The use of faecal microbiota transplant as treatment for recurrent or refractory *Clostridium difficile* infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines.

Supplementary Material 3: Basic requirements for implementing a FMT service:

1. Basic requirements for implementing a FMT service:

1.1. General considerations:

Although it is possible to prepare and administer FMT on an individual patient basis in a single hospital, the regulatory requirements are more readily fulfilled by a specialist centre approach for the production of a safe FMT product. This particularly applies to record keeping and staff expertise in quality control and production. Recent European consensus advice suggests that FMT should be administered in a referral centre[1], however an alternative approach which limits the need for patient transfer is to undertake controlled production in a large centre and transport treatment to the patient, a supply model which has been well established in the USA (OpenBiome)[2] and has also been successfully replicated in the UK in a large centre in Birmingham, which has supplied FMT to nine NHS Trusts across three regions[3]. This service design only requires that a responsible clinician is capable of administering the FMT safely at the satellite clinical site. It also eliminates the need for patient transfer between clinical sites, which in the case of severe CDI may not be practical.

The working group encouraged the use of frozen FMT material supplied from a carefully controlled production site. This allows donor screening more closely to meet regulatory requirements, ensuring that the window period between donor testing and FMT production is maintained to a minimum. The costs of donor screening are substantially reduced using this supply model, as a single donor can provide multiple FMT donations under a single screening period.

The working group also noted that given the novelty of FMT, awareness of this as a potential treatment option for recurrent or refractory CDI may be low amongst certain groups of clinicians. For instance, clinicians working in primary care, or those whose practice is not located near to an FMT centre, are likely to have less knowledge about the potential suitability of FMT for patients with CDI, or be unaware of referral pathways. As such, there is a responsibility for FMT centres to raise awareness and educate as wide a range of clinicians as possible about the potential role for FMT.

Furthermore, microbiology staff processing stool samples for *C difficile* assays from the community should proactively liaise with primary care teams where recurrent positive tests are received from a single patient to raise awareness and suggest the option of FMT.

Similarly, given the expectation that FMT and/ or other 'microbiome therapeutics' are likely to play an increasing role within medicine over future years, there is also an expectation for FMT centres to not only educate about the potential role for FMT, but also to train relevant healthcare professionals in the practicalities of delivering an FMT service, to enable longer-term ongoing provision of services. This is likely to be most of relevance to specialty trainee and consultant physicians specialising in gastroenterology, infectious diseases and/ or medical microbiology, but potentially to other healthcare professionals too, including infection prevention and control nurses, infectious diseases pharmacists, etc.

Recommendations:

i. The development of FMT centres should be encouraged (GRADE of evidence: very low; strength of recommendation: strong).

ii. We suggest that FMT centres should work to raise awareness about FMT as a treatment option amongst clinicians caring for patients with CDI, and provide training to relevant healthcare professionals on the practicalities of delivering an FMT service (GRADE of evidence: very low; strength of recommendation: weak).

1.2. Legal aspects and clinical governance:

In the United Kingdom, FMT is now considered a medicinal product based on the definitions of purpose and efficacy, in The Medicines Directive 2001/83 and The Human Medicines Regulations[4]. As the competent authority for medicines regulation, the Medicines and Healthcare products Regulatory Agency (MHRA) has indicated that the approach to regulation will be proportionate, depending on factors such as supply being within or outside a legal entity and FMT production scale. Specifically:

- When FMT is supplied on prescription on a named patient basis, then supply under a pharmacy exemption may be used subject to ensuring proper governance and traceability[4].
- If production scale reaches an '*industrial*' level, defined '*by virtue of the batch sizes, the extent of processing and/ or whether potential use includes supply between legal entities'*[4], the route to regulation is via adherence to HMR and formal Manufacturer's 'Specials' (MS) license.

- If a supply is to a clinical trial, then an MIA (IMP) manufacturing license is required (further information on license applications[5] and specials[6] is available online).

Centres establishing an FMT service should undertake steps to ensure practice meets the required compliance levels and seek guidance from the MHRA. If pharmacy exemption is applied, there should be justifiable processes in place to ensure traceability, health and safety, governance and to prevent cross-contamination. FMT is regulated as a medicine, rather than a tissue, but no products have been licensed following an assessment against the criteria of safety, quality and efficacy, for there is a possible risk that donor screening protocols will not be sufficiently considered, a step which is critical to the quality of the product and therefore safety of the patient[7]. To mitigate this, it is advisable that donor screening protocols are under regularly review and risk assessment, and to ensure that consideration is also given to the Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment, particularly Annex B related to donor testing[8]. When formal licencing is sought, this is overseen by a Production Manager and Quality Control Manager if under an MS, or by a Qualified Person if under an MIA (IMP). Both should follow the Good Manufacturing Practice (GMP) guidelines, found within The Orange Guide Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2017[9], or at: https://ec.europa.eu/health/documents/eudralex/vol-4_en .

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The working group noted that outside the UK, the legal and regulatory framework relating to FMT was highly variable between different countries. They agreed that FMT should only be administered after appropriate approval from the competent body of each country.

Recommendation:

In the UK, FMT must be manufactured in accordance with MHRA guidance for human medicines regulation. When FMT is supplied on a named patient basis, within a single organisation, a pharmacy exemption may be used, subject to ensuring proper governance and traceability. All centres that are processing and distributing FMT should seek guidance from the MHRA and where necessary obtain appropriate licenses prior to establishing an FMT service. This is a legal requirement. In countries other than the UK, FMT should only be manufactured following appropriate approval from the national authority of that country (GRADE of evidence: very low; strength of recommendation: strong).

1.3. Multidisciplinary teams:

To promote safe and high quality FMT supply, it is strongly recommended that providers adopt a multidisciplinary team approach. The choice of the team required is subject to the scale of production, but should involve as a minimum a clinical gastroenterologist, microbiologist/infectious diseases clinician, state-registered experienced healthcare scientist and pharmacist. Governance and quality expertise will be required, which may be provided by consultation. If FMT production is to be under a 'specials' licence, the team should be expanded to include a Qualified Person, Quality Manager and Production Manager, all with GMP training.

Recommendation:

We recommend that a multidisciplinary team should be formed to deliver FMT services (GRADE of evidence: very low; strength of recommendation: strong).

1.4. Infrastructure:

Dedicated laboratory facilities for FMT production are recommended to ensure that the process adheres to Health and Safety requirements, to reduce the risk of cross-contamination, and to facilitate standardisation of the production process. In some studies, FMT has been prepared in a clinical environment[10]; however, this may not be advisable because of the risks of cross-contamination. The manipulation of human stool should be conducted in a Containment Level 2 laboratory according to current Health and Safety guidance (Health and Safety at Work Act 1974, COSHH Control of Substances Hazardous to Health Regulations, 2002), and at least within a microbiological safety cabinet which provides user protection (Class I) or, ideally, user and product protection (Class II). To meet the requirements of GMP, this facility should be sole use or be risk assessed for multipurpose use with adequate separation of different activities. The working group recommend that the facility complies with the new GMP production facility classification of 'clean not sterile'. The use of personal protective equipment - such as laboratory coat, gloves and face mask - is also recommended to prevent production contamination. It is essential to risk assess the process and develop control measures to reduce microbial ingress into the facility and monitor the microbiological cleanliness of the production suite. FMT preparation under a 'specials' licence should ensure that the production process is integrated into a Quality Management System, to safeguard production and maintain the minimum criteria for audit, monitoring, standard operating procedures, document control, training, facilities, equipment and storage. With regard to storage, it is essential that the freezer system has real-time temperature monitoring which provides notification outside pre-set limits.

Recommendation:

We recommend utilisation of suitable laboratory facilities and infrastructure for FMT production (GRADE of evidence: very low; strength of recommendation: strong).

1.5. FMT manufacturing:

It is strongly recommended to employ a batch numbering system to track FMT preparations from production to use. It should be possible from records to identify an individual FMT aliquot, trace it to a specific donation, and identify all other FMT aliquots prepared from the same donation. It must also be clear which FMT aliquots patients have received, which should be verifiable from the donor to the patient and vice-versa. It is therefore strongly recommended that a treatment directory be maintained documenting all production and use of FMT, and that an unambiguous record is created in the patients' clinical notes to identify the specific FMT batch number. Further to this, it is also recommended that treatment directories also record clinical outcome, such as that developed in the USA[11] and Germany[12] to standardise and improve future clinical practice.

Recommendation:

We recommend ensuring the traceability of supply (GRADE of evidence: very low; strength of recommendation: strong).

1.6. FMT production quality control:

Safety and clinical governance is a central responsibility for FMT centres, particularly in light of the absence of phase III licensing trials for FMT, which would normally be required for a novel medicinal product. Reporting and investigating adverse events and reactions contributes to knowledge of the FMT safety profile, while also identifying previously unknown safety issues. Governance structures and processes must be in place to monitor, notify and investigate all FMT-related adverse events or reactions locally, and FMT users are encouraged to use the MHRA Yellow Card Scheme for formal notification. FMT supply should be suspended if serious adverse events or reactions occur which are directly attributable to FMT, and there should be a clear documented pathway to achieve this. To facilitate a 'look-back exercise' if required, it is advisable to store documentation and reference samples, both product-based and donor/ patient-based. Specifically, retention of production documentation should be for at least five years after the use of the batch; retention of reference FMT

samples (and stool samples from donors and recipients) should be for at least one year after the last use. Retention of excipient samples should be for at least one year after expiry of the excipient.

Recommendation:

We recommend monitoring, notification and investigation of all adverse events and reactions related to FMT (GRADE of evidence: very low; strength of recommendation: strong).

1.7. Donor screening governance:

The testing requirements for donor screening have been discussed previously; however, it is worth noting here the pertinent clinical governance issues which should be addressed. Donor anonymity should be maintained at all times. The laboratory undertaking testing of donor samples should be competent for such activity, demonstrable by accreditation with the United Kingdom Accreditation Service (UKAS). The results of donor testing should remain confidential. There should be appropriate standard operating procedures to ensure that the outcome of donor screening is built into a robust FMT batch release process. To ensure unbiased autonomy during donor screening, it is suggested that a clinician independent to the FMT production team is responsible for ratifying FMT donors prior to donation. Finally, the duration of donor follow-up should be considered and extend beyond the period of active donation to capture acute and chronic health changes.

Recommendation:

We recommend ensuring the clinical governance of donor screening (GRADE of evidence: very low; strength of recommendation: strong).

2. References:

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