

## Supplementary materials

A: Full version of the guideline

B: Glossary

C: Guideline development and conflicts of interest

D: Consultation

E: Continuing Professional Development

F: Lay materials

A: Full version of the guidelines

A full version of the guideline is available **below**, at HIS website: <https://his.org.uk/resources-guidelines/faecal-microbiota-transplant/>, and on BSG website.



2. FMT full  
version.pdf

## B: Glossary

**Antisecretory medication:** a medication that reduces the normal rate of secretion of a body fluid. In terms of FMT, this medication reduces stomach acid secretion (e.g. proton pump inhibitory and H<sub>2</sub>-receptor antagonist medications).

**Bookend testing:** A type of screening/assessment which aims to capture changes to donor eligibility, as well as risk factors for pathogen acquisition, in the interval between donor acceptance and donation. Bookend testing should identify asymptomatic pathogen acquisition in the interval between donor acceptance and donation. Depending on donation and screening frequency, this may allow for an exemption from direct testing at, and of, each donation.

**Bowel lavage (prep):** a process which involves an administration of a solution to clean the colon for colonoscopic examination.

***Clostridioides difficile*** (commonly known as *C. diff*): a type of bacterium which causes diarrhoea and inflammation of the colon (known as *C. diff* infection or CDI).

**Complicated CDI:** a severe CDI infection characterized by life-threatening features such as shock, sepsis or colon perforation.

**Engraftment:** a process in which it is evident that bacteria from the stool donor successfully colonised and populated the colon of the recipient.

**Faecal microbiota transplant:** a treatment which involves transfer of healthy bacteria from a stool of a healthy person to the intestine of the patient.

**Fidaxomicin:** a relatively new class of antibiotics which is specifically used for the treatment of *Clostridioides difficile* infections.

**Immunocompetent:** a person with fully functioning immune system

**Immunocompromised:** a person in whom the immune system is not functioning at the optimal level.

**Immunosuppressed:** a person with fully functioning immune system who is undergoing a therapy which slows down the immune system (e.g. post-transplant, autoimmune diseases or cancer chemotherapy).

**Inflammatory bowel disease:** a group of disorders which cause a long-term inflammation of the bowel (intestines). IBD term includes ulcerative colitis and Crohn's disease.

**Lyophilised:** freeze-dried, a process in which a specimen is frozen and the water is removed.

**Pseudomembranous colitis:** a severe colonic infection in which plaques appear in the colon and combine to form a growth known as pseudomembranes. This form of colitis is usually associated with *Clostridioides difficile* infections.

**Recurrent CDI:** *Clostridioides difficile* infection which initially responded to the antibiotic treatment but which since came back (relapse). Most clinicians consider the infection to be recurrent if it comes back within eight weeks.

**Refractory CDI:** *Clostridioides difficile* infection which did not respond to the antibiotic treatment. This is usually when symptoms persist, although for some patients infection may be cured while they still experience symptoms.

**Sediment:** a portion of the faecal sample which has been centrifuged. After this process, after a short period of time (e.g. 15-30min), contents separate into lighter liquid (see **supernatant**) with the heavier, solid portion of the stool (sediment).

**Slurry:** A mixture of solid matter (which in terms of FMT, come from stool) suspended in water.

**Supernatant:** a portion of the faecal sample which has been centrifuged. After this process, after a short period of time (e.g. 15-30min), contents separate into lighter liquid (supernatant) with the heavier, solid portion of the stool (sediment).

Vancomycin: an antibiotic which is used for treating a wide range of bacterial infections. When taken orally, it is not absorbed into the body, therefore it has an opportunity to act on *Clostridioides difficile*.

## C: Guideline development and conflicts of interest

### *Guideline development process*

National Institute of Health and Care Excellence. Developing NICE guidelines: the manual. Process and methods; 2018. Available at: <https://www.nice.org.uk/process/pmg20/chapter/introduction> [last accessed October 2023].

### **The Working party members declared following conflicts of interest:**

**BHM** has received consultation honoraria from Ferring Pharmaceuticals, Finch Therapeutics, Summit Therapeutics and speaker fees from Yakult. BHM is also a member of editorial board for Journal of Hospital Infection and Infectious Disease Reports.

**BM** received speaker fees from New Scientist.

**MNQ** received speaker fees from BMS, Parapharm, Tillots, Janssen and Takeda.

**AB** declared no conflicts of interest.

**CG** declared no conflicts of interest.

**DM** declared no conflicts of interest.

**RP** declared no conflicts of interest.

**NE** has received speaker fees from a company not related to the topic of this guideline.

**JS** received speaker fees from Takeda, AbbVie, Pfizer and BMS.

**NS** received consultancy fees for advisory board for Pharmacosmos

**BMa** declared no conflicts of interest.

**GK** declared no conflicts of interest.

**SM** declared no conflicts of interest.

**AH** received fees for consultancy and speaker for AbbVie, Arena, Atlantic, Bristol-Myers Squibb, Celgene, Celltrion, Falk, Galapogos, Lilly, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Shire and Takeda. She also serves on the Global Steering Committee for Genentech.

**CS** is a Chair for the Healthcare Infection Society.

**JK** received consultancy fees from Vedanta Biosciences and Microviable Therapeutics and received a research grant from Vedanta Biosciences. JK is a member/scientific committee of European Helicobacter Microbiota Study group, member of the Scientific Advisory Board of “Microviable Therapeutics”, a member of a steering committee

scientific study VE202 for ulcerative colitis (Vedanta Biosciences) and a founder and board member Netherlands Donor Feces Bank (academic, non-profit)

**PH** Received consultancy and speaker fees from commercial companies and is a Director Modusmedica Ltd (since 2010 onwards)

**TI** received consultancy fees from Ferring and speaker fees from Pharma cosmos. TI is a member BSG/HIS microbiome for health expert panel and a Director of University of Birmingham Microbiome Treatment Centre

**SG** received consultancy honoraria from Enterobiotix and Astra Zeneca, received speaker fees from Tillotts and has investments in biomedical company not related to the topic of this guideline.

**HW** declared no conflicts of interest.

## D: Consultation

### Internal consultation

| Section                                            | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Working Party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Anonymous response, HIS</b>                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 4.1                                                | <p><b>“First episode of CDI</b></p> <p><i>Effectiveness of FMT:</i> There was weak evidence which suggested that FMT is effective in these patients.<sup>29</sup>“</p> <p>There was an RCT of FMT for first and second episodes of CDI in Lancet Gastroenterol Hepatol 2022;7:1083-91. I have a few issues with this paper, but it is nonetheless an RCT, which should be considered in my view.</p>                                                                                                                                                                                                                                                                                                                                                                          | <p>Thank you for this comment. The section here is for first episode of CDI while the paper cited used first and second episode. Unfortunately, it is not possible to separate the data for first and second episode in this study and, therefore, we were not able to use the results to support this evidence statement. However, this study is included in the meta-analysis for the effectiveness, and it is also mentioned in the summary section where we say that the effectiveness is established but FMT is still an invasive and expensive procedure and that we do not currently know if it is justified for these patients. <b>Please note:</b> we corrected this issue after the external consultation. Please find comments in the below section.</p> |
| <b>Anonymous response, HIS</b>                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 4.<br>Rational<br>e for<br>recomm<br>endation<br>s | <p>Patients with severe, complicated or fulminant CDI Effectiveness of FMT in patients with severe CDI: There was <b>weak evidence</b> which suggested that FMT is beneficial in this patient group.<sup>16</sup></p> <p>Effectiveness of FMT in patients with severe CDI compared to patients with mild/moderate CDI: There was moderate evidence which suggested <b>there was no difference between these two patient groups</b>.<sup>17-23</sup></p> <p>Effectiveness of FMT in patients with refractory or fulminant CDI vs recurrent CDI: There was <b>inconsistent evidence</b> which suggested no difference in effect for these patient groups.<sup>24-28</sup></p> <p>Effectiveness of FMT in patients with pseudomembranous colitis compared to other patients:</p> | <p>Thank you for this comment. Please note that weak evidence is the quality of the evidence while ‘beneficial’ implies the direction and an observed positive effect. The statements can be interpreted (and this has been summarized further down) as:</p> <ul style="list-style-type: none"> <li>- evidence is weak but it still suggests that FMT is effective for patients with severe/complicated/fulminant CDI.</li> <li>- evidence was moderate but suggested that FMT is equally effective in patients with severe as well as with mild/moderate CDI</li> </ul>                                                                                                                                                                                            |

| Section                                | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Working Party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                        | <p>There was <b>weak evidence</b>, and it is not clear whether in these patients FMT may be less successful.<sup>18,21</sup></p> <p>Adverse events in patients with severe, refractory or fulminant CDI: There was weak evidence which suggested there was no increased risk associated with FMT for these types of patients.<sup>16,17,24</sup> Adverse events in patients with pseudomembranous colitis: <b>There were no studies</b>.</p> <p>Good practice points</p> <p>GPP 1.1: Consider early FMT for patients with severe or complicated CDI who are not responding to antimicrobial therapy.</p> <p>Is the guideline suggesting early FMT for severe or complicated CDI who are not responding to antimicrobial therapy without adequate evidence?</p> | <ul style="list-style-type: none"> <li>- evidence was inconsistent refractory or fulminant CDI but again, suggested that FMT is as effective as for patients with recurrent CDI</li> <li>- evidence is weak but there is a possibility that FMT is less effective for patients with pseudomembranous, which does not imply it is ineffective.</li> <li>- with the volume of the evidence published on FMT, we think that the small number of studies which point out to no effect means that it is unlikely that there is a risk of adverse events from FMT. We think the risk is greater if FMT is not given.</li> </ul> <p>Thus, we think there is sufficient evidence to recommend FMT to this type of patients. Please also note that this good practice point (not recommendation) especially states that, for these patients, FMT should be considered earlier than usual.</p> |
|                                        | <p>It doesn't have any comment on the early FMT for fulminant CDI. Does complicated CDI and fulminant CDI have the same meaning in this guideline?</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <p>Thank you. We added fulminant CDI to the recommendation.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                        | <p>How early is early for FMT in this sentence?</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <p>Thank you for this comment. Recommendation 1.3 states to offer FMT for patients who had a second recurrence. However, considering the evidence highlighted in the above response, we think it would not be best to offer FMT earlier than usual. Therefore, for the first or the second episode.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Resolution or improvement of condition | <p>One dose of FMT may be less effective in patients with pseudomembranous colitis and to achieve a desired effect, these patients could benefit from additional doses. However, clinically, this issue may not be relevant because in practice CDI patients are not routinely assessed for the presence of pseudomembranous colitis.</p>                                                                                                                                                                                                                                                                                                                                                                                                                      | <p>Thank you. We previously discussed this issue at the meetings and the consensus was that, in practice, it is usually not known whether patients have pseudomembranous colitis. In fact, the experience of most of the working party members was that it was discovered only when FMT was delivered via colonoscopy.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

| Section                                                                        | Comments                                                                                                                                                                                                                                                                                                             | Working Party response                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ns<br>followin<br>g FMT<br>(P.g 13,<br>line 309)                               | In my own clinical practice, CDI patients are assessed for the presence of pseudomembranous colitis if the patients have severe C.diff colitis features. It should have mentioned clearly which CDI patients are not routinely assessed for the presence of pseudomembranous colitis.                                | However, we do not think this changes any of our recommendations. I.e. if a patient does not respond to FMT, we recommend that another FMT is offered. Therefore, clinically, same decisions would be made for patients with and without pseudomembranous colitis.<br>Please note that for this reason, we did not make any recommendations regarding this issue. It is only mentioned in a summary to highlight how the working party interpreted the evidence. |
| Box 1:<br>Recomm<br>ended<br>Donor<br>History<br>Questio<br>nnaire<br>(P.g 25) | It should include animal exposure/contact including pets. Some GI pathogens including worms can be transmissible from animals to humans.<br>It should also ask the history of worms' infestations and any anti-helminths agents taken in the screening questions, although stool ocp are tested.                     | Thank you for your response. We discussed your comment and we do not think this is feasible. This would require the centres to have a different testing schedule. If the testing schedule stays the same regardless of whether there's a different risk and factor question, then there would be no point having the question on the questionnaire.                                                                                                              |
| Box 3:<br>Recomm<br>ended<br>Stool<br>Screenin<br>g<br>(P.g 26)                | Is Multidrug resistant Pseudomonas aeruginosa included in the stool screening for multidrug resistant bacteria?<br>Is screening of Big V carbapenemase producers enough? Does it need to be screened out of Big V like GES and many others? The guideline doesn't mention which CPEs should be clear from the donor. | Thank you, we think our advice here is adequate. With testing for microorganism, there needs to be a degree of flexibility as to which MDROs are relevant due to different epidemiology and donor risk factors. We therefore think it is up to the centre to think which MDROs are relevant to them. We have added the wording "included but not limited to..." to make it clearer.                                                                              |
| <b>Dr Bin Gao, Tianjin 4th Centre Hospital, Tianjin, China, HIS</b>            |                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| General                                                                        | Please consider adding inflammatory bowel disease before the IBD and bracketing it in Page 3, and wording IBD directly in Page 10.                                                                                                                                                                                   | Thank you, we changed this.                                                                                                                                                                                                                                                                                                                                                                                                                                      |

| Section                          | Comments                                                                                                                                           | Working Party response                                                                                                                                                                   |
|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6.1, 6.2, GPP 6.1                | Please consider choosing item of 6.2 or GPP 6.1 either, rather than both.                                                                          | Thank you, we corrected this issue.                                                                                                                                                      |
| 9.2                              | 9.2: When offering compassionate use of FMT, the following conditions must be met <b>simultaneously (at once)</b> :                                | Thank you for your comment. We do not think this is necessary. It is clear from the sentence that all conditions must be met which implies that they all need to occur at the same time. |
| (P. 6, line 64                   | Please consider adding acronym of the term “irritable bowel syndrome” followed within a bracket as IBS used in the following part of the document. | Thank you, we corrected this issue.                                                                                                                                                      |
| P. 8, line 125/144 /150          | Please check whether the reference cited here accurately reflect the corresponding text (additional reference needed).                             | Thank you, we corrected this issue.                                                                                                                                                      |
| P. 13, line 325                  | Please check whether the reference cited here accurately reflect the corresponding text.                                                           | Thank you, we corrected this issue.                                                                                                                                                      |
| General                          | Please consider adding “WHAT’S NEW SINCE 2018 GUIDELINES?” to summarize the document snappily and friendly.                                        | Thank you for this comment. We, in fact, are considering writing an editorial which will highlight these changes.                                                                        |
| <b>CSSC member, BSG</b>          |                                                                                                                                                    |                                                                                                                                                                                          |
|                                  | A very well written guideline. Excellent, detailed work written in a very clear and systematic way.<br>No concerns                                 | Thank you for your kind comments.                                                                                                                                                        |
| <b>IBD Section Member, BSG</b>   |                                                                                                                                                    |                                                                                                                                                                                          |
|                                  | no comments from me. I'm happy                                                                                                                     | Thank you for your kind comments.                                                                                                                                                        |
| <b>CSSC member, BSG</b>          |                                                                                                                                                    |                                                                                                                                                                                          |
|                                  | Very comprehensive and well written guideline. It would be very helpful if the GRADE rating for each recommendation was clearly visible.           | Thank you for your kind comments.                                                                                                                                                        |
| <b>Shanom Ali, UCLH, UK, HIS</b> |                                                                                                                                                    |                                                                                                                                                                                          |

| Section | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Working Party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 4.4     | <p>Considerations / Good practice for faecal acquisition, storage and preparation. The volume of cryoprotectant should be proportional to the mass of faecal same to assure consistency in practice. An expected cryopreservant range should be proposed. For general microbiology applications 10-15% is used. For ease of calculation 10% is practical.</p> <p>E.g. if aiming for a 50g stool, the volume of glycerol would be 5mL.</p>                    | <p>Thank you, agree that 10-15% needs to be stated. However, we think that this is not the same as 5ml of 100% glycerol per 50g of stool, as this does not account for the volume of diluent used in making a faecal slurry. This should be 10-15% of the final slurry and we added this as a GPP 4.8.</p> <p>GPP 4.8: Where glycerol is used as a cryopreservative, ensure it is at 10-15% final concentration of the prepared faecal material/slurry, with vortexing or other methods used to fully mix the cryopreservative into the material.</p> |
| 4.4     | <p>Since the water content can cause bacterial decay upon freezing, effort to assure the cryoprotectant is mixed into the faecal sample. This will assure the bacterial diversity is protected/maintained as much as possible.</p>                                                                                                                                                                                                                           | <p>Thank you, this comment is now addressed in GPP 4.8</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 4.4     | <p>When collecting faecal samples, efforts to remove as much water should be considered. E.g. by placing onto filter paper. This will help with the cryopreservation stage.</p>                                                                                                                                                                                                                                                                              | <p>Thank you for your comment. We do not think this is necessary as this is not currently established in clinical practice and it would add another step to processing (extending the processing time) and increase the risk of contamination.</p>                                                                                                                                                                                                                                                                                                    |
| 4.4     | <p>When thawing samples, the temperature difference from -80oC to ambient (#25oC) is a 105oC temperature fluctuation and will cause stress on the bacterial diversity and recovery. This could be eased by initial thawing at refrigeration temperatures before final thaw at room temperature, prior to delivery. Done in this way, samples could remain in a fridge for most part of the process and require only minimal (~10-15 minutes) at ambient.</p> | <p>Thank you for your comment. We are not aware of any data which suggest that this is a problem. Clinically, we know that the practice of leaving the samples at ambient temperature is still effective and it is practical. We think that leaving the samples refrigerated for a prolonged period of time may be more detrimental to bacterial viability.</p>                                                                                                                                                                                       |
| General | <p>For reference, due to environmental legislation and energy consumption consideration, -40oC freezers are being promoted over -80oC freezing.</p>                                                                                                                                                                                                                                                                                                          | <p>Thank you for your comment. We discussed the freezer temperature in the full text and we have a research recommendation on this topic.</p>                                                                                                                                                                                                                                                                                                                                                                                                         |

## External consultation

| Section                                             | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Working party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Gut/Journal of Hospital Infection reviewer 1</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|                                                     | <p>This is the second edition of the British guideline on the manufacture and use of FMT products. This update is per se very important and welcome as the evidence in this field is evolving rapidly. I feel that all important points have been addressed appropriately in the guideline. I still have some minor suggestions for improvement:</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <p>Thank you for your kind comments</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                                     | <p>1) To those who use FMT in clinical practice, it is clear that it is administered as a follow-up to antibiotic treatment directed at <i>C. diff</i>. This means, it is intended for secondary prophylaxis. At various points in the guideline, the non-expert reader may think that it is administered for treatment of acute CDI and possibly alone. I think the wording on this in the entire document should be clearer to avoid an misinterpretation.</p> <p>Example 1: line 134: „Clinical trials that contributed to the licensing of these products investigated the performance of these agents compared to standard-of-care anti-CDI antibiotics“</p> <p>This is not correct. Both arms received standard of care antibiotics. Subsequently, one received placebo and one the study drug.</p> <p>Example 2: Line 227 and following: „Effectiveness of FMT vs standard care or placebo: There was strong evidence which</p> | <p>Thank you for this comment. We recognise different viewpoints of FMT as either a tool to prevent recurrence (after anti-CDI antibiotics as definitive treatment), or alternatively as a key part of treatment (alongside anti-CDI antibiotics) during an episode of CDI. We have added additional text to explain this difference in viewpoint.</p> <p>We feel that this added section clarifies that FMT is typically used in conjunction with antibiotics. We would also like to draw the reviewer’s attention to recommendation 1.4 which also states that we recommend that FMT is preceded by antibiotics.</p> <p>Additionally, please note that much of the information which appears to be missing is included in evidence statements in a full version of the document which is available in the appendices as well as on HIS/BSG website.</p> |

| Section | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Working party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|---------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         | <p>suggested that FMT is more effective than standard care or placebo for treating CDI in general population.“</p> <p>Again, it is not clear that standard of care antibiotic treatment comes first and subsequently there is a randomization against FMT when it comes to secondary prophylaxis. This is not sufficiently clear from the text. I do understand that there are also studies in which additional doses of vancomycin or fidaxomicin were randomized against the FMT, but I still see the need for a bit more clarification.</p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|         | <p>2) „GPP 1.1 Consider early FMT for patients with severe, fulminant or complicated C. difficile infection who are not responding to antimicrobial therapy.“</p> <p>It is not fully clear what „early“ refers to in this context. After the first episode instead of the second or should the antibiotic treatment be interrupted for an FMT?</p>                                                                                                                                                                                             | <p>Thank you, we addressed this comment by changing the phrasing of the recommendations to highlight that we mean earlier than until after second recurrence.</p>                                                                                                                                                                                                                                                                                                                                                 |
|         | <p>3) „GPP 1.2: If FMT was given via endoscopy, ensure that immediate management after administration is in line with any local protocols.“</p> <p>I am not sure which point you are trying to get across here. What are you trying to improve or avoid based on this statement?</p>                                                                                                                                                                                                                                                           | <p>Thank you for this comment. We added “post-endoscopic management” to make it clearer. This is based upon the experience of Working Party members that endoscopic management post-FMT has been described in certain settings as being more ‘relaxed’ and less rigorous than after conventional GI endoscopy, running the risk of missing potential early post-endoscopic complications (including issues related to sedation, bleeding, etc.). As such, we felt that this point was important to emphasise.</p> |
|         | <p>4) Lines 731-735: Could you describe your approach for pooling samples in more detail? Ist he test sensitivity still sufficiently high, if samples are pooled?</p>                                                                                                                                                                                                                                                                                                                                                                          | <p>Thank you for this comment. Pooling is a fairly frequent procedure in clinical laboratories. The technique, which has been used for e.g. screening for MRSA and COVID-19, and is used when the incidence or prevalence of the condition is expected to be low. Pooled testing combines samples from a</p>                                                                                                                                                                                                      |

| Section | Comments                                                                                                                                                                                                                                                                           | Working party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         |                                                                                                                                                                                                                                                                                    | <p>number of people into one test. If a pooled sample is negative, all people included are considered negative. If the pooled sample tests positive, individual samples are tested to identify positive individuals. With PCR, a context in which we recommended pooling, sensitivity will not be affected as even one copy of the DNA will be sufficient for positive results. The technique has a potential for saving the time and cost of testing each individual.</p> <p>We think that, at the moment, the technique is widely used in clinical laboratories and that relevant persons will be familiar with the concept. As such, we do not think this requires an explanation in the guidelines document itself. The procedure is also described in the study here: <a href="https://linkinghub.elsevier.com/retrieve/pii/S2589537020300456">https://linkinghub.elsevier.com/retrieve/pii/S2589537020300456</a></p> |
|         | <p>5) „Known prior exposure to HIV and/or viral hepatitis.“ Does this mean that such an exposure would exclude donation? Or does it just mean, that this would need to be explored and decided on an individual basis?</p>                                                         | <p>Thank you for pointing this out. We meant in the last three months, which we now added to the document.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|         | <p>6) The statement made in line 859 seems somewhat contradictive to several of the other statements made following that statement. I assume that is due to the definition of the different research questions. Maybe this could somehow be addressed in the explanatory text.</p> | <p>Thank you, we rephrased this and we hope this is now clearer. Colonoscopy seems to be slightly better than other routes but when we compare other administration methods e.g. GI or capsules to other methods combined, this probably diluted the effect of colonoscopy in these statements.</p> <p>We would also like to state that the aim of this section was to identify all methods which could be considered effective as opposed to identifying the most effective method. As a result, we did not consider conducting a network-metaanalysis (if one was even possible) for this part of the guideline.</p>                                                                                                                                                                                                                                                                                                     |

| Section                                             | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Working party response                                                                           |
|-----------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
|                                                     | <p>7) Maybe this last comment is a bit picky, but I would still like to point it out. In the chapter on compassionate use, you discuss the use of FMT in emerging indications. I am not sure the term „compassionate use“ really applies here. According to EMA, compassionate use applies if a product is not licensed (indeed true in this case). However, the product should normally also be used in clinical trials (also true here). It should also be made available free of charge (I do not know the British conditions concerning this point). Also, I am assuming that not all FMT services produce the exact same FMT product, but legally these would be many different product. So, taken together, this seems more like a named patient access concept for use in an individual healing attempt according to the declaration of Helsinki to me. This discussion of terms may seem exaggerated, but if you want your guideline to convince regulators, you need to make sure that you use their language correctly.</p> | <p>Thank you for your comment. This is correct and we changed this accordingly as suggested.</p> |
| <b>Gut/Journal of Hospital Infection reviewer 2</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                  |
|                                                     | <p>In this BSG and HIS practice guidelines on FMT for CDI, Dr. B Mullish and colleagues provided an update from the last rounds of guidelines since 2018 with a growing body of evidence and should be congratulated on this tremendous effort. The manuscript is well written and the recommendations practical.</p> <p>I have the following relatively minor comments/suggestions for the authors to consider:</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <p>Thank you for your kind comment.</p>                                                          |

| Section | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Working party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|---------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         | <p>1. The term “refractory” CDI: this term is rather ambiguous. Does this mean fulminant CDI, or does it mean diarrhea does not resolve with C difficile directed therapy, in which case other potential etiologies such as IBS, IBD etc. may also be contributing. Perhaps consider avoiding this term throughout this manuscript. In some places, refractory CDI and fulminant CDI seem to be used interchangeably.</p>                                                                                                                                                                                                    | <p>Thank you. Please also see a comment above. We added this information to make the definitions clearer. As described above, we used the definitions which were provided by the authors of the papers. Given the heterogeneity and overlap of different terms of CDI pattern/ severity used between studies, we felt that this approach was the most transparent. We also do not think it is possible to clinically define some of these conditions. Indeed, patients could have refractory and fulminant disease or can fall into one of these categories.</p> <p>There are only a few studies which assessed different types of CDI. From the pragmatic point of view, we do not think there is a need for separate evidence statements because the evidence suggests that whatever the category of CDI, most patients seem to benefit from FMT and some may need more than one. The message which we tried to convey, which we think is reflected in recommendations is that the decision whether FMT should be given or not, cannot be based on the category of CDI but on the state of the individual patients. If a patient does not respond to a treatment or the symptoms are severe, it is not important clinically which category they belong to but that they are given FMT earlier.</p> |
|         | <p>2. “1.5. Offer FMT to all types of patients, regardless of their health status, except in those with anaphylactic food allergy” or “2.1. Do not refuse or delay FMT therapy due to any recipient risk factors”. Lines 257-263 immunocompromised or immunosuppressed patients with CDI. Lines 377-8 “the only absolute contraindication for FMT is the presence of anaphylactic food allergy”. How about in those who are severely immunocompromised, such as neutropenic patients? There is no data to support safety in this particular group of patients, and many experts in the field would suggest waiting until</p> | <p>Thank you for this comment. Based on the reviewed literature, the working party think that this is an important consideration but not necessarily a contraindication. The degree of immunosuppression needs to, of course, be balanced against the severity of disease thought to be CDI, as this would likely determine how keen a clinician was to consider faecal transplant, since a reasonable possibility of death from CDI may be a worse outcome than a risk of bacteraemia secondary to a faecal transplant.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

| Section | Comments                                                                                                                                                                                                                                                                                                                                                                                            | Working party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         | neutropenia resolves before proceeding with FMT over concerns of bacterial translocation. Most often neutropenia is a relatively transient state, and waiting till neutrophil count recovers may be a safer approach.                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|         | 3. “4.2. Start processing stools within 150 min of defecation”. I am not aware of any study that suggests a longer interval such as 8 hours or even 24 hours after defecation would render donor stool ineffective, especially if it is kept at 40C? It may pose another challenge for a stool bank if such a restriction is in place without a good reason.                                        | Thank you for this comment. Our intention was to indicate that it is considered likely that the complexity of microbiota in a stool donation diminishes over time and so greatest benefit is thought to arise when the processing time is kept to a reasonable minimum. 150 minutes is a threshold used with in a number of studies, reflecting a balance between enough time to pragmatically transfer stool from production by donor to an FMT laboratory, and yet a short enough time to mitigate alterations to microbiome composition and functionality. Upon review, we think this is probably better placed as good practice point, which is where we moved it to. |
|         | 4. Line 229: “FMT is more effective than standard care or placebo for treating CDI.” FMT is used to prevent CDI recurrence. I think it is more accurate to use the term “preventing CDI recurrence”, rather than “treating CDI”. Similarly, line 245: the cited reference #29, FMT was used to prevent CDI recurrence after first episode; and line 250: in “treating” CDI in patients with ICD.    | Thank you. Please also see a comment above. We have made changes as requested.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|         | 5. Line 231: “Adverse events following FMT vs standard care of placebo: There was strong evidence which suggested no negative effect of FMT.” I would suggest rephrasing this. Although it is generally accepted that FMT is likely safe, adverse event rates have been low and possibly underreported. The most recent Cochrane review also found that “there was no conclusive evidence regarding | Thank you for this comment. We do agree that adverse events may occur and that they could be due to pathogens being transferred via FMT, the route of administration and the FMT itself. However, in the context here, we stated that FMT had no negative effect when compared to patients who received standard care or placebo. This means that the incidence and severity was similar in both groups. This may be clearer in a full version of the                                                                                                                                                                                                                     |

| Section                                      | Comments                                                                                                                                                                                                                                                                                                                                                                                              | Working party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                              | the safety of FMT for the treatment of rCDI as the number of events was small for serious adverse events and all-cause mortality; CIs around the summary estimates were wide” (Cochrane Database Syst Rev 2023 Apr).                                                                                                                                                                                  | document which is available in the supplementary files and on HIS/BSG websites.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|                                              | 6. Line 238: Effectiveness of FMT in patients with refractory or fulminant CDI vs recurrent CDI etc. Do the authors imply that refractory CDI and fulminant CDI mean the same?                                                                                                                                                                                                                        | Thank you for your comment. As requested by other reviewer, we added definitions in a box to clarify the meaning of these conditions. We are not saying that these are the same things, but that we kept researchers’ definitions as they used them in their studies for the sake of transparency, and sometimes they were combined. Since there are no universally accepted definitions and ‘states’ can overlap, and the fact that FMT seems to be overall comparably effective in different ‘states’, we only used this evidence to highlight that FMT treatment should not be refused based on a CDI severity or its definition. |
|                                              | 7. Line 240: effectiveness of FMT in patients with pseudomembranous colitis etc. Most patients with pseudomembranous colitis have fulminant CDI. I am not sure if lines 238 and 240 need to be separate recommendations?                                                                                                                                                                              | Thank you for this comment. We think this is correct as is. Pseudomembranous colitis patients will likely be classified as fulminant CDI, although fulminant CDI does not necessarily mean that there is a presence of the pseudomembranes.                                                                                                                                                                                                                                                                                                                                                                                          |
|                                              | 8. Line 1011. “There was weak evidence which suggested FMT is effective in inducing remission in patients with CD”. The reference cited #126 is in a study where patients were induced into remission by steroid, then randomized to either FMT or placebo to maintain remission. Please make this correction. As far as I know, there is no published study on using FMT to include remission in CD. | Thank you for this comment. We agree with this suggestion and we have changed this as requested.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Gut/Journal of Hospital Infection reviewer 3 |                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

| Section | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Working party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         | <p>This is a comprehensive update of the BSG/HIS guidelines of FMT. Authors have released an extensive document which encompasses all necessary updates of this topic.</p> <p>I have some comments: 1) I am not used to the NICE approach to guidelines, so I found the text a bit dispersive overall. I acknowledge that, being these guidelines aimed mostly at a national level, this will not be an issue. However, I am suggesting, in the next specific comments, some points that would be improved by a major clarity</p> | <p>Thank you for your kind comments.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|         | <p>2) Line 48: please provide the website address</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | <p>Thank you, this comment will be addressed when a final document is available.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|         | <p>3) Line 81: I would avoid the term "poo", even if it's for patients</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <p>Thank you for this comment. We do not think that this is up to us to decide. Our lay summary – including use to this term – was selected and approved by our lay members and, as such, we are honouring their decision.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|         | <p>4) Line 240: There is a RCT (Ianiro et al - APT 2018) and several papers from the Fischer group, showing that multiple FMT is effective in PMC, and more effective than single FMT. Generally, PMC is basically a proxy for severe CDI, so I would align the two entities</p>                                                                                                                                                                                                                                                  | <p>Thank you. However, the working party viewed there to be more complexity than is suggested here. Specifically, there are patients with severe CDI who have no evidence of the presence of pseudomembranes. Additionally, the presence of pseudomembranes is not always known clinically (certainly in UK practice, only a proportion of patients with CDI – including severe CDI – would undergo lower GI endoscopy). Indeed, the working party members reported that these are often discovered at the time the patient is given FMT colonoscopically. We also do not think that, based on the knowledge of whether pseudomembranes exist in an individual patient, this would change any clinical decisions and the course would be the same if our guidelines were followed, i.e.: severe disease would warrant an early FMT and no</p> |

| Section | Comments                                                                                                                                                                                                                                                                                                                                                                                                       | Working party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|---------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         |                                                                                                                                                                                                                                                                                                                                                                                                                | symptom improvement or symptom recurrence would require another dose of FMT, regardless of whether or not pseudomembranes are present.                                                                                                                                                                                                                                                                                                                                                                                                                         |
|         | 5) Line 244: the studies above have reported adverse events in PMC                                                                                                                                                                                                                                                                                                                                             | Thank you for this comment. We reviewed the two studies which mentioned PMC specifically and not in combination with severe CDI (ref 18 and 21). Both studies were risk factors studies which compared patients with PMC (and other potential risk factors) to patients without PMC. One of these studies reported adverse events but this was for the entire patient population and it is not possible to determine which and whether any of these events occurred in patients with PMC specifically.                                                         |
|         | 6) Line 248: also here there are studies reporting AEs for FMT as first-line therapy of CDI (i.e. Baunwall et al, Lancet Gastro Hep)                                                                                                                                                                                                                                                                           | Thank you. We checked and these data do are not reported by the authors as stratified for first and second episode. However, we have since been in communication with the authors and requested and received these data, which are now included in the report.                                                                                                                                                                                                                                                                                                 |
|         | 7) Line 316: It is true that FMT has not been studied with the specific purpose of assessing its efficacy in patients with multiple comorbidities, but a) most patients with CDI have multiple comorbidities; b) several studies (i.e. Ianiro et al - Ann Intern Med 2019), or studies on immunocompromised patients (i.e. those from Colleen Kelly) have evaluated FMT in patients with several comorbidities | Thank you for this comment. We are just following the “script” for our inclusion criteria within PICO questions, and therefore what was reported in the literature. Nevertheless, having reviewed the available evidence, we do not think this is specifically a problem. Most CDI patients will likely have multiple comorbidities which were not reported. Furthermore, even though the presence of multiple comorbidities may slightly affect the effectiveness of FMT, we do not think this affects any decisions as it is clearly still effective enough. |
|         | 8) Lines 371-373: also here, I would not focus on PMC but would make a general statement for severe CDI, as the clinical management does not change                                                                                                                                                                                                                                                            | Thank you, we agree and we added severe to the sentence.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

| Section | Comments                                                                                                                                                                                                             | Working party response                                                                                                                                                                                                                                                                                                                                         |
|---------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         | 9) GPP 1.4: you should discuss, even briefly, this concept in the text, and not only in the box.                                                                                                                     | Thank you for pointing this out. This was included in a longer version of the document in supplementary files but was removed from the shorter version. We do agree that it is important to retain this information and we included it in a shorter version.                                                                                                   |
|         | 10) GPP 1.6: testing should be done if the patient has a pre-existing disease that can cause diarrhea (i.e. IBS or IBD)                                                                                              | Thank you. This is exactly what we suggest – we imply that if someone has no symptoms, they do not have to be tested. Testing may therefore be needed for those who are still symptomatic (practically, those who have diarrhoea) to establish whether this is because of CDI or other reasons, such as those suggested by the Reviewer.                       |
|         | 11) Line 423: Poor bowel preparation and severe CDI are risk factors for failure of FMT (see Ianaro et al - Clin Microbiol Infect)                                                                                   | Thank you for this. We agree, but please note that we included these factors in other sections, i.e. severe CDI is in a section reporting on CDI characteristics, and bowel preparation/lavage is reported in a section about FMT administration. We did identify and report both as potential risk factors for failure.                                       |
|         | 12) Line 697: I would also mention that the engraftment of donor strains after a single FMT is usually temporary, and disappears after some months, so the real procarcinogenic risk may be even lower than expected | Thank you. We added this to the discussion.                                                                                                                                                                                                                                                                                                                    |
|         | 13) Line 724: You did not introduce before the concept of direct stool screening, that would deserve some more discussion                                                                                            | Thank you for this comment. Respectfully, after further review, the working party feel that this is clear enough without any changes. Given that this guideline is targeted at those who already have familiarity with FMT processes, we think that the concept will be familiar to the majority of readers and does not need further introduction to readers. |
|         | 14) Recommendation 3.6: you should clearly state the interval between each screening repetition                                                                                                                      | Thank you. We discussed this on numerous occasions, but we do not think that the interval should be didactically defined. We think this needs to be                                                                                                                                                                                                            |

| Section                                                                                                                                                        | Comments                                                                                                                                                                                                                              | Working party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                |                                                                                                                                                                                                                                       | defined locally based on a number of individualised factors, including what is feasible to achieve and the prevalence of different conditions within potential donors.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                                                                                                                                                                | 15) GPP 4.7: also here, please introduce this concept in the text also, and not only in the box                                                                                                                                       | Thank you. We added this to the discussion.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|                                                                                                                                                                | 16) I am concerned of the recommendation for the use of NGT to deliver FMT. There are several cases of aspiration pneumonia through the upper route and especially through NGT. I would curb the statements that allow the use of NGT | Thank you, the Working Party agreed that this is overall safe and clearly effective, and was an appropriate option to consider for patients. Recognising the potential risk of aspiration associated with NG administration, we have included a good practice point about limiting the volume of slurry administered to only 100ml.                                                                                                                                                                                                                                                                                                                                                            |
|                                                                                                                                                                | 17) GPP 5.4: why wouldn't you do FMT by suspending antibiotics just the same day of the procedure? using antibiotics until the FMT day is also ethical, as you don't leave the patient without therapies while waiting for FMT        | Thank you for this comment. The working party noted that this was an 'evidence light' zone, but intuitively recognised that there was a balance to be struck between sufficient anti-CDI antibiotics to minimise the burden of <i>C. difficile</i> prior to antibiotics vs enough of a gap from antibiotics to minimise the risk of residual antibiotics within the gut damaging the new microbiome provided through FMT. The opinion of the working party was that 24 hours met an appropriate balance. However, recognising the limited clinical evidence, this is only a good practice point and it is not an absolute requirement for FMT administration. We added this to the discussion. |
|                                                                                                                                                                | 18) Recommendation 6.2: also gastroenterologists with expertise in antibiotics or microbiome may give this answer                                                                                                                     | Thank you for this comment. We addressed this.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Dr Simon Mark Dahl Baunwall and Prof Christian Lodberg Hvas; Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark</b> |                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Recommendation 1.1: First-line                                                                                                                                 | We read with great interest the draft version of the updated BSG guideline for <i>Clostridioides difficile</i> infection. The guideline is a comprehensive and valuable update, serving as a potential key                            | Thank you for your considered comment. We do agree that there is clinical evidence that FMT is safe and effective in the first and second episode of CDI and we agree that the use of the term "avoid FMT as initial treatment for                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| Section                | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Working party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| recommendations of FMT | <p>reference in the field. It provides a comprehensive evidence-based assessment that guides the most important clinical questions currently posed in the field.</p> <p>We wish to comment on the phrasing of guideline recommendation 1.1 to “Avoid FMT as an initial treatment for C.difficile infection (I.e. first episode)” due to limited evidence.</p> <p>While we understand the caution and although extensive elaboration is provided later in the guideline, the current wording may oversimplify the complex clinical spectrum of C. difficile infection. Different disease severities and varied responses to antibiotics necessitate a more nuanced approach and statement. For instance, in TJ Louie et al.'s study (NEJM, 2011), 12-15% of patients did not respond to standard antibiotic therapies. This significant subset of antibiotic non-responders might benefit from a stratified approach to early use of FMT, especially in patients with severe or treatment-refractory disease. In both scenarios, the mortality risk is high and may be reduced using effective treatments such as FMT. The guideline includes sections that elaborate handling of severe, fulminant infection and refractory disease, and highlighting this in the recommendation by referring to these sections may improve the general interpretation.</p> | <p>CDI...” implied it actively did harm, when this is clearly far from the case. We do appreciate that this may not have been clear in our recommendation, and we have rephrased it:</p> <p>1.1: Offer antibiotics in preference to FMT as an initial treatment for C. difficile infection (i.e. first episode).</p> <p>The conclusion of the working party discussions on this topic was that standard of care anti-CDI antibiotics (vancomycin and fidaxomicin) have a very established evidence base for first CDI, are clinically and cost effective, and are widely available. While the quoted Louie study does indeed demonstrate a notable rate of non-response to standard of care antibiotic treatments, it nonetheless demonstrates up to 88% of patients responding to such therapy. Indeed, trial data of FMT in the context of first CDI appropriately gives the FMT only after a course of such antibiotics. Collectively, while the working party recognised an evidence base that was supportive for FMT having a potential role in first CDI, the relatively nascent nature of this evidence, weighed against the highly established evidence base for anti-CDI antibiotics, coupled with the uncertainties highlighted by the contributors themselves regarding ability to meet demand by FMT services, and cost effectiveness - meant that they still felt that anti-CDI antibiotics should be overwhelmingly the key treatment choice for the majority of primary CDI patients.</p> <p>Please also note that our recommendations 1.2 and 1.3 provide a caveat and a way for people with severe CDI or those who did not respond to antibiotics early in the treatment, a way to get FMT sooner. We think this is a person-centred decision but that the default situation should be antibiotic</p> |

| Section                                               | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Working party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | treatment. We also make a research recommendation for cost-effectiveness of FMT which we hope will help us making more informed decisions in the next edition of these guidelines.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Recommendation 1.1: First-line recommendations of FMT | <p>In the GRADE assessment and PICO framework focusing on first-episode C. difficile infection, we note the exclusion of studies addressing both first and second infections. This approach differs from current guidelines and the landmark antibiotic studies (e.g., TJ Louie et al., NEJM 2011; MH Wilcox et al., NEJM 2017) and may inadvertently underevaluate the evidence for FMT efficacy.</p> <p>In the comment to anonymous reviewer, we noticed that on a comment mentioning our recent RCT (Baunwall et al 2022, Lancet Gas Hep) it is stated that the manuscript does not provide the stratified data for first and second episode and is therefore omitted. This is incorrect. In the manuscript, the stratified results for patients with first and second C.difficile infection are reported and detailed.</p> | <p>Thank you for your comment and the additional data which we received. We added these data as advised and we changed the strength of this statement from weak to moderate. The working party considered that they could not justify changing the evidence to strong based on one study.</p> <p>The working party would also like to note that this, and the Wilcox study, report an unusually high rate of CDI recurrence compared to other literature. Based on clinical experience, the working party did not recognise recurrence rates as being typically so high in their own practice and, as highlighted above, could not, at this moment, justify FMT use for first CDI episode based on just one study when alternative methods are established in practice.</p> |

| Section | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Working party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|---------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|         | <p>If applicable, we will gladly provide any supplementary data for the authors if necessary.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|         | <p>The working group rationale for not recommending FMT first-line treatments cites concerns about “FMT is more invasive and more expensive, and that a relatively high success rate can be achieved with anti-CDI antibiotics alone”.</p> <p>We propose further clarification on these points:</p> <ul style="list-style-type: none"> <li>• Invasiveness: Encapsulated FMT is an available administration form of equal (non-)invasiveness to the antibiotics.</li> <li>• Antibiotic efficacy: In the MODIFY I and II studies (MH Wilcox et al., NEJM 2017), a sustained cure was achieved in only 54% of patients treated with standard care antibiotics and placebo. This statistic highlights the need for additional treatment options, particularly considering the typical patient demographics of <i>C. difficile</i> infection.</li> <li>• Cost: While FMT's cost is a valid concern, it should be compared contextually, considering its role as an adjunct to antibiotics, similar to bezlotoxumab.</li> </ul> | <p>Thank you for your comment. We do agree that FMT in encapsulated form is less invasive physically than colonoscopy or upper GI route; however, the relatively limited availability of capsulised within UK FMT practice compared to slurry means that this is a relevant consideration within our settings.</p> <p>Thank you for your other comments. We note that the study included a rather large proportion (over 25%) of patients who had a recurrent CDI, and it is difficult to separate these data but, considering that a recurrence is a risk factor for further recurrences, it is reasonable to expect that many of the initial failures or later recurrence could have been in this group. We do not know whether this is significant, but the number of patients who previously had a recurrence seems to be slightly higher in the placebo group than in groups which received an active antibody. It is therefore possible that, removing these patients from the analysis, the incidence of recurrence for the first episode of CDI would be similar to that reported by other studies. Thus, we do not think we can extrapolate the results from this study to recommendations in our guidelines. Here, the argument is whether or not we should offer FMT to patients with first recurrence but the cohort in this study contains both types of patients. Please also note that:</p> |

| Section                                           | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Working party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                   | <p>A nuanced, important argument against first-line recommendations for FMT is its current limited availability to physicians and the absence of standardized treatment protocols to make generic treatment recommendation. Stating this as the major reasons might be more accurate and acknowledge the current required developments and clarifications before broad recommendations.</p> <p>In summary, we suggest refining the recommendations to reflect the complexity of C. difficile infection management, considering the diversity in disease severity and treatment responses.</p> | <p>1. It was not our intention to provide recommendations for CDI treatment in general but to offer advice on when FMT should be considered, how it needs to be administered and how it can be made safe and more effective.</p> <p>2. Guidelines for CDI treatment exist and our recommendations are in line with these guidelines, e.g. NICE <a href="https://www.nice.org.uk/guidance/ng199/chapter/Recommendations">https://www.nice.org.uk/guidance/ng199/chapter/Recommendations</a>, ESCMID: <a href="https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00568-1/fulltext#secsectitle0085">https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00568-1/fulltext#secsectitle0085</a></p> <p>CDC: <a href="https://www.cdc.gov/cdiff/clinicians/faq.html">https://www.cdc.gov/cdiff/clinicians/faq.html</a></p> <p>Cost/resources issues – these are indeed difficult to compare and if we are talking contextually, setting up more FMT services and providing more FMT administration, adding the cost of screening, staff time for running facilities – this is still very expensive and only a good cost-analysis study could resolve this issue, which is what we recommended in further research.</p> |
| Supplementary material answers during consultancy | We noted a reference to our recent RCT (Baunwall et al. 2022, Lancet Gastroenterol Hepatol) in the anonymous reviewer comments of the consultation process in the supplementary material. Contrary to the answer provided, our manuscript does indeed provide stratified data for first and second C. difficile infections. We will gladly share these data if deemed useful for the guideline’s accuracy.                                                                                                                                                                                    | Thank you for providing these data. As highlighted above, we addressed this issue.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

| Section                                                                           | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Working party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Dr Nehal Draz; Kingston Hospital Nhs Foundation Trust, London UK</b>           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <p>Page 11 line 232</p> <p>Patients with severe, complicated or fulminant CDI</p> | <p>It was mentioned that effectiveness of FMT in patients with severe CDI: There was weak evidence which suggested that FMT is beneficial in this patient group.</p> <p>There was only one study included as a reference (ref no.16). However, there is one study, a systematic review, not included in the included or excluded studies. This study concluded the following:</p> <p><i>FMT appears effective in treating SFCDI patients with low adverse events but requires multiple treatments with a significant proportion of patients requiring additional anti-CDI antibiotics to achieve resolution. The optimal route of FMT delivery remains unknown. The presence of pseudomembranous colitis may guide additional FMT or anti-CDI antibiotic treatment.</i></p> <p>Yi Nong Song, BSc, David Yi Yang, MD, Sander Veldhuyzen van Zanten, MD, MSc, MPH, PhD, Karen Wong, MD, Eric McArthur, MSc, Claire Zhao Song, Gianluca Ianiro, MD, Giovanni Cammarota, MD, Colleen Kelly, MD, Monika Fischer, MD, MSc Fecal Microbiota Transplantation for Severe or Fulminant <i>Clostridioides difficile</i> Infection: Systematic Review and Meta-analysis</p> <p><i>Journal of the Canadian Association of Gastroenterology</i>, Volume 5, Issue 1, February 2022, Pages e1–e11, <a href="https://doi.org/10.1093/jcag/gwab023">https://doi.org/10.1093/jcag/gwab023</a></p> | <p>Thank you for this comment. This study was not picked up by our search, the reason for this is that the journal is currently not indexed in either Medline or Embase, which are the two major databases for conducting systematic reviews.</p> <p><a href="https://www.ncbi.nlm.nih.gov/nlmcatalog/?term=J+Can+Assoc+Gastroenterol">https://www.ncbi.nlm.nih.gov/nlmcatalog/?term=J+Can+Assoc+Gastroenterol</a>.</p> <p><a href="https://www.elsevier.com/products/embase/content">https://www.elsevier.com/products/embase/content</a></p> <p>Furthermore, in saying this, the review included studies which we have excluded (as such, review itself would have been excluded) based on the fact that they did not meet our inclusion criteria, mainly because one study compared FMT to FMT, another study reported mortality rather than symptom improvement/resolution.</p> <p>For the remaining studies (all case series), six were out of our date range and would have been considered in the first edition of these guidelines. The remaining case series had less than 10 patients which was our criterion for including a study with no comparison group.</p> <p>We do believe that despite these exclusion criteria, our conclusions are similar to the ones reached by the authors of this systematic review. Specifically, even though the evidence is weak (no comparison group makes it difficult to draw inferences and GRADE handbook considers this very weak evidence, which we upgraded to weak based on a large magnitude of an effect), we concluded that FMT is effective for this group of people.</p> |

| Section                                        | Comments                                                                                                                                                                                                                                                                                                                                                                                                                | Working party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                |                                                                                                                                                                                                                                                                                                                                                                                                                         | Moreover, our next evidence statement - which includes seven studies that compare patients with severe CDI to those with non-severe form - convinced us that FMT is equally effective in these different groups. Collectively, even if we did update our inclusion criteria and allowed the inclusion of these studies, the quality of evidence, our conclusions - as well as our recommendations - would remain the same.                                                                                                                                                                                                                                                      |
| Page 3<br>Executive summary of recommendations | <p>Good practice points GPP 1.1: Consider early FMT for patients with severe, fulminant or complicated <i>C. difficile</i> infection who are not responding to antimicrobial therapy.</p> <p>This was recommended while not supported by what was mentioned later at page 10 (see my previous comment)</p>                                                                                                              | Thank you for this comment. Despite us finding only a small number of studies which, by design, would be considered weak quality, the next evidence statement - which compares outcomes for patients with severe and non-severe CDI - convinced us that there appeared to be no difference in outcomes, and that FMT is effective in patients with severe CDI. We also made a comment that more than one FMT may be required. Considering this, and the fact that people with these types of infections have very limited options for treatment, we think it is good practice to offer FMT earlier in their disease course (and by extension, to offer further FMTs if needed). |
| <b>Royal College of Pathologists</b>           |                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                                | The Royal College of Pathologists have nothing to add to these guidance notes.                                                                                                                                                                                                                                                                                                                                          | Thank you for your comment.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Dr Tom Butler, University of Manchester</b> |                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| General                                        | To reach a wider audience, consider a definitions box/section, to ensure all readers understand terms such as <i>C. difficile</i> recurrence, refractory <i>C. difficile</i> , severity of <i>C. difficile</i> (severe, fulminant, complicated). Also, is 'fulminant' <i>C. difficile</i> an accepted term, I thought severe and life-threatening used to categorise <i>C. difficile</i> severity in clinical settings? | Thank you for this. We think that, clinically, these categories are difficult to define, as there is no universality in definitions of CDI severity, and patients may have more than one of these terms to describe their CDI disease state at the same time. We used definitions as provided by the authors of the individual papers. As a response to the comment, we included an additional                                                                                                                                                                                                                                                                                  |

| Section                                                               | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Working party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | box which provides definitions for these categories and explain the difficulties in using them clinically.                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| General                                                               | Perhaps a good practice point on consideration for research enrolment, especially when FMT used for non-CDT indications. May fall into Compassionate use section.                                                                                                                                                                                                                                                                                                                                      | Thank you for this comment. We added the information about the research enrolment, which is in fact a requirement for consideration for compassionate use.                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Mrs Susie Dodd, ARHAI Scotland, NHS National Services Scotland</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Page 4 2.1                                                            | Recipient factors influencing the outcome of FMT for patients with C. difficile infection 2.1: Do not refuse or delay FMT therapy due to any recipient risk factors e.g. age over 75 years old. However Above on page 3 1.5 states that Offer FMT to all types of patients, regardless of their health status, except in those with anaphylactic food allergy. This could possibly be misinterpreted therefore consider noting the exclusion of those with anaphylactic food allergies in section 1.5. | Thank you, we added this condition as recommended.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Page 7 (10.1)                                                         | Self-banking of stool for potential future autologous FMT – Consider providing a definition of self-banking.                                                                                                                                                                                                                                                                                                                                                                                           | Thank you. We think the relevant context is provided in the first sentence and that a definition is not necessary, especially since the concept is more abstract than based on existing facilities .                                                                                                                                                                                                                                                                                                                                                  |
| Page 14 line 343                                                      | Editorial comment should read year not yar.                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Thank you. We corrected this issue.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Page 15 Line 379-384                                                  | “In previous guidelines, there was a concern that FMT may cause harm in some types of patients, including those who are immunocompromised or immunosuppressed, those with liver or kidney disease or those with IBD. However, the evidence now suggests that the incidence of adverse events, regardless of their severity, appears to be similar in different types of patients. Thus, the Working Party 383 agreed that FMT should still be considered as                                            | Thank you for this comment. Respectfully, this summary of working party evaluation is straight after the extensive presentation of evidence in Section 4.1 related to impact of different comorbidities upon likelihood of success of FMT for rCDI. We think that, from the evidence statements, it is clear that the incidence of adverse events is relatively low, when compared to patients who are not immunocompromised/suppressed. Due to a word count, we are not able to fully elaborate on this but a full version of the guideline which is |

| Section                            | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Working party response                                                                               |
|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
|                                    | a treatment option for patients with comorbidities based on its safety.” In the absence of – any discussion or reference to the evidence makes this section difficult to understand, particularly the reference to “the evidence now suggests that the incidence of adverse events, regardless of their severity, appears to be similar in different types of patients” Was a particular group of patients studied if so can the patient characteristics be detailed? | available in supplementary materials as well as on BSG/HIS websites provides sufficient information. |
| Page 27<br>Narrative below<br>*GDH | Asterisk relates to toxin B – Consider including Glutamate Dehydrogenase in full prior to abbreviation                                                                                                                                                                                                                                                                                                                                                                | Thank you, we added this as recommended.                                                             |

Post-submission comments:

| Section                                             | Comments                                                                                                                                                                                                                                                                                                                                                  | Working party response                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Gut/Journal of Hospital Infection reviewer 3</b> |                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                                                     | <p>thank you for the excellent and comprehensive revision. All my comments are addressed. I wanna just comment on one point of my previous review:</p> <p>" Recommendation 3.6: you should clearly state the interval between each screening repetition".</p> <p>You stated: "Thank you. We discussed this on numerous occasions, but we do not think</p> | <p>Thank you for your kind comment. We discussed this again and made a recommendation for defining the longest period which we think is safe for the donors to donate without testing and we agreed on four months. We hope that this definition and subsequent new recommendation 3.7 (pages 4 and 27). We hope that this is a pragmatic approach which ensures patient safety but also prompts the individual centres to assess whether more frequent testing is more appropriate for their setting.</p> |

| Section | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Working party response |
|---------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
|         | <p>that the interval should be didactically defined. We think this needs to be defined locally based on a number of individualised factors, including what is feasible to achieve and the prevalence of different conditions within potential donors£.</p> <p>I still believe that this point should be standardized, as delegating this choice at a local level may increase safety risks. If an agreement between the guideline panel has not been reached, I would suggest to align your recommendations with previous consensus initiatives and guidelines.</p> |                        |

## E: Continuing Professional Development

1. When should treatment of CDI with FMT be considered?
  - a. When a patient is diagnosed with CDI and has risk factors for recurrence
  - b. After first recurrence
  - c. After two or more CDI recurrences.
  - d. After first recurrence of refractory CDI
  - e. FMT can be offered to any patient with FMT.
2. Why should cancer patients not receive FMT for treatment of CDI?
  - a. FMT is not effective in this group of patients
  - b. They are at high risk of experiencing severe adverse events
  - c. They can receive treatment but only after cancer treatment has ended
  - d. Cancer patients cannot be transported to facilities where FMT is given
  - e. There is no reason to suggest that cancer patients cannot receive FMT
3. Which route of FMT administration is less likely to be successful for treatment of CDI?
  - a. Colonoscopy
  - b. Enema.
  - c. Upper GI to stomach
  - d. Upper GI to duodenum
  - e. Oral capsules.
4. Which donor factors make FMT less effective for treatment of CDI?
  - a. Age.
  - b. Mismatched sex
  - c. Microbiota composition
  - d. Presence of MDRO
  - e. None of the above
5. For which conditions, other than CDI, FMT may be considered?
  - a. Ulcerative colitis
  - b. Crohn's disease
  - c. IBS
  - d. MDRO
  - e. Obesity

F: Lay materials

Please follow the link below for useful information on FMT:

**FAECAL MICROBIOTA TRANSPLANTATION**

**[gutscharity.org.uk/info/FMT](https://gutscharity.org.uk/info/FMT)**