, France, Belgium, the Netherlands, and Denmark. These fora serve as models for dialogue development in other member countries.

Our understanding of the complex interaction between the intestinal microbiome and the human host faces additional complexities when introducing a highly diverse donor microbiome in FMT[38]. Currently, the kinetics and mechanisms of action in FMT remain speculative[39]. Moreover, while the donor factor may influence the clinical efficacy of FMT[40,41], specific donor characteristics associated with clinical effect have been investigated only in a limited number of studies[42-44]. Thus, further research is warranted. A comprehensive understanding of microbial engraftment dynamics and an integrative metagenomic analysis linked to clinical outcomes may potentially refine FMT as a precision-based, microbial therapeutic approach. Establishing a consensus on FMT protocols is essential when extending the use of FMT to new indications where the clinical characteristics of each disease may differ. This includes specific protocols for optimising route of delivery, amount of infused faeces, application *via* capsules and/or colonoscopy, as well as preconditioning of the donor or recipient using antibiotics or diet.

Our understanding of how microbial communities evolve and affect human health has expanded massively in the past decade[45,46]. A critical aspect is obtaining an in-depth understanding of host-microbiome interactions and factors that may enhance the efficacy of FMT, summarised in Figure 3. Important factors contributing to the variability in efficacy may include diet, and consequently, the resulting composition and diversity of the donor microbiome and those of the patient's microbiome at baseline[38]. The immune system also has a critical role in supporting FMT[47]. A more extensive characterisation of the intestinal metabolome and an in-depth understanding of how it shapes the host's immune system are needed to understand the relative contribution of bacterial-derived metabolites such as secondary bile acids, short-chain fatty acids and tryptophan metabolites.

Data support a strong link between reduced intestinal microbial diversity and an overabundance of harmful species in chronic conditions, such as obesity, diabetes, inflammatory bowel disease, liver disease, frailty, depression and Parkinson's disease. The intestinal microbiome also harbours microbes resistant to multiple antibiotics and plays a key role in the development of antimicrobial resistance (AMR).

The EurFMT Network is uniquely positioned, owing to its collection of diverse expertises in FMT clinical trials, microbiome sequencing, metabolomics, mucosal immunology, and microbiology. We aim to guide the field in addressing these unanswered key questions related to the mechanisms of FMT to allow microbiome modulation with FMT to reach its full potential for restoring the functional capacities of the intestinal microbiome and maximising the benefits to patients, clinicians and researchers alike.

The European FMT Registry

Documentation and monitoring of clinical activity and safety parameters, including the occurrence of adverse events related to FMT, are pivotal to the safe use of donor faeces. Registry data facilitate monitoring of annual activity and identification of any safety challenges. The availability of such data also facilitates large-scale investigation of donor-recipient and procedural factors. A system to enter or export activity data, pseudonymised

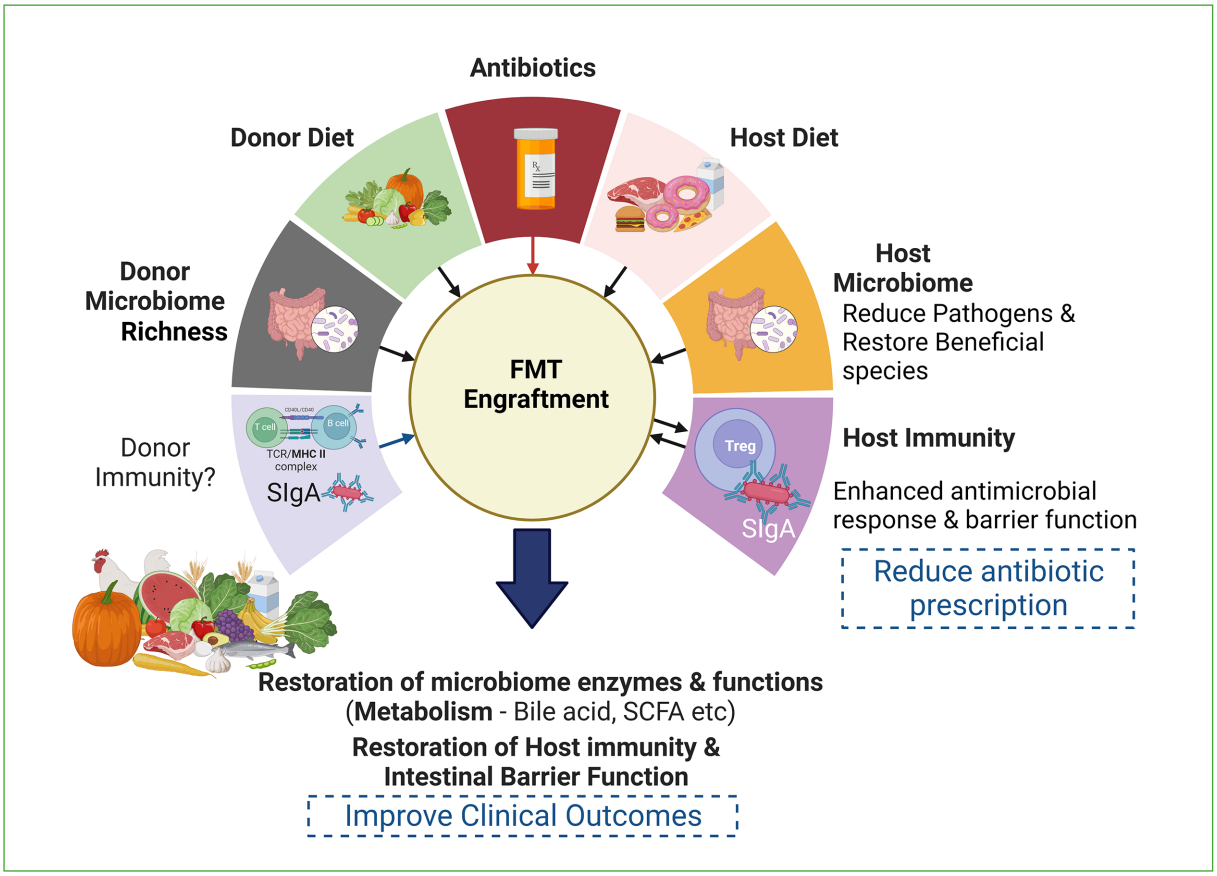

Figure 3. Potential factors that determine FMT efficacy towards restoration of the intestinal microbiome and host immunity leading to enhanced clinical outcomes. Graphics were created with Biorender.

or anonymised depending on current legal and ethics regulations, has been established and is hosted by the Goethe University in Frankfurt, Germany. The development and completion of the European FMT Registry will be a primary task for the network in the coming years.

Regulatory Framework and Harmonisation of Best Practice

The current European Union regulative on tissues and cells does not include SoHOs. Instead, it leaves it to each EU member country to establish the appropriate regulatory framework[48]. Consequently, the regulatory landscape across Europe is fragmented. National regulations range from FMT being regulated entirely as a drug in countries such as France, Germany, and the United Kingdom, to borderline countries including Netherlands, Denmark and Belgium, and, finally, countries such as Italy regulating FMT entirely as a tissue.

Following the recent publication of the technical guide for the safety and quality of tissues and cells[29] alongside a proposal for revision of the EU tissue and cells directive to include SoHOs[30], and after a thorough impact assessment conducted by the European Commission in the first half of 2022, the area now potentially embraces the complexity of microbiome therapies. In this context, donors' role has not been more firmly established. Indeed, unpaid, voluntary faeces donation is fundamental to any FMT establishment. The EDQM guide now therefore addresses not only the technical aspects related to FMT but also stipulates how donors' basic human rights are secured and respected.

The development of donor-dependent[49,50] or donor-derived[51] products for commercial use may serve to meet the need for scalability, patient-tailored treatments and access for all patients in need. Conversely, market exclusivity claims may challenge a transparent development

of the field[52,53]. However, following initial disputes[54,55], the dialogue between academia and industry has evolved into a collaborative exchange, resulting in several mutually beneficial innovation strategies for advancing donor-dependent therapies.

Simultaneously, qualification of regulations for both SoHOs and medicinal products are undergoing revisions. A shared understanding is emerging, where donor faeces is regarded a SoHO and products may either remain SoHOs with minimal manipulation or they may undergo standardisation, enrichment or other substantial manipulations, thereby transitioning into medicinal products (Figure 1). Ideally, such medicinal products should be fully standardised and composed of well-defined components from the gut microbiome. This means that even if the components are initially identified and isolated from human donor faeces, the production process should not rely on recurrent faeces donations.

CONCLUSIONS

Modulation of the intestinal microbiota to obtain health benefits using donor faeces-derived products is now well established in clinical practice. As we explore new potential indications, some of which may require ongoing maintenance therapy, clinical services face challenges related to financial compensation, scalability and safety. To address these challenges, an enhanced understanding of host-microbiome interactions and additional knowledge of how precision medicine may guide the use of microbiota therapies are warranted. Eventually, these elements have the potential to take us beyond the current one-size-fits-all approach. An academic network that unites clinicians and basic scientists to advance these therapies may prove pivotal in fostering these developments.

Acknowledgements

The authors take this opportunity to express their gratitude to Merve Kaya and Line Thomassen for organisational assistance.

Funding Sources

BHM is the recipient of a National Institute of Health Research (NIHR) Academic Clinical Lectureship (CL-2019-21-002). CLH holds a clinical investigator grant from the Novo Nordisk Foundation (grant no. NNF22OC0074080).

Conflict of Interest

Christian Lodberg Hvas: Lecture fees from Tillotts Pharma, Janssen-Cilag, BMS.
Benjamin H. Mullish: Consultancy fees from Finch Therapeutics Group
Josbert Keller: Research grant Vedanta, Advisory Board Microviable Therapeutics.
No other authors have any conflicts of interest to declare.

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