Minimum Requirements for Reporting Fecal Microbiota Transplant Trial

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Fecal microbiota transplant (FMT) research trials are growing in diverse intestinal and extraintestinal conditions that are thought to be either caused or correlated with gut microbiota dysbiosis. Although, the mechanism by which the microbiota results in disease initiation or progression is not fully understood, it is speculated that restoring the symbiosis by FMT could have therapeutic benefits.

FMT is currently approved by the US Food and Drug Administration (FDA) for the treatment of recurrent pseudomembranous colitis caused by *Clostridium difficile*; which is a direct consequence of alteration in microbiota composition caused by long-term antibiotics consumption. Because the disease is directly linked to an altered microbiota composition, it is intuitive that restoring the normal composition -by using non-stringent criteria to define 'normal'- will alter the niche in a way that the commensals will outcompete *C. difficile* bacteria and hence, the infection will be controlled in an ecological manner.[1]

So far, 15 trials have been conducted and published with completely successful results for the treatment of pseudomembranous colitis caused by *C. difficile*.[2-16] However, unlike *C. difficile* infection, FMT in other conditions, such as ulcerative colitis (UC) and Crohn's disease (CD) have had controversial results.[17-24] UC and CD are complex disorders that arise as a result of a complex interplay of host genetics, gut microbiota, host immune response, and environmental factors. It is crucial to identify confounding factors in FMT trials in complex diseases in order to perform more uniform and effective trials in the future.

Except the CONSORT checklist that is used for clinical trials,[25] there is currently no specific minimum requirement for the report of an FMT trial. We can identify two different types of FMT trial. The first type focuses primarily on treating a debilitating, life-threatening condition (e.g., refractory *C. difficile*-induced colitis and in exceptional cases IBD); for which no other therapeutic option is currently available. The second type of trials aims to investigate the efficacy of FMT in conditions where other treatment options are available but are associated with high side effect profiles or high cost (e.g. morbid obesity and non-alcoholic steatohepatitis). In both types the donor inclusion

Table 1: Donor assessment criteria for fecal microbiota transplant trial (adapted and modified from Bakken et al.[1])

Exclusion criteria	•Age <18 or >65 years •Previous or current history of autoimmune, atopic, metabolic, and mood disorders •Previous or current history of gastrointestinal diseases including IBS, IBD, constipation, celiac disease, and gastrointestinal cancer. •Previous or current history of cardiovascular, respiratory, pancreatobiliary, and genitourinary diseases •Diabetes (FPG ≥126 mg/dL or 2-h PG ≥200 mg/dL) •Impaired fasting glucose (110 mg/dL ≤FPG <126 mg/dL or 140 mg/dL ≤2-h PG <200 mg/dL) •Obesity (BMI ≥ 30) •Parkinson disease •Abnormal result of the stool and blood tests (see below) •History of major gastrointestinal surgery (e.g. gastric bypass) •Personal or family history of malignancy •Dementia, severe depression, major psychiatric disorder, or other incapacity for adequate cooperation •Chronic pain syndromes (eg. chronic fatigue syndrome, fibromyalgia) •Allergy to food and drugs •Use of immunosuppressive or chemotherapy agents •Antimicrobial treatment or prophylaxis within the last 6 months •Pregnant or breast-feeding women •Tattoo or body piercing within the last 6 months •Travel to areas with endemic diarrhea during the last 3 months •Alcohol consumption> 15 units /week for women and > 22 units /week for men •Illicit drugs consumption •Shift work
Stool testing	•*Clostridium difficile, Listeria monocytogenes, Vibrio cholerae/Vibrio parahemolyticus, Salmonella, Shigella, Campylobacter, Yersinia, β-lactamase-resistant bacteria, Strongyloides stercoralis, Cryptosporidium sp., Cyclospora sp., Entamoeba histolytica, Giardia intestinalis, Isospora sp., Microsporidium, Anguillules, Giardia intestinalis* •*Adenovirus, Astrovirus, Norovirus, Sapovirus, Enterovirus, Virus Aichi, Rotavirus, HAV, HEV* •Ova
Serologic testing	•HIV, type 1 and 2 •HTLV •Hepatitis B surface antigen, hepatitis B core antibody (both IgG and IgM), and hepatitis B surface antibody •Hepatitis C virus antibody •*Treponema pallidum* •*Strongyloides stercoralis, Toxoplasma gondii, Trichinella sp.* •Laboratory indices (FPG, HbA1c, AST, ALT, ALP, bilirubin, AFP, BUN, creatinine, uric acid, triglyceride, cholesterol, HDL, LDL) •CMV viral Load •EBV viral Load

2-h PG, 2 hour plasma glucose; AFP, alpha fetoprotein; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CMV, Cytomegalovirus; EBV, Epstein–Barr virus; FPG, fasting plasma glucose; HAV, Hepatitis A virus; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HEV, Hepatitis E virus; HIV, human immunodeficiency virus; HTLV, Human T-Cell Leukemia Virus; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; LDL, low-density lipoprotein.

and exclusion criteria have been developed, which are summarised in Table 1. It should be noted that endemic infectious diseases of each region should also be assessed as part of donor exclusion criteria. However, for the investigational FMT trials it is advisable to take into account the complexity of the gut microbiota.

Donor is currently selected based on ascertaining the individual's healthy state by medical history, physical examination, and laboratory tests. The donor is also screened for a number of infective agents including human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). However, given the multitude of genetic and environmental factors that can modify the gut microbiota, it is apparent that lack of clinical diseases does not correlate with having a 'normal' microbiota. In addition, one cannot exclude the possibility that a 'healthy' donor, whose microbiome is considered 'normal', would not develop a disease later in life, that maybe known to be associated with abnormal microbiota. Therefore, it seems reasonable to ascertain the normal composition of the donor microbiota prior to the procedure. In addition, even if the donor is clinically healthy and the microbiota composition is assessed to be 'normal'; it is imperative to select the donor based on the expected beneficial alterations that are exerted on the

Table 2: Specific recommended additions to the CONSORT checklist in investigational fecal microbiota transplant trials

Topic	Item no.	Checklist item	Recommendation
Participants	4a	Donor inclusion criteria	Based on the gut microbiota composition of the donor and the expected beneficial alteration in the recipient
Intervention	5	The interventions for each group with sufficient details to allow replication	Include a microbiota composition analysis for both donor and recipient
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures	Durability assessment should be mandatory

patient microbiota by the donor fecal microbiota (Table 2). Therefore, we recommend that there are two potential ways to select healthy donors based on criteria outlined in Tables 1 and 2. In one approach, one ad hoc donor is selected for each FMT recipient whereas in the second one, universal donors are identified to use for all FMT recipients in a trial. The advantage of universal donors is that for a given trial all patients will receive identical donor microbiota and thus potential confounding effect of different transplanted microbiota is eliminated. By incorporating microbiota analysis in all FMT trials we would expect to observe more consistent and informative results in future FMT trials.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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