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Establishing fecal microbiota transfer in Germany – a steep and stony path



Potential Conflicts of Interest

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Research grants: 3M, Astellas Pharma, DaVolterra, Evonik, Glycom, MaaT Pharma, Merck/MSD, Organobalance, Seres Therapeutics

Speaker fees: Astellas Pharma, Basilea, Falk, Gilead Sciences, Merck/MSD, Organobalance, Pfizer

Consulting: Alb Fils Kliniken GmbH, Astellas Pharma, DaVolterra, Ferring, MaaT Pharma, Merck/MSD

Overview

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- Current situation
- Vision
- Wish list

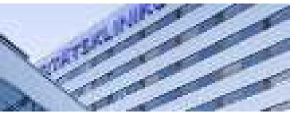

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Table 1. Overview of currently existing donor faeces banks.

Location, founded	Legislation	Donors	Products	Indications	No of issued products[a]	Contact address and website
Leiden University Medical Centre The Netherlands 2015	Allowed for CDI, no legal guideline	Healthy unrelated donors, unpaid	Fresh frozen stool samples	Recurrent/refractory CDI Pilot study for IBS Clinical trial for MDR bacteria	51	info@NDFB.nl http://www.ndfb.nl
OpenBiome, Somerville, Massachusetts, USA 2012	Regulated as an investigational biologic, "enforcement discretion" permits use of FMT for rCDI without IND	Rigorously screened universal donors; compensated $40 per donation	Fresh frozen stool samples in 3 delivery formats: upper delivery, lower delivery and oral delivery (capsules)	CDI not responding to standard therapies Clinical trials for all other indications	33 000	info@openbiome.org http://www.openbiome.org/
Birmingham, UK 2015	MHRA manufacturers licence needed for clinical trial use. Special licence for CDI	Healthy unrelated donors, unpaid	Fresh frozen stool samples	Recurrent/refractory CDI	>200	PHE Public Health Laboratory Birmingham [illegible]@nhs.net
Portsmouth UK 2013	Officially under MHRA as a medicinal product	Healthy, unrelated donors, unpaid	Fresh and frozen stool samples (frozen since July 2015)	Recurrent/refractory CDI	76	fmt@porthosp.nhs.uk
Saint Antoine Hospital, AP-HP, Paris France 2014	Allowed for CDI (considered as a drug). Clinical trial for other indications	Healthy related or unrelated donors, unpaid (paid for clinical trials)	Fresh frozen stool samples	Recurrent CDI Clinical trial for Crohn's disease	33	Prof. Dr. Harry Sokol Gastroenterology Department Saint-Antoine hospital harry.sokol@aphp.fr
University Hospital Cologne, Germany, 2014	No legal guideline	Healthy, unrelated donors, unpaid	Frozen preparations for endoscopic application, enema or in capsules	Recurrent CDI	83	Clinical Microbiome Research Group, Dr. Maria J.G.T. Vehreschild Department of Internal Medicine, University Hospital, Cologne
Hospital Ramon y Cajal, Madrid, Spain 2016	No legal guideline	Healthy related or unrelated donors, unpaid	Fresh frozen stool samples	Recurrent CDI in [illegible] local patients only	11	Dr. [illegible] Gastroenterology Hospital Ramon Y Cajal 28034 Madrid
Medical University Graz, Austria 2012	Allowed for CDI based on national guideline. Other indications need ethics committee board approval	Healthy related and unrelated volunteers. Clinical trials compensated with €30 /donation	Fresh and frozen faecal samples ready to use for lower GI endoscopy	Recurrent CDI Severe CDI Idiopathic colitis Colitis in cancer [illegible] patients Clinical trials for UC, IBS, GvHD	400	Theodor Escherich Laboratory for Microbiome Research www.[illegible]graz.at
Asian Microbiota Bank, Hong Kong 2016	No legal guideline	Healthy unrelated donors, paid	Frozen processed microbiota samples (no fresh or whole stool samples available clinically)	Recurrent CDI Primary CDI Clinical trial for IBS, IBD and MDR bacteria	In process, to be determined	health@asiabiobank.com www.asiabiobank.com

Terveer. Clin Microbiol Infect. 2017 May 18. pii: S1198-743X(17)30275-6.

US Regulation of FMT

- FDA classification: drug
- Does not require an Investigational New Drug Application (IND) for physicians performing the procedure and stool banks providing fecal matter for individuals with *Clostridium difficile* infection (CDI) not responding to standard therapies.
- IND required for other indications

Regulatory history of FMT in Germany

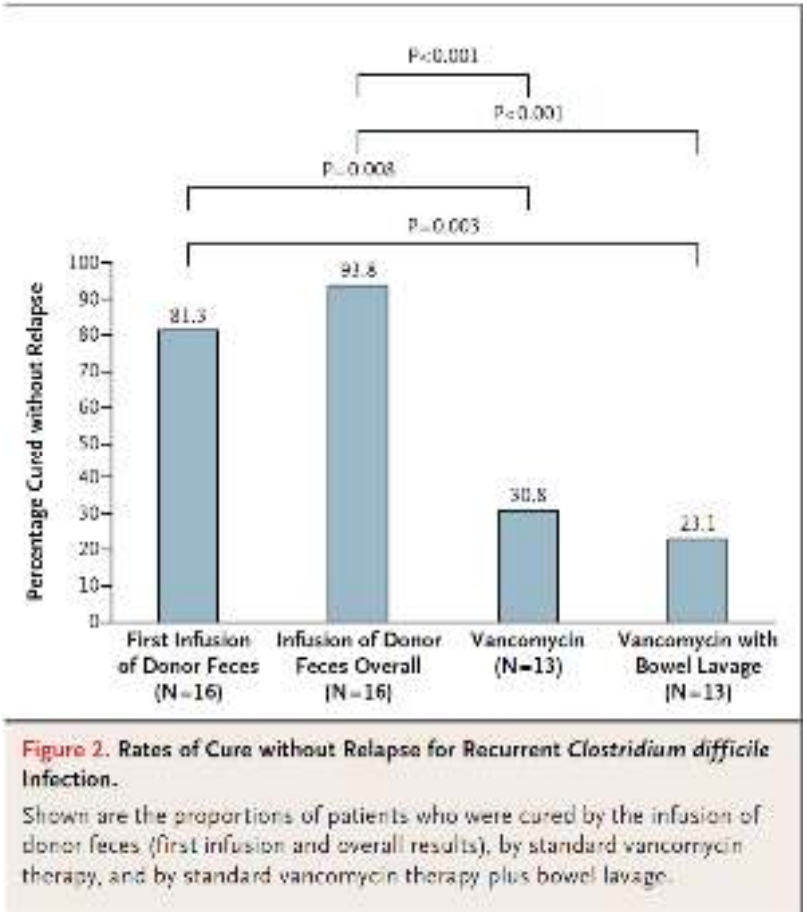


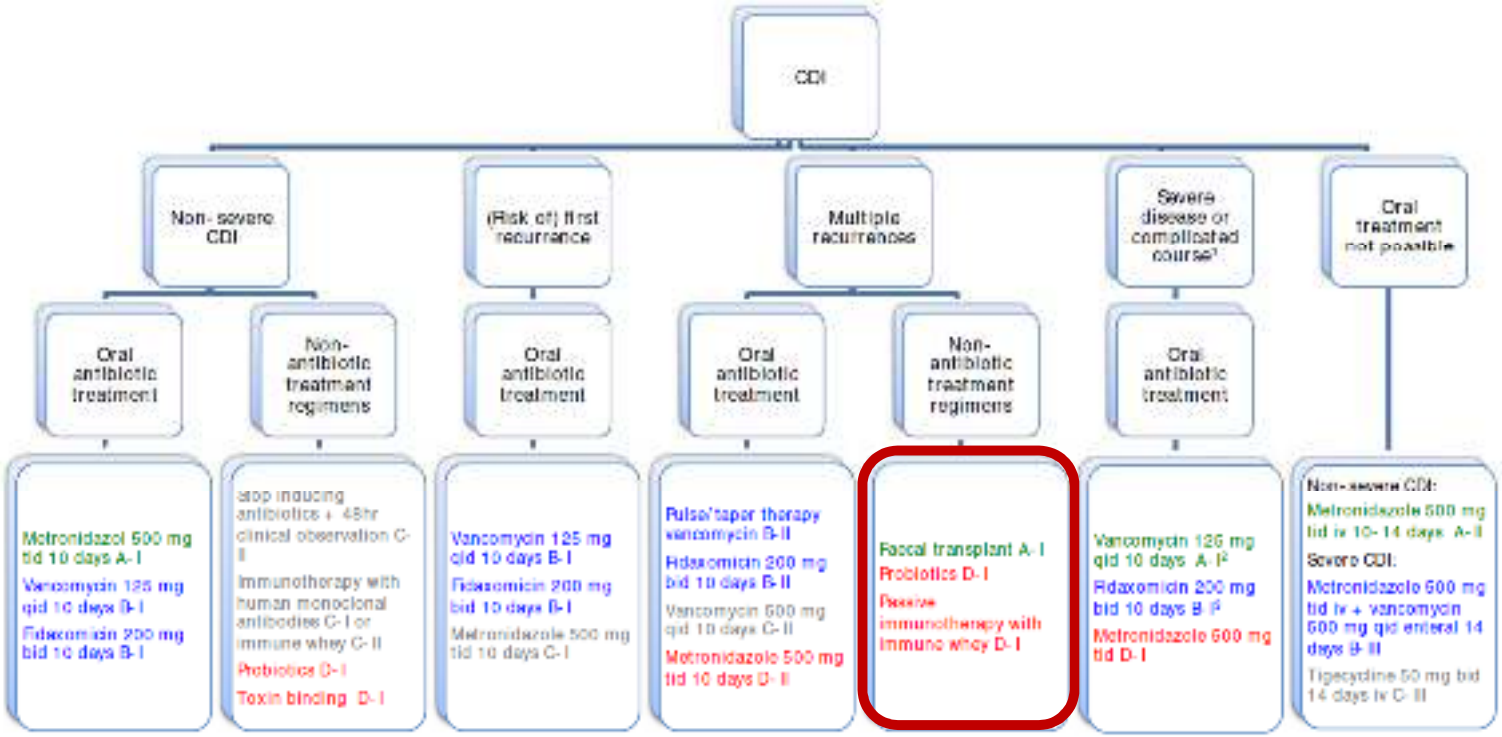
Figure 2. **Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.**

Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

The study that
"got the ball rolling"

Van Nood et al. NEJM 2013; 368(5):407-15.

Update ESCMID Guideline



Debast Clin Microbiol Infect. 2014; 20 Suppl 2:1-26.

FMT in ulcerative Colitis

TABLE 4 Summary of donor stool delivery and processing methods in randomised controlled trials of FMT for UC

	Rossen[30] et al. 2015	Moayyedi[27] et al. 2015	Paramsothy[30] et al. 2017	Costello[29] et al. 2017
FMT route	Nasoduodenal	Enema weekly	Colonoscopy (x1) and Enema (x8)	Colonoscopy (x1) and Enema (x2)
FMT treatments during trial	2	6	40	5
Preparation Fresh/Frozen	Fresh	Fresh / Frozen	Frozen	Frozen
Stool processing oxygen exposure	Aerobic	Aerobic	Aerobic	Anaerobic
Stool weight per FMT (g)	Median 120 g (85-200 g)	6.3 g	37.5 g	Colon 50 g, Enema 25 g
Stool weight week 1	120 g	6.3 g	187.5 g	100 g
Average stool weight per week of trial	30 g/w	6.3 g/w	187.5 g/w	12.5 g/w
Diluent	Saline (500mls)	Water (50mls)	Saline 97.5mls (65%)	Saline (65%)
Stool additive during preparation	Nil	Nil	Glycerol 15mls (10%)	Glycerol (10%)
Stool donor relationship with recipient	Anonymous	Anonymous	Anonymous	Anonymous
Donor stool	Single donor	Single donor	Pooled (3-7 donors)	Pooled (3-4 donors)

FMT, faecal microbiota transplantation; UC, Ulcerative colitis; g, grams; w, week.

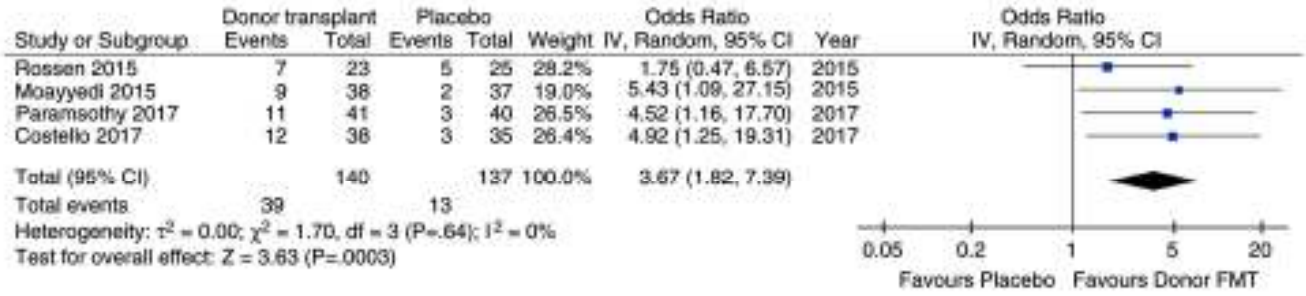


FIGURE 2 Forest plot for remission in randomised controlled trials of faecal microbiota transplant (FMT) for ulcerative colitis. Remission was variably defined as per Table 3

Costello et al. Aliment Pharmacol Ther. 2017 Aug;46(3):213-224. doi: 10.1111/apt.14173.

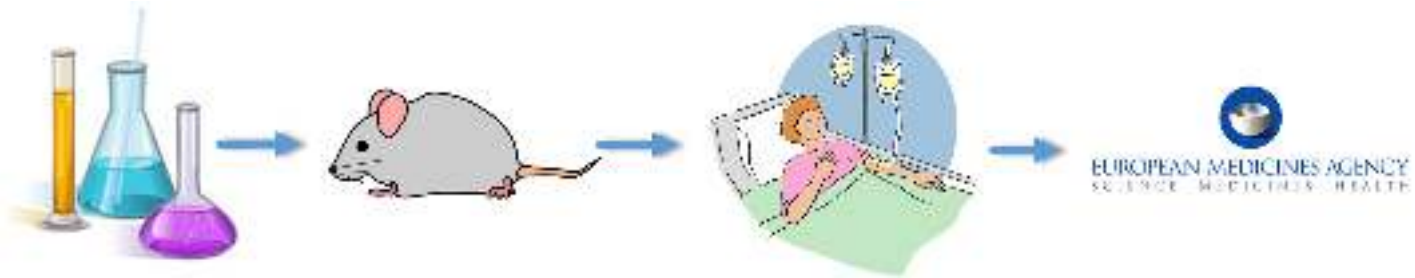
Regulatory history of FMT in Germany

- Physicians and scientists worldwide approach authorities for regulatory categorization of FMT
- The PEI (Paul Ehrlich Institute), national authority for vaccines and biomedicines is approached first

Paul-Ehrlich-Institut

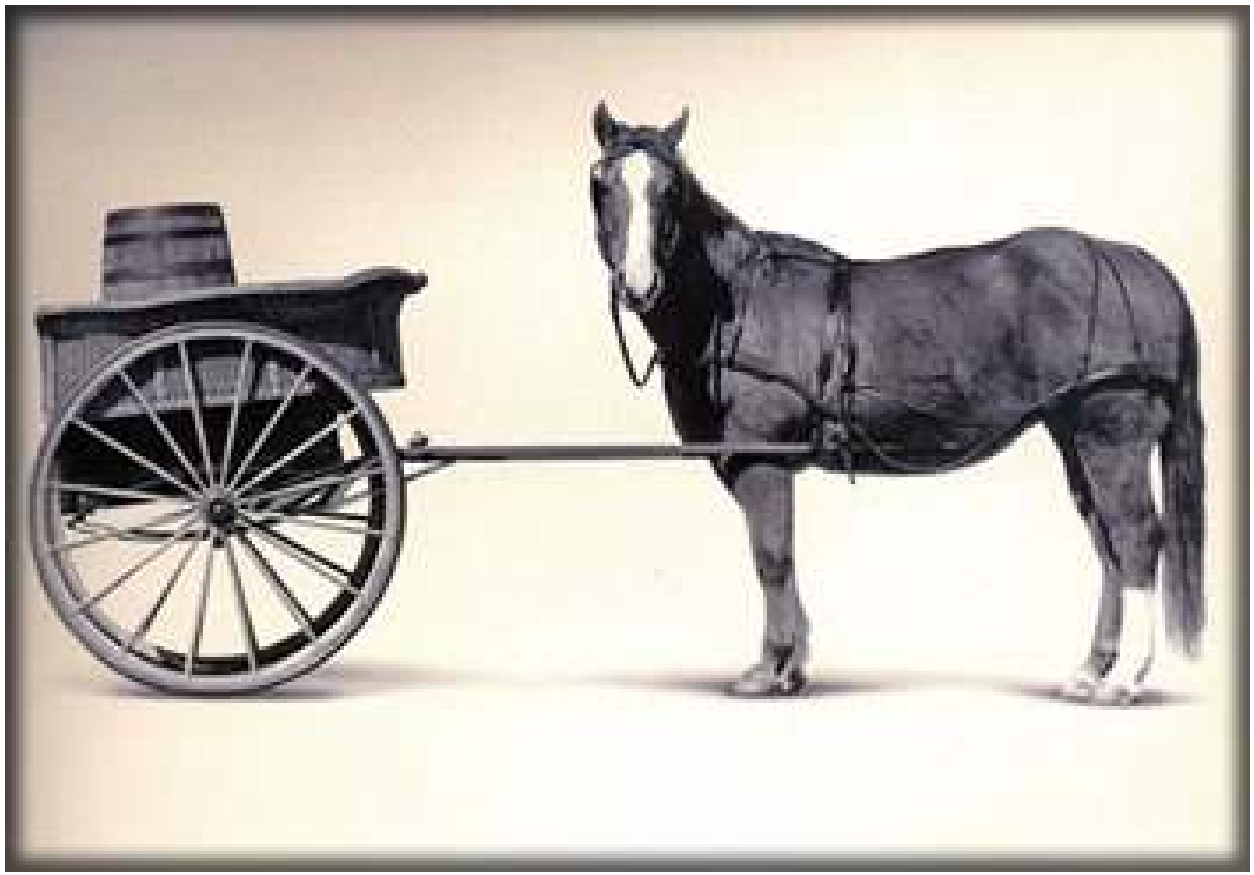
- The PEI denies competence for regulation of FMT and the issue is passed on to the BfArM (Federal Institute for Drugs and Medical Devices)

Classical Drug Development



Basic research | Animal model | Phase I-III | Registration

Fecal microbiota transfer (FMT) – Putting the cart before the horse



Regulatory aspects - FMT

Subject to German Medicines Act
(Arzneimittelgesetz; AMG)

Current legal interpretation:
Individualized clinical trial (Individueller Arzneimittelheilversuch)

Regulation - individualized clinical trial

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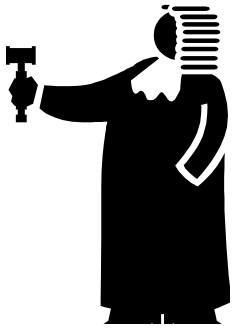
- Individualized choice to use a non-registered drug, when:
  - all registered treatments have failed
  - research suggests a favourable effect
- Treating physician bears complete responsibility
- Despite the word „trial“, not intended to generate research results
- No financial compensation by insurance companies
- Definition by omission



Regulation - Manufacture

- § 13 Abs. 2b AMG und § 20d AMG
- Physicians administering a non-registered drug may do so, if they manufactured it themselves
- For delegation of manufacture, permission from local authorities necessary
- Good manufacturing practice (GMP) facility required

MicroTrans Register

Response to treatment **n=256**

Route of application (%)	D30	D90
All	191/240 (79.6)	153/196 (78.1)
Upper GIT	79/104 (76.0)	68/93 (73.1)
Lower GIT	84/97 (86.6)	63/73 (86.3)
Oral Capsule	33/44 (75.0)	25/33 (75.8)
Combination*	4/4 (100.0)	2/2 (100.0)

*direct endoscopic jejunal and colonoscopic

GCMSG – German Clinical Microbiome Study Group

Vehreschild et al. *United European Gastroenterol J.*, under revision.

Microbiota Transfer - Safety

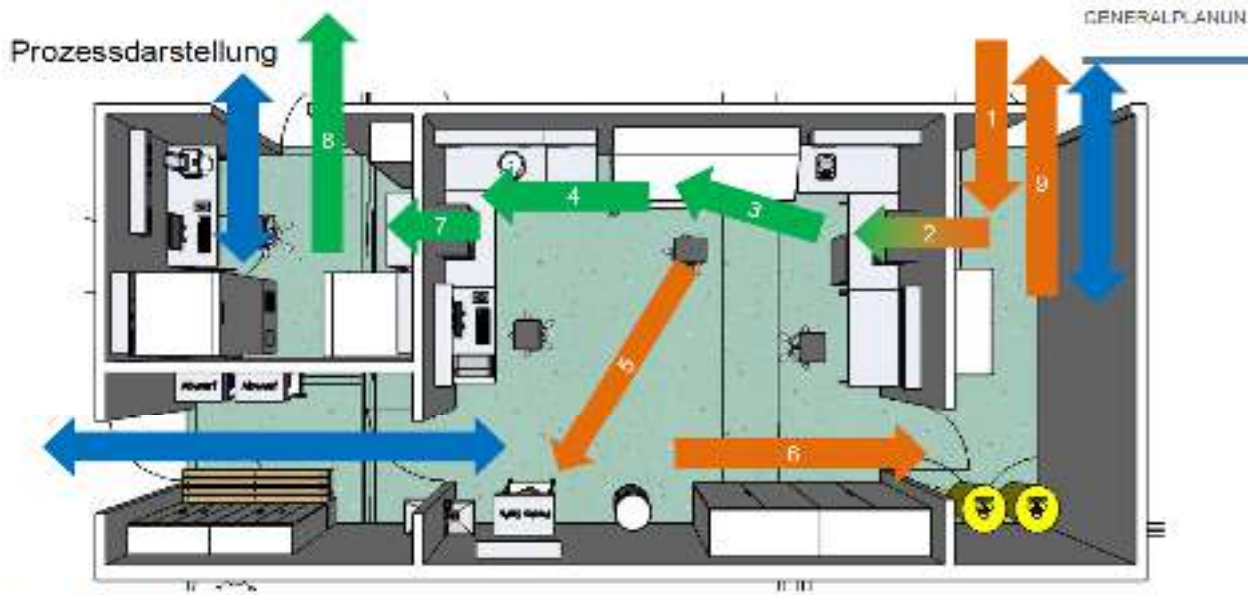
Patients with adverse event (%)	**19 (7.4)**
Type of adverse event – no. (%)	
Nausea	6 (2.3)
Fever	3 (1.2)
Belching	3 (1.2)
Abdominal pain	2 (0.8)
Emesis	2 (0.8)
Food intolerance[3]	2 (0.8)
Aspiration pneumonia	2 (0.8)
Others (retrosternal pressure, hemorrhage, pharyngeal pain, irritable bowel syndrome, loss of a tooth, polyneuropathy, weight gain[4], bloody diarrhea, hypertension, increased peristaltic activity)	Each 1 (0.4)
No adverse events	216 (84.4)

n=256

Vehreschild et al. *United European Gastroenterol J.,* under revision.

Good manufacturing practice facility

Definition: System for ensuring that products are consistently produced and controlled according to quality standards



GMP facility

- First approved GMP-facility in Europe
- Commercial approach
- Focus on hematology/oncology

www.maatpharma.com

Good manufacturing practice in the academic setting

Challenges in the academic setting:

- Laboratory space is extremely scarce in university hospitals
- Exclusive use of facility for FMT production, but moderate expected production volumes
- High-volume air filtration systems
- Necessity of different airlocks
- Establishment of validation steps
- etc.

→ High construction and maintenance costs

FMT GMP facility in Nanjing, China

Academic centers in Germany working on opening a GMP facility

- Cologne:
  - supported by DZIF
  - focus: CDI
- Jena:
  - supported by DLR
  - focus: ulcerative colitis
- Regensburg:
  - supported by DFG
  - Focus on Graft versus Host disease
- Ulm (?)
- Others, I am not aware of ?

But isn‘t FMT outdated anyway?

Yes, I know, but…

- …so far, no effective microbiota-based products available in Germany
- …regulation of microbiota consortia products similarly complicated (one study arm per strain?!)
- …even if a microbiota-based product is successfully registered in Germany, insurance companies may not be obliged to pay for it
- …German academia has no basis for interventional microbiome research. We need to start somewhere!

=

My plead to the BfArM and EMA

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- Transparent guidance documents on requirements for
  - stool banks
  - defined microbiota consortia
- Uncomplicated and safe access to FMT products for patients with rCDI
- Harmonization at the EU level

Federal Institute for Drugs and Medical Devices

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Clinical Microbiome Research Group

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