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Ethical considerations in microbial therapeutic clinical trials

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Abstract

As understanding of the human microbiome improves, novel therapeutic targets to improve human health with microbial therapeutics will continue to expand. We outline key considerations of balancing risks and benefits, optimising access, returning key results to research participants, and potential conflicts of interest.

The last ten years has seen a dramatic expansion in understanding of the composition and function of microbial communities found across human anatomic sites. The sum total of the members of these microbial communities are described as the microbiota and the sum of the genes of these microbes is labelled the microbiome. As scientific understanding of the human microbiome matures, enthusiasm also grows for applications of this understanding to treatment of human diseases associated with apparent microbiome disruption, described as dysbiosis.

The clearest example of therapeutic microbiota enrichment is faecal microbiota transplantation (FMT) for recurrent *Clostridium difficile* infection (RCDI). FMT for RCDI is relatively inexpensive and is approximately 90% effective when including repeat treatment, a higher cure rate than seen for antibiotic treatment for RCDI.(van Nood *et al.* 2013, Cammarota *et al.* 2015, Kelly *et al.* 2016, Merlo *et al.* 2016, Waye *et al.* 2016) As dysbiosis is increasingly associated with a wide range of other diseases, the success of FMT for RCDI has spurred a wave of pilot studies registered on clinicaltrials.gov, academic speculation and even home experimentation (www.nytimes.com/2017/04/11/opinion/gut-hack.html). (Didesch *et al.* 2016)

However, clinical translation has come in fits and starts, in part because of changes in regulations and requirements from the U.S. Food and Drug Administration (FDA) that reflect the challenges of establishing safety in microbiota manipulation. Given the early state of clinical translation, it is especially important to ensure that clinical trials are conducted ethically. This brief article aims to outline major ethical issues regarding clinical trials of microbial therapies, including concerns about access, implications of limited understanding

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of risks and benefits, and potential for conflict of interest concerns specific to these interventions.

RISK TO BENEFIT RATIO OF MICROBIAL THERAPEUTICS

Potential benefits

Numerous studies have shown FMT to be highly efficacious in treating RCDI. In addition, there appear to be other promising applications for FMT, including treatment of inflammatory bowel disease, treatment of graft versus host disease in hematopoietic cell transplant patients, reduction in intestinal carriage of multidrug resistant organisms (MDRO), and other conditions with more speculative microbiome associations. These potential benefits are generally in the near term and the potential counterbalancing risks in the long term are not well delineated, which is the main concern from the FDA's standpoint.

Understanding of potential benefits of microbial therapeutics is in a nascent state. The mechanisms of FMT efficacy are poorly described, which limits more targeted therapeutic application or attempts to develop treatments with fewer aesthetic barriers. Many microbiome study designs and analytic approaches include point estimates of diversity and abundance of microbial taxa but there are fundamental challenges in establishing temporal causal relationships with point estimates. Further, faecal material is composed of more than just identifiable taxa. Transplanted faecal material includes human cells, metabolites and incompletely digested material. Longitudinal study designs that establish temporal trends in changes in diversity and abundance and other components of faecal material may help, but establishing causality according to the traditional frameworks of Koch's postulates and Bradford-Hill criteria will require rigorously conducted placebo-controlled, blinded randomised clinical trials.(Proctor 2016)

There are additional technical difficulties to surmount when establishing causality. For example, many studies have used a 16S ribosomal gene sequencing approach, which measures taxonomic diversity but does not directly allow for study of the function of the represented taxa. Functional similarity between human microbiome anatomic sites overrode taxonomic similarity in the Human Microbiome Project healthy adult cohort study and demonstration projects, and may be a more relevant measure than taxonomic similarity for interventional microbiome studies.(Proctor 2016) Improved understanding of the benefits of microbial therapies and establishing causality will only come with rigorously conducted blinded randomised clinical trials. Until such trials are conducted, investigators should be cautious to avoid overstating potential benefits of microbial therapeutics.

Potential risks

The FDA's decision to exercise enforcement discretion with regard to FMT for RCDI was contingent on patient provision of informed consent. However, informed consent in therapeutic microbiota studies need to acknowledge the limits to what is known about potential risks and benefits. We have previously outlined challenges in optimal selection and screening of potential faecal donors for FMT but concerns about screening with an perspective to the microbiome associations with colorectal cancer serves as a key example of

unknown risk.(Woodworth *et al.* 2017) It is not known whether an 80-year-old who has been appropriately screened for colorectal neoplasia might be a more ideal donor than a 30-year-old without any such screening who could have a sub-clinical rapidly progressive neoplasm. Another example of an unknown risk pertains to the ideal time for a person to receive microbial therapy. The apparent importance of establishing a healthy microbiome early in life and the passive microbiome transfer that occurs from mother to child raises important ethical considerations about microbiome manipulation in pregnant or early post-partum mothers when there may be unrecognised long-term risks to the child, and potentially their children.

Minor risks have been reported in clinical studies of FMT. Minor adverse effects (AE) of FMT for RCDI like abdominal discomfort have been reported in 15% of a series of 80 immunocompromised patients and in 28.5% in a larger meta-analysis of published FMT case reports/series and clinical trials.(Kelly *et al.* 2014, Wang *et al.* 2016) Recently, a national registry was established to advance understanding of risks and benefits of microbiota therapeutics, with plans to enroll 4,000 patients across 75 sites in the United States.(Kelly *et al.* 2017) While these data are still being collected, informed consent should acknowledge the limited understanding of long term outcomes of microbiota therapies. As for self-directed microbiota transplantation, we are unaware of any reports of poor outcomes directly attributable to home FMT to date, but online instructions currently available leave room for serious harms that may be inappropriately weighed against unreasonable expectations of benefit. The notion of informed consent—or perhaps, ‘informed use’ for home ‘gut hacking’ seems uniquely problematic and infeasible to regulate.

Many clinical trials of microbial therapies have included administration via endoscopy — perhaps because many principal investigators in microbiome studies are gastroenterologists. However, in studies of adverse events related to FMT, the worst outcomes are directly attributable to the endoscopic procedure and not the microbial material itself. Endoscopy also carries significant financial costs, as well as risks of sedation and complications of endoscopy like colonic perforation. It is infrequently mentioned in the literature that delivery of microbial therapeutics in oral capsules has similar efficacy to trials with endoscopic delivery. The route of FMT is also being collected by the FMT registry and further study may inform the risk to benefit ratio of endoscopic vs non-endoscopic FMT.(Kelly *et al.* 2017) Study designs of microbial therapeutics should prioritise optimising the risk-benefit ratio by limiting procedures whenever possible.

Inconsistent composition of the material itself

Further complicating matters of understanding risks and benefits of FMT are the challenges of ensuring consistency and reliability of these therapeutics. The human gut microbiome is thought to be composed of bacteria, archaea, viruses, phages, fungi and possibly protists. The function of these species is not well understood, largely because of difficulty in isolation and culture using traditional microbiology techniques. While the efficacy of FMT for RCDI is thought to mechanistically rely on increased bacterial diversity, the true active ingredient(s) and its corresponding metabolic function is not well established. The risks and benefits associated with FMT likely vary by the abundance of each of these components in a

specific faecal sample or microbial therapeutic. A recent report of efficacy of a faecal filtrate prepared to prohibit transfer of bacteria or spores was effective in treatment of RCDI.(Ott *et al.* 2017) This raised further questions about active agents of faecal material in suggesting that bacteria may not be necessary although further study is needed.

The current spectrum of potential microbial therapeutics ranges from single-species over-the-counter probiotics, to processed faecal matter from screened donors, to highly selected, controlled and proprietary arrangements of live microbes or spores. Probiotics are commonly marketed as food supplements, which have minimal regulatory requirements, and thus content and live colony counts can be highly variable. Microbial components of faecal material are also thought to be fairly variable and influenced by many behavioural factors, leading some to suggest that the process of screening and manufacture for FMT should be the point of regulation, and not the composition itself.(Edelstein *et al.* 2015, Sachs and Edelstein 2015) To protect patients and research participants, professional societies like the American Society for Microbiology, the Infectious Diseases Society of America, and the American Gastroenterological Association, in conjunction with representatives from the FDA and pharmaceutical companies should seek common definitions of probiotics and microbial therapeutics to improve quality assurance and disambiguation of what therapies are actually being tested or used.

RESTRICTION OF ACCESS TO MICROBIAL THERAPEUTICS

Access to potential benefits of FMT was restricted when the FDA announced in May 2013 that FMT should not be performed without an approved investigational new drug (IND) application, citing safety and efficacy concerns, and classifying faecal material as a biologic product. However, after public comment from clinicians and community members about potential limitations in access, the FDA instead elected to exercise enforcement discretion and allowed use of FMT for RCDI without an IND, but stipulated that patients give informed consent, with particular focus to unknown long-term effects. While this revision eliminated one potential barrier to access, the conversation about access to FMT will only grow more ethically and logistically fraught during this age of increasing antibiotic resistance.

In general, conditions associated with dysbiosis that might be treated by microbial therapeutics are chronic, with greater morbidity than mortality. However, a case was recently reported of a woman who had travelled extensively in India and after returning home to Reno, Nevada, she succumbed to a fatal infection with an isolate of *Klebsiella pneumoniae* that was resistant to all 26 antibiotics tested and not susceptible to any known antibiotics. (Chen *et al.* 2017) This clear failure of medical treatment garnered significant attention in the press. The event was characterized as a herald of the waning ability of antibiotic development to keep pace with emerging antibiotic resistance. If cases such as this were to become increasingly frequent, calls for access to potential therapeutic alternatives to antibiotics, such as FMT, could become more urgent and desperate.

There are instances when the scientific community and general public have partnered to prioritise expansion of access to a novel therapeutic when there is a pressing need. During

the Ebola outbreak in West Africa from 2014–2016, community leaders and scientists in affected areas advocated on an international level for roll out of novel vaccine candidates, given the high mortality and limited treatment options for this disease.(Adebamowo *et al.* 2014) Ultimately, the ‘Ebola ça suffit!’ trial was designed such that all trial participants would receive the vaccination, though a proportion would be randomised to delayed vaccination.(Henao-Restrepo *et al.* 2015) In the case of FMT for MDRO infection or colonisation (or for other indications of microbial therapeutics), the ethical question remains: what is the critical threshold of need that should trigger expanded access? In the case of the Ebola vaccine, some have argued that more could have been done to deploy available vaccines earlier, and the medical community should be mindful of ensuring appropriate access to microbial therapeutics if there is possible benefit and acceptable risk.

RETURN OF RESULTS TO MICROBIAL THERAPEUTIC CLINICAL TRIAL PARTICIPANTS

McGuire et al have commented on the ethical questions of returning microbiome sequencing results to participants in the Human Microbiome Project (HMP).(McGuire *et al.* 2008) They note that while return of clinically actionable results may be important in the future, the clinical significance, validity and reliability of such findings have not yet been firmly established for microbiome studies. They suggest that policies regarding actionable individual-level research findings should be reviewed by institutional review boards (IRB) and to leave case-by-case participant result reporting to the discretion of principle investigators. This is a valid approach for cross-sectional studies such as the HMP. For clinical trials, however, participant result reporting rules should be considered during study design if there is a possibility that research findings could reliably inform intervention.

Others have outlined concerns about potential individual-level identifiability of microbiome samples, particularly from potential upload of human gene sequencing data to public databases. Among other issues that have been identified in genetic studies in general (see Figure 1), there may be potential downstream impacts on employment, criminal investigations, and insurance premiums, and these impacts must be considered during the informed consent process for participation in microbiome studies (Meller 2015, Chuong *et al.* 2017). Users of data shared through common databases or data sharing agreements should inform principle investigators of actionable findings for consideration of reporting back to research participants.

There is further concern that return of results to clinical trial participants may include information of unclear clinical significance such as abundance of potentially pathogenic organisms or antibiotic resistance genes. Anxiety and uncertainty about importance of such results could expose research participants to unanticipated harms and unnecessary antibiotic or other treatments. Developing understanding of these risks warrant attention in future microbial therapeutic clinical trials.

CONFLICTS OF INTEREST SPECIFIC TO MICROBIAL THERAPEUTICS

The changing landscape of regulation of FMT by the United States Food and Drug Administration (FDA) and other regulatory agencies in addition to the frequently acknowledged ‘yuck factor’ of processing and ingesting faeces have fostered growth of several stool banking and entrepreneurial groups aiming to develop and market targeted therapeutics for diseases associated with dysbiosis. However, this raises significant ethical questions about core values in microbiome research and potential conflicts of interest. On one hand, the complexity and expense of performing microbiome sequencing and analysis has supported a culture of data and code sharing, especially by the HMP.(Proctor 2016) On the other hand, the NIH has been reluctant to fund clinical trials of microbial therapeutics, so new pharmaceutical companies like Rebiotix and Seres, among others, have worked directly with leaders in clinical microbiome research to develop and fund these clinical trials. Faecal material is classified as a biologic, which has more extensive patent protections than small molecule drugs. However, to our knowledge, there are no patent test court cases of microbial therapeutic patents. The more pharmaceutical companies that enter this marketing space, the less likely it seems that one group could control a monopoly. Such relationships were not uncommon early in the global HIV pandemic when many clinical researchers closely collaborated with pharmaceutical companies. The ethical directive, though, should be to maintain transparency in these relationships and the roles of the funders in all published work, including study design, data storage, analysis, interpretation and composition of and decision to publish manuscripts.

There are other potential economic risks and conflicts of interest involved with manipulation of the gut microbiota. Understanding of genetic engineering techniques of prokaryotic organisms is mature and microbial therapeutics have already progressed to the point of artificial selection and curation of microbial communities. Bioengineering microbes to produce small molecules for pharmacologic purposes is a conceivable possibility but will open whole new avenues of ethical concern in conflicts of interest that will require ongoing attention. Recognising and limiting conflicts of interest will be key to maintaining public faith in microbial therapeutics in the future.

CONCLUSIONS

In summary, improved understanding of the composition of the human microbiome has generated great enthusiasm for novel microbe-based approaches to improve health. We encourage ongoing study of potential long term risks as scientific and medical communities rush to expand access to microbial therapeutics for increasingly understood near-term benefits. We believe that further study of trends in composition of the gut microbiome over time and in stress states will greatly advance providers’ capacity to inform patients and participants of risks and benefits in microbial therapeutic clinical trials. We stress the importance of ensuring access to microbial therapeutics, especially in scenarios with unique applicability such as colonization with organisms with extreme antibacterial resistance, for which there may be limited treatment options. Such scenarios may be special cases that should be considered in regulatory approaches to microbial therapeutics. We also outline

areas of potential conflict of interest that should inform review of study design and manuscript publication of findings from microbial therapeutic trials.

We support ongoing translational investigation of microbial therapeutics. Simultaneously, we advocate for thoughtful consideration of the ethical issues specific to clinical trials of microbial therapeutics to maintain the trust of the public in clinical researchers, minimise risk and optimise ultimate benefit to patients.

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Figure 1.
Venn diagram of ethical issues related to microbial therapeutic clinical trials and genetic research.