1. Introduction

1.1 Scope and purpose

The purpose of this clinical protocol is to ensure patient safety and enable Health Care Professionals to follow a procedure to administer a Faecal Microbiota Transplant (FMT) for the treatment of *Clostridioides difficile* infection (CDI).

This protocol should be used in conjunction with local clinical guidelines concerning consent and the insertion of nasogastric tubes or PEG/PEJ use.

FMT is a 50ml filtered suspension of faeces, which has been prepared in the GMP-MU at the University of Birmingham from a healthy human donor stool. It is used for the treatment of CDI and is usually administered to the patient via an upper GI route. Direct delivery to the colon (lower GI route via colonoscopy, sigmoidoscopy or enema) is also a valid alternative, however, this will require a larger volume of FMT (3 aliquots are supplied) and should be discussed in advance with the UoBMTC Clinical team.

Under NICE approval, FMT treatment can be offered to the following patient with:

Multiple recurrence of CDI

- Patients who have suffered from ≥3 episodes of CDI and failed to respond to standard antibiotic treatment

Other conditions where FMT will be considered:

- Refractory CDI. Patients who have received a course of vancomycin and have not had clinical resolution of diarrhoea. Although not NICE approved FMT can be considered for use in patients with refractory CDI as outlined in recent National guidelines (Mullish et al., *Gut*, 2018) and a recent European Consensus position paper on FMT (Cammarota et al., 2017)
- Severe CDI. As outlined in recent National guidelines (Mullish et al., *Gut*, 2018) and a recent European Consensus position paper on FMT (Cammarota et al., 2017).
- CDI cure rate from a single FMT treatment approaches 80% and exceeds 90% with a second treatment (Quraishi et al. AP&T, 2017). Patients in whom a single infusion is unsuccessful in resolving symptoms of CDI or have a relapse in symptoms within 7 days should be considered for a second infusion. Consideration of a second infusion would require a new application to be made with the relevant clinical details and outcomes.
- The use of FMT for the management of diverse pathologies is currently the subject of numerous clinical trials, most particularly in IBD. Under the conditions of a “specials licence” it is possible for clinicians to request FMT for patients with conditions other than CDI, where the clinician considers the use of FMT to be justified and appropriate for the individual patient. These requests will be considered on a case-by-case basis by the UoBMTC Clinical Team. In the case of FMT for the treatment of ulcerative colitis this would most likely require treatment at our facility in Birmingham according to our published trial protocol. Payment for this treatment would be discussed on a case-by-case basis.

2. Methodology

2.1 Patient inclusion and exclusion

The following inclusion and exclusion criteria must be met for patient treatment:

Inclusion

- Patient meets indication criteria
- Patient suitable for nasogastric tube (NGT) insertion

- Patient is refractory to antibiotic treatment or has had one or more recurrences of *C.difficile* infection
- Patient has vancomycin refractory *C.difficile* infection
- Informed consent

Exclusion

- Ulceration/bleeding of the upper gastrointestinal tract
- Life threatening food allergy e.g. peanuts

Patients on ITU can be treated with FMT when a decision to treat has been made between a Consultant Microbiologist/ID and the ITU consultant in charge of care and documented in the patient's notes.

2.2 Patient consent

Explain the procedure and its risks using the FMT patient information leaflet (form FMT-DON-011), following local consent policy. The standard consent forms should be signed by the patient and the clinician and retained in the patient's notes. Risks of FMT can include:

- Low risk of perforation from NGT insertion
- Risk of aspiration while NGT in place
- Low risk of transmission of an unknown infectious agent
- Risk associated with colonoscopy (perforation/haemorrhage). This is generally considered a very low risk occurring once every 1000 procedures or less.

Whilst FMT can be a lifesaving treatment in immunocompromised patients with CDI it should be remembered that we use donors who could be CMV positive. If you are considering treating an immunocompromised patient who is at risk for infectious agent that we have not screened for please discuss the case with one of our medical advisors. For those patients considered to be immunosuppressed ensure the patient is informed of the theoretical increased risk of adverse events and record discussion of risk on the consent form.

2.3 Requesting FMT

- For CDI requests meeting the NICE indications (patients who have suffered from ≥3 episodes of CDI and failed to respond to standard antibiotic treatment) or have refractory CDI FMT requests for patient treatment should be submitted by email, using the FMT request form (FMT-DON-009) sent together with order form (FMT-DON-010), to the University of Birmingham Microbiome Treatment centre (UoBMTC) via bhs-tr.FMT@nhs.net
- For all other requests outside of the NICE indications, an agreement to treat the patient should be confirmed after a clinical discussion with one of the UoBMTC clinical consultants regarding appropriateness of FMT. Once agreed the request for patient treatment should be submitted by email, using the FMT request form (FMT-DON-017 FMT request form Unlicensed Specials), to the UoBMTC via bhs-tr.FMT@nhs.net
- The UoBMTC Clinical Consultants are Prof Tariq Iqbal, Dr Mohammed Nabil Quraishi, Dr Naveen Sharma and Dr Christopher Green
- On receipt of completed request and order form accepting the UoB Terms and Conditions for supply, the UoBMTC clinical team will assess information on the request form against approved indications for FMT.
- If the FMT request is ratified by the UoBMTC, a delivery date and time will be arranged in accordance with the requested date and time as stated on the submitted order form accompanying the request. If this not possible it will be discussed with the requesting clinician to arrange a suitable alternative.
- In the case of ground for rejection of the request, the requesting clinician will be contacted by email and/or telephone call to explain why the proposed FMT treatment is inappropriate or to obtain further clinical information.

2.4 Logistics of FMT treatment

- FMT is supplied in 50ml aliquots, one aliquot should be used for Nasogastric administration.
- If colonoscopic administration is planned then three aliquots of FMT (150ml) should be requested (request sent in advance to UoBMTC).
- All FMT aliquots are sent with an accompanying FMT Specials Release Certificate, and FMT Certificate of analysis which should be retained in the patient's clinical notes.

2.5 FMT delivery

- Subject to reasonable logistics, all FMT treatments will be delivered by the Blood Bikes. In the event the Blood Bikes are unable to deliver FMT, a courier will need to be arranged by the requesting clinician.
- All clinical sites must identify a single site address for delivery of FMT and a named person for receipt accompanied by a contact number.
- The UoBMTC operates different delivery protocols depending on the distance of the requesting NHS Trust from UoBMTC or specific logistical requirements.
  - As a standard for NHS Trust that can be reached within 6 hours by road from UoBMTC. FMT will be supplied for same day use.
  - For NHS Trusts >6 hours by road transport from the UoBMTC, FMT can be supplied either:
    1. For same day use, via a sepcialist courier. In this instance the FMT would be despatched on dry ice to remain frozen in transit. The FMT would arrive around 09:00am on the day of intended administration, to begin defrosted on arrival for administration.
    2. Frozen on dry ice for storage overnight at between -80℃ to -40℃ to be administered the day after receipt. Again, this delivery would require a specialist courier to ensure the FMT remained frozen whilst in transit.
       - FMT supplied frozen should be stored at between -80℃ to -40℃ immediately upon receipt and used within 24 hours of receipt (the next day). To use thaw at room temperature for 3 hours and administer within 9 hours of removal of the FMT aliquot from the local freezer.

- For same day use:
  - FMT will usually arrive at the requesting site fully defrosted and ready to administer to the patient. However, this depends on the duration of the delivery and external temperature on the day of delivery. Typically, an FMT aliquot takes up 3 hours to defrost at ambient room temperature.
  - For sites >3 hours away from UoBMTC the FMT will be despatched frozen to begin defrosting en-route, in order to maximise useable life of the FMT once received by the requesting site (FMT must be administered to the patient within 6 hours of being fully defrosted).
  - For sites less <3 hours from UoBMTC, the FMT will be removed from -80℃ to begin defrosting prior to being collected for delivery to try and ensure the FMT is received fully defrosted and ready to administer.
  - The FMT Specials Release Certificate accompanying the FMT will indicate an expiration time, 9 hours from when the FMT is removed from -80℃ storage (3 hours assigned to defrost time at ambient room temperate, followed by 6 hours useable life once fully defrosted).

Questions relating to transport/delivery can be directed to:

Ms Sahida Shabir (Tel: 0121 414 4547)

Email: bhs-tr.FMT@nhs.net

2.6 FMT administration

- In the case of *C. difficile* treatment ensure the patient has received at least 4 days antibiotics for treatment of *C.difficile* prior to FMT. **Stop the antibiotics the evening before FMT treatment**
- For nasogastric administration the following protocol is suggested:
  - FMT can be administered by a doctor or a staff nurse on any ward by clinicians trained and competent in the placement of nasogastric (NG) tubes.
  - In order not to waste FMT treatments (which are limited in stock), the NG tube should be in place, positioning confirmed and the patient is happy with the NG tube, preferably within day time hours.
  - The patient should be nil by mouth 6 hours prior to FMT administration.
  - Give a STAT dose of oral **omeprazole 20 mg** (adult dose, or an appropriate paediatric dose) or appropriate PPI 2 hours prior to FMT administration.
  - Give a STAT dose of oral domperidone 10 mg 2 hours prior to FMT administration.
  - In the rare situation where patients may be “nil by mouth” but have a naso-gastric tube in situ, PPI and prokinetic agent (in this case metoclopramide) may be administered parenterally.
  - Transfer the FMT to an enteral syringe.
  - Connect FMT enteral syringe to the NG tube and administer 50ml of FMT into the stomach, slowly over 2-3 minutes.
  - Flush the NG tube with 30 ml of saline.
  - Remove NG tube one hour after the procedure.
  - The patient can eat 1 hour following the procedure, providing the responsible clinician is happy with the patient’s condition.
  - For a pre administration checklist refer to appendix 3.

- For colonoscopy administration the following protocol is suggested:
  - If FMT treatment is to be given by colonoscopy, antibiotics should be stopped the evening before administration.
  - The bowel should be prepared according to local practice.
  - A total of three aliquots of thawed FMT should be drawn up into 50ml syringes.
  - 150ml FMT should be delivered via spray catheter through the endoscope. It is recommended that the FMT should be delivered as far into the colon as possible (ideally proximal transverse) to ensure adequate retention.
  - Following colonoscopy 2mg of loperamide is given orally to the patient to aid FMT retention.
  - For a pre administration check list refer to appendix 4.

2.7 Disposal in the event FMT is not used

- In the event that an FMT aliquot is not used, dispose of the capped syringe or primary container directly into the clinical waste stream.
- The FMT Specials Release Certificate and FMT Certificate of Analysis can be discarded into the confidential waste.

2.8 Serious adverse events (SAE) and serious adverse reactions (SAR)

In the event of a Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or a Sudden Unexplained Serious Adverse Reaction (SUSAR) immediately contact, by phone, a member of the Microbiome Treatment Centre's Clinical team listed below.

Professor Tariq Iqbal	Dr Mohammed Nabil Quraishi
Mobile Number: 07713575156	Mobile Number: 07561101015
Dr Naveen Sharma	Dr Christopher A Green
Mobile Number: 07801924818	Mobile Number: 07900243065

Please follow up all calls with an e-mail to bhs-tr.FMT@nhs.net within 24 hours

- Following notification of the SAE/SAR, a Root Cause Analysis (RCA) must be performed, by the SAE/SAR review team within 5 days as documented in Appendix 1.
- A serious adverse event (SAE) or serious adverse reaction (SAR) is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or causes prolongation of existing hospitalisation. In the case of FMT we are, in particular, interested in adverse events relating to infectious disease an unexpected adverse reaction (UAR) is an adverse reaction that is not consistent with the product information in the SPC. A suspected unexpected serious adverse reaction (SUSAR) is any UAR that results in death, is life-threatening, requires inpatient hospitalisation or causes prolongation of existing hospitalisation.
- Following investigation if the FMT is thought to be linked to the SAE/SAR the MHRA will be notified within 15 calendar days.

Appendix 1: FMT Serious Adverse Event/Reaction Root Cause Analysis (RCA)

Introduction

This form is to be used to conduct a RCA following a serious adverse event or reaction relating to an infection that occurred within 48 hours of the patient receiving a Faecal Microbiota Transplant (FMT), prepared and administered by the protocols defined in *GMP-SOP- 0199 Preparation of Faecal Microbiota Transplants* and the UoBMTC FMT Clinical Protocol guideline. Such an infection will be considered to have been likely or possibly due to members(s) of the flora in the FMT at the time of delivery. A gram-negative bacteraemia (e.g. “coliform”), or unexplained enteric infection, e.g. norovirus are examples.

This RCA must be conducted within 5 days of the incident, and no further FMT treatment will be dispatched from the same donor samples until the review process has been done, corrective and preventative actions completed, and the full process is confirmed as safe.

The overall aim of the RCA process is to:

Review all the necessary documentation to determine if there is a clear cause or route of transmission, from the FMT, or from any another source.

- To identify and address any shortcomings in the process.
- Develop and implement corrective and preventative actions.
- Address any wider issues with this incident, e.g. bay/ward norovirus outbreak. The documentation arising from that should be included as an addendum in this report.
- To give reassurance to all users and relevant organisations (UoBMTC, local Trust, MHRA).

The RCA review group must include:

- Professor T Iqbal UoBMTC Director
- Dr C A Green UoBMTC Clinican (Infectious Diseases)
- Dr M N Quraishi UoBMTC Scientific Advisor (Gastroenterology)
- Dr N Sharma, UoBMTC Clinican (Gastroenterology)
- Patient’s Consultant
- Ward nursing lead (or alternate)
- Trust Infection Control nurse, as necessary
- UoBMTC Qualified Person
- Dr Sue Manzoor UoBMTC Production Manager
- Ms Sahida Shabir UoBMTC Service Manager
- GMP Quality Manager

The RCA can be conducted by teleconference. The following proforma should be completed in full.

It is a requirement of Specials use of an unlicensed medicine that:

- Manufacturers should report any suspected adverse drug reaction immediately and in no case later than 15 calendar days from receipt, stating that the product is unlicensed. It is a mandatory requirement to electronically report suspected ADRs. The ICH-E2B international standard electronic report should be used and the report should be electronically submitted via the EudraVigilance European Gateway (see MHRA or EMA websites for more details).
- Prescribers or pharmacists supplying the “special” should report using a Yellow Card form or an electronic Yellow Card (found at http://www.mhra.gov.uk/yellowcard), stating the manufacturer and indicating that the product is unlicensed.

Patient details	
NHS Trust	
Patient Name	
Hospital number	
Date of Birth	
Indication for FMT	
Please provide evidence for indication to treat	
Place of FMT administration	
Date of admission	
Date and time of administration	

History of the patient	
Past medical history and co-morbidities	
Relevant microbiology results in the 30 days prior to FMT, include date of collection and laboratory numbers	

Antibiotics prescribed in the 30 days prior to delivery of the FMT, with indications	
Date of first *C. difficile* positive result (toxin or gene positive), with laboratory number	
Date of subsequent specimens and results (as above) **Treatment given: agent, dose, duration with dates.**	
Recent relevant medical interventions	

Details of SAR	
Summary of relevant events in the period from the administration of the FMT to the time the SAR	

Was treatment given in response to the SAR, if yes please specify?	
What was the outcome of this SAR for the patient?	

SARs involving infection post FMT	
Was treatment given for this infection? If yes please specify	
What was the cause of the infection and the identified organism?	
Date and time of specimen collection for investigation of infection	
Specimen number	
Has the organism and specimen been saved?	
What was the outcome of this infection for the patient?	
Did the infection have any effect in the clinical area (further cases in patients and staff)? **If yes include lists of patients, staff and clinical areas affected**	
If so what were the infection control interventions? (the Infection Control documentation from that incident should be cross-referenced)	

Patient pathway for FMT administration	
FMT batch number	
FMT lot number	
Had consent been obtained, and the treatment discussed with the patient? Provide evidence	
Was the protocol for administration followed? Provide evidence	
Was the FMT used within the documented expiry? Give details	
Please give details of any post FMT administration medication or follow up	
Provide a summary of MEWS scores post FMT	

Review of the process of FMT preparation (all donor information on this form is anonymous)	
Was donor screening complete? Please provide evidence	
Was the FMT processing record complete and were there any processing anomalies or deviation from SOP?	

If yes to above, were they addressed at the time of production? What was the outcome?	
Are daily balance records, cleaning records and environmental monitoring records complete and within tolerance? **Provide evidence**	
Do temperature records for -80°C freezer storage demonstrate maintenance of appropriate storage temperature? **Provide evidence**	

Transport	
Where there any deviations from SOP during transportation? **Provide evidence**	

Assessment of the likely source

Based on the available evidence, the source of the infection should be agreed, please provide details below:

.....
.....
.....
.....
.....
.....
.....

Actions

Have all the steps in the process been fully addressed?

.....
.....
.....
.....
.....

.....
.....

If the FMT is the confirmed or likely source, confirm donation has been suspended by this person, and that necessary re-screening is done before the donor can resume donation.

.....
.....
.....
.....
.....
.....
.....

Are there other necessary interventions that need to be done?

.....
.....
.....
.....
.....
.....
.....

Can the FMT service be reinstated?

.....
.....
.....
.....
.....
.....
.....

Have all the relevant authorities been informed?

.....
.....
.....
.....
.....
.....
.....

Appendix 2: "Specials" other than for CDI

As outlined in MHRA guidance note 14, FMT produced in the UoBMTC under the existing "specials" licence can be supplied for use for human medicinal use when ordered by a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber provided that the order is:

- in response to an unsolicited order;
- manufactured and assembled in accordance with the specification of a person who is a doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber;
- for use by a patient for whose treatment that person is directly responsible in order to fulfil the special needs of that patient; and meets the conditions specified in regulation 167(2)-(8).

As described in the MHRA guidance note Regulation 167 of the Human Medicines Regulations 2012 sets out the exemption from the requirement for a medicinal product, placed on the market in the UK to hold a marketing authorisation. This comes from Article 5(1) of Directive 2001/83/EC which states:

'A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under his direct personal responsibility.'

Under this regulation UoBMTC is able to supply FMT in response to an order to meet the special needs of an individual patient where an equivalent licensed medicinal product cannot meet the special needs. Responsibility for deciding on this "special need" which a licensed product cannot meet should be a matter for the clinicians involved in the patient's care. The supplier (MTC) must also be satisfied as to the existence of a special need for the unlicensed medicinal product

Further to MHRA guidance it is incumbent on MTC, as a supplier of "specials" under Regulation 170 of the Human Medicines Regulation 2012 to:

(a) Keep the following records for at least 5 years:

- the source from which and the date on which the person obtained the product;
- the person to whom and the date on which the sale or supply was made;
- the quantity of the sale or supply;
- the batch number of the batch of that product from which the sale or supply was made; and
- details of any suspected adverse reaction to the product so sold or supplied of which the person is aware or subsequently becomes aware.

(b) Make these records available for inspection by the Licensing Authority;

(c) Report serious suspected adverse drug reactions (ADRs) to MHRA;

- Manufacturers should report the suspected ADR immediately and in no case later than 15 calendar days from receipt, stating that the product is unlicensed. It is a mandatory requirement to electronically report suspected ADRs. The ICH-E2B international standard electronic report should be used and the report should be electronically submitted via the EudraVigilance European Gateway (see MHRA or EMA websites for more details).

- Prescribers or pharmacists supplying the “special” should report using a Yellow Card form or an electronic Yellow Card (found at http://www.mhra.gov.uk/yellowcard), stating the manufacturer and indicating that the product is unlicensed.

These obligations are placed on any person selling or supplying “specials”, not only manufacturers, importers and distributors but also pharmacists, doctors, dentists, nurse independent prescribers, pharmacist independent prescribers and supplementary prescribers where appropriate.

In relation to FMT it is expected that the most common request for use for special need other than CDI for named patients will be in the case of the treatment of inflammatory bowel disease where the patient has run out of licensed options and is unable to fulfil the entry requirements for recruiting clinical trials. In this case the lead clinician for the patient will make unsolicited contact with the UoBMTC office in the form of a formal letter/email or telephone call, explaining their professional status and the nature of the special need of the individual patient concerned is outlined. It should be made clear that where a licensed alternative is available, why that is not clinically appropriate. There is no legal requirement for the individual patient’s name to be supplied. A member of the UoBMTC team will then supply the requesting clinician a copy of FMT-DON-017 Faecal Microbiota Transplant Request Form Unlicensed Special.

Once the request has been received by UoBMTC it will be assessed by the UoBMTC clinical team comprising:

Professor Tariq Iqbal
Dr Mohammed Nabil Quraishi
Dr Naveen Sharma
Dr Christopher Green

Appendix 3: Pre FMT administration Checklist (Upper GI)

Please use this checklist prior to administering the FMT:

At least 12 hours before the procedure

- ☐ You have read and are familiar with our **suggested** clinical protocol.
- ☐ Have obtained consent from the patient, as per your local guidelines.
- ☐ Ensured the patient has stopped receiving *C. difficile* related antibiotics the **evening before** FMT treatment. Ideally, all antibiotics should be omitted, during the FMT administration period. However, this is dependent upon the patient's clinical presentation.

At least 6 hours before the procedure

- ☐ The patient should be nil by mouth (minimum 6 hours prior to FMT)

Two hours before the procedure

- ☐ Given a STAT dose of oral omeprazole 20 mg 2 hours prior to FMT administration
- ☐ Given a STAT dose of oral domperidone 10 mg 2 hours prior to FMT administration
- ☐ Where the patient is "nil by mouth" but has an NG tube in situ the PPI and prokinetic (metoclopramide) may be given parenterally 2 hours prior to FMT.

Immediately before the procedure

- ☐ The positioning of the enteral tube has been checked if NG or NJ are the intended route of administration (not relevant for delivery via PEG).
- ☐ Are satisfied the FMT is fully defrosted at room temperature and no frozen lumps are visible on inversion.
- ☐ Ensure you will be administering the FMT prior to its expiration, as indicated on the FMT Specials Release Certificate you will receive alongside the FMT.

Post procedure

- ☐ If NG or NJ route used, remember to flush the tube as per clinical protocol after administering the FMT.
- ☐ Remove the NG tube an hour after the procedure.
- ☐ Document the procedure and treatment in the patient's clinical notes alongside the Validation certificate.
- ☐ Ensure the FMT outcomes are reported back using the online tool at day 7 post FMT or on discharge (whichever is the earliest). 90-day feedback is also required which you will be prompted for closer to the time.

Appendix 4 Pre FMT administration Checklist (Lower GI tract)

Please use this checklist prior to administering the FMT:

At least 12 hours before the procedure

- ☐ You have read and are familiar with our **suggested** clinical protocol.
- ☐ Have obtained consent from the patient, as per your local guidelines.
- ☐ Ensured the patient has stopped receiving *C. difficile* related antibiotics the **evening before** FMT treatment. Ideally, all antibiotics should be omitted, during the FMT administration period. However, this is dependent upon the patient's clinical presentation.
- ☐ The patient's bowel should be prepared as per local practise if administering via colonoscopy.

Immediately before the procedure

- ☐ Ensure you will be administering the FMT prior to its expiration, as indicated on the FMT Special Release Certificate you will receive alongside the FMT.
- ☐ Are satisfied the FMT is fully defrosted at room temperature and no frozen lumps are visible on inversion.
- ☐ Three 50ml aliquots of FMT should be drawn up into 50ml syringes. The whole dose (150ml FMT) should be delivered via spray catheter through the endoscope. It is recommended that the FMT should be delivered as far into the colon as possible (ideally proximal transverse colon) to ensure adequate retention.

Post procedure

- ☐ Oral administration of 2mg loperamide to aid FMT retention.
- ☐ Document the procedure and treatment in the patient's clinical notes alongside the Validation certificate.
- ☐ Ensure the FMT outcomes are reported back using the online tool at day 7 post FMT or on discharge (whichever is the earliest). 90-day feedback is also required which you will be prompted for closer to the time.