SUPPLEMENTARY METHODS:

Microbiota analysis

Microbial DNA was isolated from stool samples as previously described (1). *Bacterial ribosomal RNA Gene Sequencing***:** The V1 and V2 variable regions of the bacterial 16S ribosomal RNA (rRNA) gene were sequenced using Multitag fusion primers and sequenced on an Ion Torrent Personal Genome Machine next-generation sequencer.

Bioinformatics Analysis: 16S rRNA gene sequence data were utilized for bioinformatics analysis. Fasta files were demultiplexed using custom PERL scripts and sequences were filtered for quality scores and length. The clean 16S sequences were clustered into operational taxonomic units (OTUs) using the USEARCH algorithm (2). A sequence identity of 97% was used to generate OTUs representing distinct bacterial species. The taxonomic identity of reference sequences was determined using the RDP11 Classifier (3). We used the George Mason University Metabiome Portal to organize raw data, track clinical metadata, and track analysis. The portal consists of a Drupal based interface wrapped around a MYSQL database that uses PHP to manage the relational database. The system has built in safeguards to curate the data, keep is secure, and to assure quality control. We then analyzed the data for this project through these pipelines and distribute the data through this interface.

Microbial Bio-statistical Analysis: Bacterial community composition was characterized using OTU counts generated as described above. OTU counts were converted to measures of relative abundance to account for variation in sequencing coverage between samples. Statistical analysis was carried out using the statistical software package R (www.r-project.org). Changes in abundance of individual taxa were analyzed using traditional univariate non-parametric statistical methods and UNIFRAC(4). We used LEfSe (Linear discriminant analysis Effect Size) to determine the microbial taxa differences between groups (5).

Cognitive testing:

EncephalApp Stroop is a validated smartphone App version of the Stroop test(6). This involves presentation of an easier “Off” Stage in which subjects have to identify the color of the pound-signs presented on the phone and a more difficult “On” stage in which subjects have to correctly identify the color of a discordant word presented. For example the word “GREEN” will be presented in blue colored letters and the correct response would be blue and not green. The App has two practice runs and requires 5 correct runs in the Off and On Stage. The total time required for 5 correct On and 5 correct Off stage runs is the “OffTime+OnTime” which is of relevance in HE(7).

Inflammatory analysis:

Serum levels of Interleukin-6 (IL-6) were determined using the Quantikine ELISA kit from R&D Systems (cat.# 6050), with the equivalent of 0.5 ul serum per well, in duplicate. Serum levels of Lipopolysacharide (LPS) Binding Protein (*LBP*) were determined using Hycult Biotech Human LBP ELISA kit (cat.#HK315-02) with the equivalent of 0.1 ul of serum per well, in duplicate.

Bile Acid Analysis details:

Chemicals and reagents: Authentic reference bile acids were purchased from the Sigma-Aldrich Corporation (St. Louis, MO) as follows: CA, CDCA, UDCA, DCA, LCA, GCA, GCDCA, GUDCA, GDCA, GLCA, TCA, TCDCA, TUDCA, TDCA, TLCA, HCA, GHCA and THCA. HDCA, GHDCA and THDCA were purchased from Steraloids, Inc. (Newport, RI). (Abbreviations expanded in table S1). The substances [2,2,4,4-d_4]-CA (d_4-CA, internal standard (IS) for unconjugated bile acids), [2,2,4,4-d_4]-GCA (d_4-GCA, IS for glycine-conjugated bile acids), and [2,2,4,4-d_4]-TCA (d_4-TCA, and IS for taurine-conjugated and double-conjugated bile acids) were obtained from C/D/N Isotopes, Inc. (Pointe-Claire, QC, Canada). The 3-sulfates for CA, CDCA,

UDCA, DCA, LCA, GCA, GCDCA, GUDCA, GDCA, GLCA, TCA, TCDCA, TUDCA, TDCA, and TLCA were honestly received from Professor Iida. iso-CA, 3-oxo-CA, 7-oxo-DCA, 12-oxo-CDCA, iso-CDCA, 3-oxo-CDCA, 7-oxo-LCA, UCA, iso-DCA, 3-oxo-DCA, iso-LCA, 3-oxo-LCA, allo-iso-LCA were honestly received from Professor Iida. Ethanol, methanol, acetonitrile, and water were of high-performance liquid chromatography (LC-MS) grade; ammonium acetate was analytical grade; and all were purchased from Kanto Chemical Co., Inc. (Tokyo, Japan). An InertSep C18-B (100mg/1ml) solid phase extraction cartridge was obtained from GL Sciences Inc. (Tokyo, Japan).

Preparation of standard solutions: The individual stock solutions of bile acids were prepared separately at 1 mg/ml in ethanol and the stock solutions were stored at -25ºC. The individual stock solutions were mixed equally for analysis of unknown samples. The standard mixture was diluted to eight point-calibration standard solutions (1, 3, 10, 30, 100, 300, 1000, 3000 pmol/ml) with 20% acetonitrile. Deuterium labeled IS (d_4-CA, d_4-GCA, d_4-TCA) stock solutions were mixed equally which was diluted to final concentration of 100nmol/ml for each bile acid with 50% ethanol. These standard solutions were stable in analytical glass tubes for at least 1 weeks at 4ºC.

Sample preparation: *Serum specimen***:** 10µl (100pmol) of the IS solution, 250µl of methanol were added to a 100µl of serum sample. The tube is vortexed over 1min. After centrifugation (3,000g, 4ºC, 10min), the supernatant (200µl) was transferred into a new glass tube and was evaporated to dryness by the centrifugal vacuum concentrator. The residue was re-dissolved in 0.5 ml of H_2O. The solution was transferred onto a solid-phase extraction cartridge (InertSep C18-B 100mg) which had been preconditioned with 1 ml of methanol and 3 ml of H_2O. The cartridge was washed with 1 ml of H_2O and the desired bile acids were eluted with 1ml of 90% ethanol. After evaporation of the solvent by the centrifugal vacuum concentrator, the residue

was dissolved in 1 ml of 20% acetonitrile and then 5 µl of the solution was injected to LC-ESI-MS/MS.

Fecal specimen: 5.0 mg of lyophilized stool was suspended in 50 mM cold sodium acetate buffer (pH 5.6, 0.5 ml) and then refluxed with ethanol (1.5 ml) for 1 h. After centrifugation, the supernatant was diluted four times with water and applied to a Bond Elute C 18 cartridge (500 mg/6 ml; Varian, Harbor City, CA). The cartridge was then washed with 25% ethanol (5 ml) and bile acids were eluted with ethanol (5 ml). After the solvent was evaporated, the residue was dissolved in 1 ml of 50% ethanol. To an aliquot (100 ul) of this solution, 0.9 ml of 50% ethanol and 1 ml of IS, 200 pmol/ml in 50% ethanol) was added. Precipitated solids were removed by fi ltration through a 0.45 µm Millipore filter (Millex ® -LG; Billerica, MA). A 10 ul aliquot of the filtrate was injected into the LC-ESI-MS/MS system.

LC/ESI-MS/MS conditions: The LC/ESI-MS/MS system comprised a LCMS-8050 tandem mass spectrometer, equipped with an ESI probe and Nexera X2 ultra high-pressure liquid chromatography system (Shimadzu, Japan). A separation column, InertSustain C18 (150 mm × 2.1 mm ID, 3 µm particle size; GL Sciences Inc., Tokyo, Japan), was employed at 40°C. A mixture of 10 mM ammonium acetate and acetonitrile was used as the eluent, and the separation carried out by linear gradient elution at a flow rate of 0.2 ml/min. The mobile phase composition was gradually changed as follows: ammonium acetate-acetonitrile (86:14, v/v) for 0.5 minutes, ammonium acetate-acetonitrile (78:22, v/v) for 0.5-5 minutes, ammonium acetate-acetonitrile (72:28, v/v) for 5-28 minutes, ammonium acetate-acetonitrile (46:54, v/v) for 28-55 minutes, ammonium acetate-acetonitrile (2:98, v/v) for 55-66minutes, and ammonium acetate-acetonitrile (2:98, v/v) for 4 minutes. The total run time was 70 minutes. To operate the LC/ESI-MS/MS, the MS parameters are follows: spray voltage; 3000V, heating block temperature; 400°C, nebulizing gas flow; 3 L/min, drying gas flow; 10 L/min, heating gas flow; 10 L/min,

interface temperature 300°C, collision gas (argon) pressure; 270 kPa,, collision energy; 13-80 eV, all in the negative ion mode.

Untargeted metabolomics sample preparation and data acquisition

Serum and urine samples were stored in 1ml aliquots and frozen at -80^{o}C until NMR analysis. The serum and urine samples were prepared for NMR study according to published protocols(8)

All samples were gently thawed over ice. For urine NMR analysis, 540 µL urine and 60 µL 1.5 M KH_2PO_4 urine buffer were directly added to a SampleJet 5mm NMR tube (Bruker BioSpin, Germany) and mixed well. For the serum NMR study, 300 µl serum and 300 µl of 75 mM sodium phosphate buffer solution were directly added to a SampleJet 5mm NMR tube (Bruker BioSpin, Germany) and the sample was gently mixed.

Samples were transported at 4^{o}C in batches of 60 samples to the Centre for Biomolecular Spectroscopy, King's College London, and stored at 4^{o}C in the SampleJet holder prior to data collection. Pooled samples, comprising 20 µl from each of the urine or serum samples, were additionally prepared and analysed. NMR data were also acquired from internal reference samples (fetal calf serum and/or buffer) during each batch of data acquisition, to confirm stability and reproducibility of the NMR spectrometer.

Proton (^{1}H) NMR spectra were acquired, at 37^{o}C (310K) for the serum samples and at 27^{o}C (300K) for the urine samples, using a Bruker 600MHz (AVANCE NEO) NMR spectrometer and a ^{1}H/^{13}C/^{15}N TCI Prodigy nitrogen-cooled probe. Shimming was done under automation such that a 1.0-1.5 Hz linewidth for one of the alanine doublet peaks was routinely achieved. Pulse-collect (serum and urine) and spin-echo 1D (serum only) NMR data sets were acquired using PURGE water suppression and the PROJECT spin-echo sequences(9). All PURGE NMR data sets were acquired with 64 data collects, constant receiver gain, 64K points, acquisition time 2.62 s and recycle delay of 4.00 s (serum) and 5.38 s (urine). The spin-echo time for the PROJECT sequence was 78 ms (64 loops).

The 1D NMR data sets were processed using 0.3 Hz exponential line-broadening filter. Metabolite assignments were based on chemical shift and coupling patterns, with reference to published databases(10). For confirmation of urinary peak assignments, a TOCSY and a 1H-13C HSQC spectrum were acquired on a pooled sample. The TOCSY spectrum was acquired

with the Bruker pulse sequence “dipsi2gpphzs”, slightly modified to incorporate pre-saturation during the relaxation delay, with 16 scans, 512 t_1 increments, a spectral width of 13.6 ppm in both dimensions, a relaxation delay of 2 s and a mixing time of 80 ms. For the HSQC, the pulse sequence “hsqcetgpsisp2.2” was used, with 32 scans, 512 t_1 increments, with spectral width of 20.8 ppm in the ^{1}H dimension and 210 ppm in the ^{13}C dimension, and a relaxation delay of 1.75 s.

NMR spectral binning and Principal Component Analysis (PCA)

Signal intensities of metabolite regions were obtained using intellibucketing within BioRad KnowItAll® Informatics, Metabolomics Edition v17.0. NMR spectral regions excluded from the analysis at the outset were <0.5 ppm, >10.0 ppm and 4.5-5.0 ppm (residual water region). Selected intellibucket regions were manually adjusted to incorporate specific metabolite peaks.

Principal component analyses (PCA) within pre- and post-FMT groups, pre- and post-placebo groups and post-FMT and post- placebo groups were performed using the AnalyseItMVP routine within KnowItAll® Informatics, Metabolomics Edition v17.0, after each of the serum and urine data sets were mean-centred and normalised.

Partial Least Squares – Discriminant Analysis (PLS-DA)

The binned NMR spectral data outputted from KnowItAll® Informatics Metabolomics Edition v17.0 was uploaded into MetaboAnalyst v4.0 program(11). The classification performance of PLS-DA was defined by R2 (degree of fit) and Q2 (estimate of predictive ability of model) in leave-one-out cross validation(12). The variable importance in projection (VIP) scores for each region allowed an assessment of the contribution of each metabolite region to the PLS-DA model

Supplementary Table 1: Eligibility Criteria for the Study.

Inclusion Criteria	Exclusion Criteria
-21-75 years of age -Cirrhosis diagnosed by <u>any one</u> of the following in a patient with chronic liver disease (a) Liver Biopsy (b) Radiologic evidence of varices, cirrhosis or portal hypertension (c) Laboratory evidence of platelet count <100,000 or AST/ALT ratio>1 (d) Endoscopic evidence of varices or portal gastropathy -At least two HE episodes, one within the last year but not within the last month (patient can be on lactulose and rifaximin) - Able to give written, informed consent (mini-mental status exam>25 at the time of consenting) -Women of child bearing potential must agree to use effective contraception for the duration of the study and for 10 days prior and 30 days after the study -Negative pregnancy test in women of childbearing age	*Disease-related:* (1) MELD score>17 (2) WBC count<1000 (3) TIPS, non-elective hospitalization or HE within last month (4) on dialysis (5) known untreated, in-situ luminal GI cancers (6) chronic intrinsic GI diseases (ulcerative colitis, Crohn's disease or microscopic colitis, eosinophilic gastroenteritis and celiac disease) (7) major gastrointestinal or intra-abdominal surgery within three months *Endoscopy-related*: (1) Platelet count<50,000 (2) adverse reactions to sedation (3) lack of driver or other contra-indications (4) unwilling to undergo endoscopic procedures *Safety-related*: (1) Dysphagia (2) History of aspiration, gastroparesis, intestinal obstruction (3) Ongoing antibiotic use (except for Rifaximin) (4) Severe anaphylactic food allergy (5) allergy to ingredients Generally Recognized As Safe in the FMT capsules (glycerol, sodium chloride, hypromellose, gellan gum, titanium dioxide, theobroma oil) (6) Adverse event attributable to prior FMT (7) ASA Class IV or V (8) Pregnant or nursing patients (9) acute illness or fever within 48 hours of the day of planned FMT (10) immunocompromised due to medical conditions or immunosuppressive therapies (11) Probiotic use within the last 48 hours of the day of planned FMT (12) Any condition that the physician investigators deems unsafe, including other conditions or medications that the investigator determines puts the participant at greater risk from FMT

Supplementary table 2: Baseline characteristics of subjects

	FMT (n=10)	Placebo (n=10)	P value
Age	63.3±4.2	64.2±6.2	0.71
Gender (M/F)	8/2	8/2	1.0
Race (Caucasian/African-American/Hispanic)	7/3/0	7/3/0	1.0
Etiology of cirrhosis (HCV/Alcohol/HCV+ Alcohol/NASH/Others)	2/1/3/2/2	3/1/2/2/1	0.78
PPI use	10	10	1.0
Lactulose	10	10	1.0
Rifaximin	10	10	1.0
MELD score	9.5±2.6	10.9±4.2	0.39
AST	48.4±13.8	40.9±20.8	0.36
ALT	39.0±16.4	21.9±15.5	0.33
Alkaline Phosphatase	144.8±66.7	126.9±40.7	0.48
INR	1.27±0.17	1.30±0.16	0.69
Bilirubin	1.26±0.80	1.46±0.80	0.53
Serum albumin	3.3±0.5	3.3±0.6	0.67
WBC (10^3/ml)	4.65±1.43	5.4±2.0	0.37
Hemoglobin (g/dl)	13.5±1.9	12.9±2.6	0.21
Platelet count(10^3/ml)	113.0±48.5	140.4±70.5	0.33

Supplementary table 3: Outcomes between the two groups over 5 months

	Placebo Group (n=10)	FMT group (n=10)
Number of SAEs (median, range)	11 (1.0, 0-6)	1 (0, 0-1)**
Number of Patients with SAEs	6	1*
Hepatic Encephalopathy		
HE episodes (number of total episodes)	6	1
HE episodes requiring hospitalization/ER visits	6	1
HE episodes managed as an outpatient	0	0
Number of Patients with HE	3	1
Infections		
Infections (number of total infections; all needing hospitalization/ER visits)	3 (Pneumonia, n=1, Cellulitis n=1, Fever +diarrhea n=1)	2 (Pneumonia, n=1, UTI, n=1)
Number of patients with infections	3	2
Deaths	1	0
Patients with Self-limited AEs		
Constipation (number)	1	2
Diarrhea (number)	1	1
Bloating (number)	0	1
Nausea/vomiting (number)	1	0

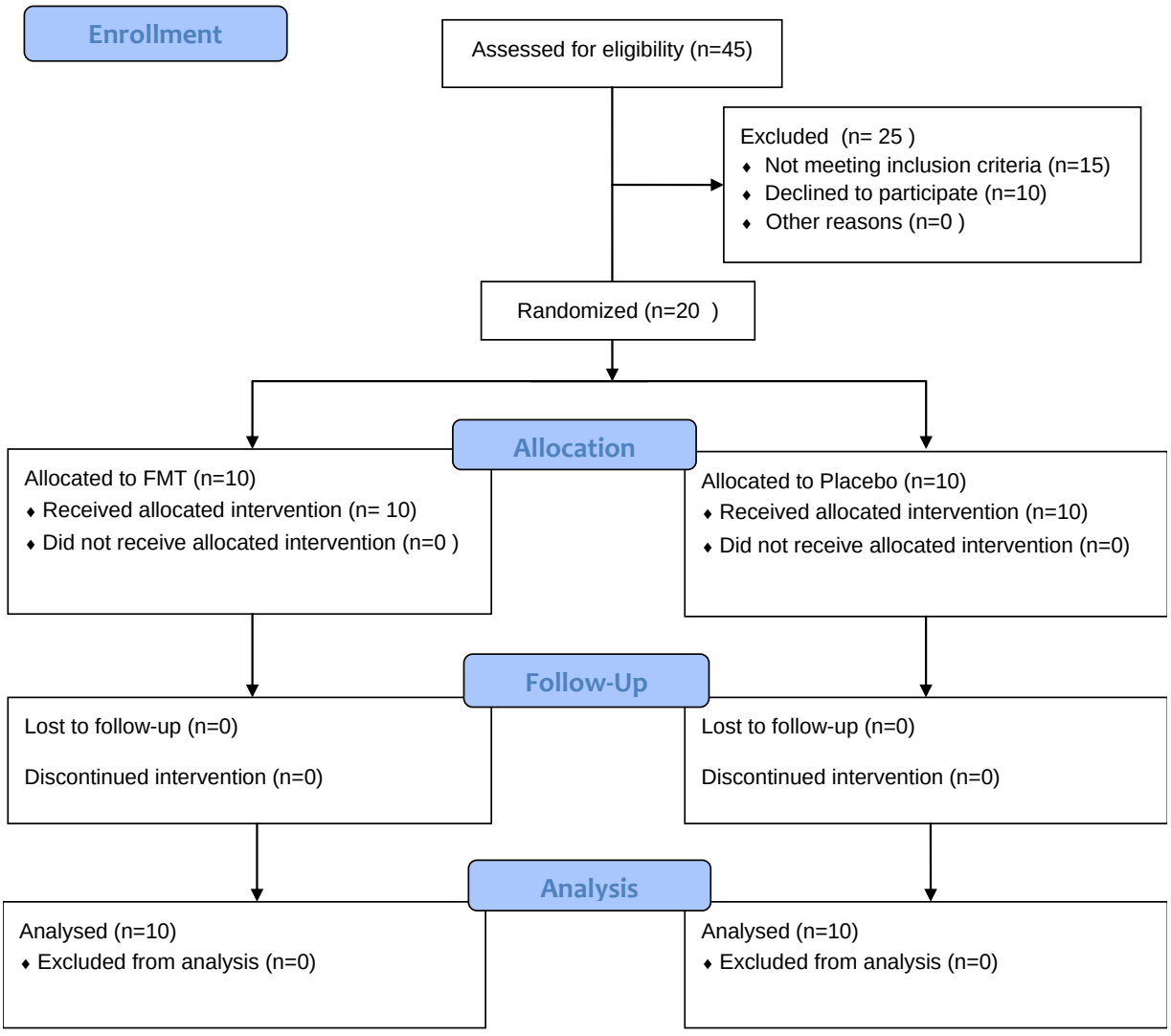
Supplementary table 4: Changes in laboratory parameters over time between groups

	Safety visit		P value	30-day visit		P value
	Placebo	FMT		Placebo	FMT	
MELD score	11.7±3.9	10.2±4.5	0.44	11.3±3.9	8.7±2.9	0.11
AST	41.0±21.4	49.4±11.1	0.29	43.4±26.0	50.2±16.3	0.50
ALT	30.9±12.4	39.0±13.2	0.18	35.1±14.6	40.4±13.6	0.42
Alkaline Phosphatase	133.7±57.3	145.8±67.0	0.67	132.2±57.6	132.9±59.7	0.98
INR	1.32±0.22	1.29±0.16	0.73	1.31±0.23	1.23±0.14	0.40
Bilirubin	1.57±0.72	1.49±0.74	0.81	1.62±0.92	1.29±0.59	0.336
Serum albumin	3.17±0.57	3.33±0.48	0.51	3.32±0.67	3.52±0.49	0.46
WBC (10^3/ml)	5.1±2.2	4.9±1.5	0.83	5.1±2.0	5.0±1.3	0.93
Hemoglobin (g/dl)	11.7±2.8	13.4±1.8	0.13	12.5±2.9	13.9±1.5	0.20
Platelet count(10^3/ml)	146.4±85.6	108.4±31.8	0.22	142.9±76.5	116.0±53.3	0.38

Safety visit is 1-2 weeks after the initial intervention; comparisons performed using unpaired t-tests

Supplementary figures

Figure 1: CONSORT Diagram:



Supplementary figure 2: Untargeted metabolomics results, PLS-DA plots for serum pre-FMT vs post-FMT, pre- placebo vs post- placebo and post-FMT vs post- placebo

Figure S2A. PLS-DA showing serum NMR pre-FMT (v2) versus post-FMT (v4) (Q2<0.00)

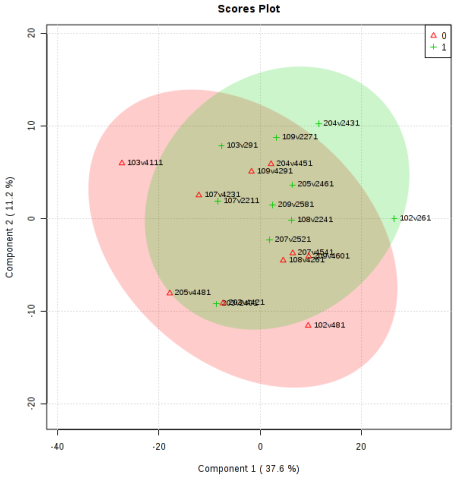


Figure S2B. PLS-DA showing serum NMR pre-placebo (v2) versus post- placebo (v4) (Q2<0.00)

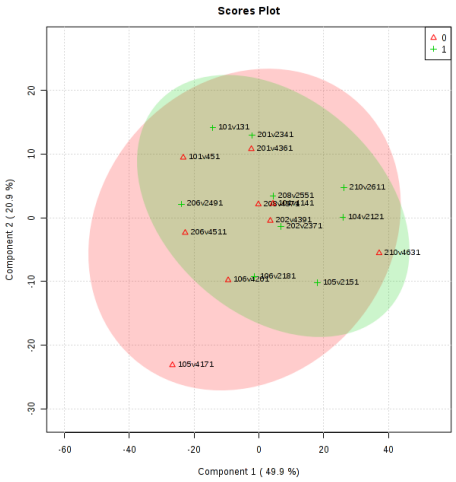


Figure S2C. PLS-DA showing **serum** NMR post-FMT (v4) vs post-placebo (v4) (Q2 0.22):

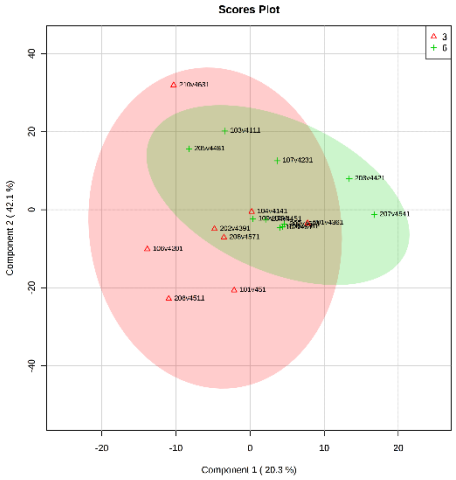


Figure S2D. PLS-DA showing **urine** NMR pre-FMT (v2) versus post-FMT (v4) (Q2<0.00)

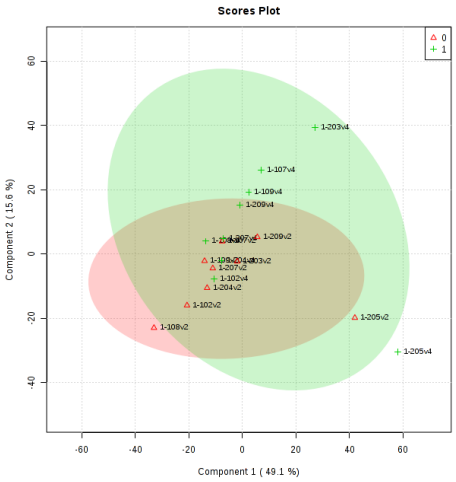


Figure S2E. PLS-DA showing **urine** NMR pre-placebo (v2) versus post-placebo (v4) (Q2<0.00)

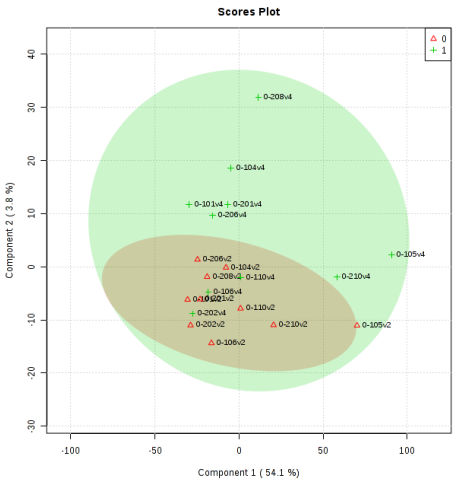
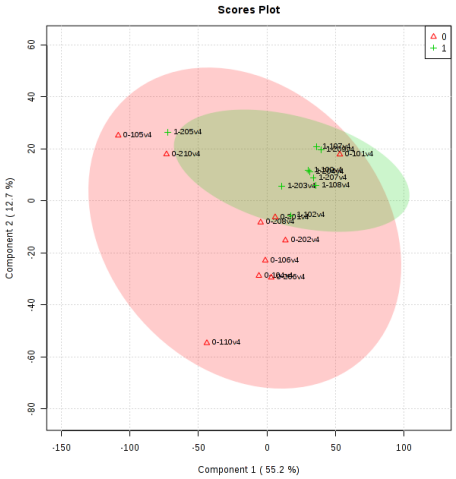


Figure S2F. PLS-DA showing **<u>urine</u>** NMR post-FMT (v4) versus post-placebo (v4) (Q2<0.00)



Supplementary references

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CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	5
	2b	Specific objectives or research questions for pilot trial	5
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	supplement
	4b	Settings and locations where the data were collected	1
	4c	How participants were identified and consented	Supplement, 13-16
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	13-16, Supplement
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	13-16, supplement
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	NA
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	NA
Sample size	7a	Rationale for numbers in the pilot trial	supplement
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	supplement
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	supplement
Allocation	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered	supplement

concealment mechanism		containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	supplement
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	supplement
	11b	If relevant, description of the similarity of interventions	supplement
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	13-16
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	CONSORT chart
	13b	For each group, losses and exclusions after randomisation, together with reasons	CONSORT chart
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Supplement
	14b	Why the pilot trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Supplement
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	All patients analysed
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	Supplement ,Tables 1-2, and figures
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Supplement, 6
	19a	If relevant, other important unintended consequences	NA
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	9-12
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	9-12
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	9-12
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	9-12

Other information			
Registration	23	Registration number for pilot trial and name of trial registry	www.clinicaltrials.gov number NCT03152188
Protocol	24	Where the pilot trial protocol can be accessed, if available	Supplement
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2
	26	Ethical approval or approval by research review committee, confirmed with reference number	7; VA number: BAJAJ022 VCU number: HM20009392

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*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.