Health-related quality of life in patients with recurrent *Clostridioides difficile* infections

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Abstract

**Background:** The health-related quality of life (HrQoL) can be substantially affected in patients with recurrent *Clostridioides difficile* infection (rCDI) but the impact of effective treatment of the infection remains unclear. This study aimed to evaluate the HrQoL in patients with rCDI and estimate the gain in HrQoL associated with effective treatment of rCDI.

**Methods:** Patients’ HrQoL was estimated based on EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) questionnaires obtained from a Danish randomised controlled trial (RCT). In the RCT, 64 patients with rCDI were randomised to receive either vancomycin (*n* = 16), fidaxomicin (*n* = 24) or faecal microbiota transplantation (FMT) preceded by vancomycin (*n* = 24). The primary outcome in the RCT was rCDI resolution. Patients were closely monitored during the RCT, and rescue FMT was offered to those who failed their primary treatment. Patients’ HrQoL was measured at baseline and at 8- and 26-weeks follow-up. Linear regression analyses conditional on the differences between baseline and follow-up measurements were used to assess statistical significance (*p* < 0.05).

**Results:** Within 26 weeks of follow-up, 13 (81%) patients treated with vancomycin, 12 (50%) patients treated with fidaxomicin, and 3 (13%) patients treated with FMT had a subsequent recurrence and received a rescue FMT. The average HrQoL for untreated patients with rCDI was 0.675. After receiving effective treatment, this value increased by 0.139 to 0.813 (*p* < 0.001) at week 8 and by 0.098 to 0.773 (*p* = 0.003) at week 26 of follow-up compared with baseline.

**Conclusion:** The HrQoL was adversely affected in patients with an active episode of rCDI but increased substantially after receiving an effective treatment algorithm in which rescue FMT was provided in case of a primary treatment failure.

**Trial registration:** The RCT was preregistered at EudraCT (j.no. 2015-003004-24, https://www.clinicaltrialregister.eu/ctr-search/trial/2015-003004-24/results) and at ClinicalTrials.gov (study identifier NCT02743234, https://clinicaltrials.gov/ct2/show/NCT02743234).

**Keywords:** health-related quality of life, clostridioides difficile, fecal microbiota transplantation

**Background**

*Clostridioides difficile* infection (CDI) is a frequent hospital-acquired infection causing symptoms ranging from mild diarrhoea to life-threatening, fulminant colitis.1–4 CDI commonly occurs following antibiotics exposure with subsequent disruption of the colonic microbiota.1,2 Primary treatment of CDI is antibiotics, consisting of either vancomycin or fidaxomicin, directed against *C. difficile*, but 15–30% of all patients with CDI develop recurrent CDI (rCDI).5–7 Faecal microbiota transplantation (FMT) is a recent treatment alternative and has been found to be superior to antibiotics in obtaining clinical resolution of symptoms without recurrence in patients with rCDI.5 The health-related quality of life (HrQoL) of patients with CDI can be substantially affected by the infection due to physical and psychological
The presence of diarrhoea may affect the patients’ ability to perform their usual activities and have adverse social impacts. In addition, emotional distress can present as a consequence of the disease and most patients fear worsening of symptoms and recurrence of CDI. Studies indicate that these impacts may persist even after receiving effective treatment.

Evidence on the gain in HrQoL after receiving effective treatment is important for evaluating the effectiveness and cost-effectiveness of alternative treatment strategies. Precise and relevant quantitative estimates of HrQoL based on preference-based measures are essential for cost-utility analyses in which quality-adjusted life years, combining patients’ HrQoL with the length of time spent in a specific health state, are applied to assess the value gained from a medical therapy.

Only a few studies have quantitatively measured HrQoL in patients with CDI. However, the studies were limited by including patients with ongoing treatment and the lack of a prospective measurement of patients’ gain in HrQoL after effective cure of the infection. In addition, recent systematic reviews on health economic evaluations comparing FMT with antibiotic treatment alternatives have found substantial variations in the values applied for the HrQoL of patients with rCDI. HrQoL measurements of these patients have therefore been called for to reduce the uncertainties of future evaluations.

This study aimed to evaluate the HrQoL in patients with rCDI based on HrQoL measurements from a recent randomised controlled trial (RCT) comparing vancomycin, fidaxomicin and FMT for patients with rCDI, and consequently estimate the gain in HrQoL associated with effective treatment of rCDI. Because patients were untreated for their infection at the time of inclusion in the RCT, this study represents a unique opportunity to investigate the HrQoL associated with rCDI.

Methods

Study design
This study is based on data from an open-label RCT conducted by Hvas et al. at a Danish public referral gastroenterology centre between 5 April 2016 and 10 June 2018. The RCT compared vancomycin monotherapy, fidaxomicin monotherapy, and FMT preceded by vancomycin to resolve symptoms and prevent additional recurrences of CDI in patients with rCDI. Patients aged above 18 years diagnosed with rCDI, defined by three or more liquid stools and a positive PCR of toxin A, toxin B or binary toxin, were included. Patients were required to have received at least one prior treatment of CDI with vancomycin or fidaxomicin. Patients were excluded if they were pregnant, breastfeeding, did not speak or understand the Danish language, received ongoing antibiotic treatment, used drugs with known interactions with either vancomycin or fidaxomicin, had an allergy to either vancomycin or fidaxomicin, had fulminant colitis contraindicating medical treatment or if the physician judged that the patient could not tolerate inclusion.

The study assessed 120 patients for inclusion, of which 64 patients were randomised to treatment with either vancomycin (125 mg QID) for 10 days ($n=16$), fidaxomicin (Dificlir®) (200 mg BID) for 10 days ($n=24$) or pre-treatment with vancomycin (125 mg QID) for 4–10 days (mean 7 days) followed directly by FMT ($n=24$). FMT preceded by vancomycin was considered an experimental treatment and clinical evidence was limited at the time of designing the study. FMT was performed using a frozen-thawed, single-donor preparation of 50 g donor faeces and administered through either colonoscopy or naso-jejunal tube. All donations were received from voluntary unpaid donors and screened for pathogens following a previously published approach.

Patients were closely monitored during the RCT, and based on a patient-tailored treatment approach, patients who experienced CDI recurrence following the primary allocated treatment were offered open-label rescue FMT. As a relatively large proportion of patients received rescue FMT, we analysed patients collectively independent of randomisation in the main analyses in this study. The study is, therefore, reported in accordance with the STROBE reporting guideline where applicable.

HrQoL
HrQoL was registered as a part of the RCT; patients answered the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) questionnaire at baseline,
before treatment, and at follow-ups in weeks 8 and 26 after primary treatment. If patients experienced CDI recurrence before week 8, they were asked to fill in the questionnaires at 8 and 26 weeks after the first or second rescue FMT (after cure without recurrence).

The EQ-5D-3L-questionnaire consists of two parts: the EQ-VAS and the EQ-5D-3L descriptive system.23 EQ-VAS is a visual analogue scale on which respondents rate their health at the present day from 0 (worst imaginable health) to 100 (best imaginable health). The EQ-5D-3L descriptive system is a generic questionnaire with preference-weights for HrQoL. It consists of five domains – mobility, self-care, usual activities, pain/discomfort and anxiety/depression – and three levels of impact, resulting in 243 possible health states.23 In this study, a social tariff estimated from a representative sample of the Danish population using the time-trade-off method24 was applied to transform each patients’ response to the EQ-5D-3L descriptive system into a utility weight representing the HrQoL at each follow-up.

Missing data
Missing data is a common challenge with clinical trial data.25,26 In this study, one (1.6%) patient had missing data for the EQ-5D-3L descriptive system at baseline, increasing to three (4.7%) patients at week 8 and 12 (18.8%) patients at week 26. The corresponding numbers for the EQ-VAS were 1 (1.6%), 4 (6.3%) and 11 (17.2%) patients. Five patients (7.8%) filled out the week-8 questionnaire during a relapse (clinical symptoms and positive CDI test), and one patient (1.6%) filled out the week-26 questionnaire during a relapse. Because we aimed to estimate the HrQoL after effective treatment of rCDI, that is, after resolution of symptoms or persisting symptoms combined with a negative stool test for C. difficile, these data were excluded from the analyses and handled as missing data. Complete data on HrQoL were available for 40 (62.5%) patients.

We found no statistically significant predictors for missing data on HrQoL. Data were, however, considered to be missing at random, and multiple imputation using chained equations (MICE) and predictive mean matching (knn = 3) was used to impute data for missing variables. Due to the relatively small number of patients and the amount of missing data, we restricted the imputation model to 10 variables, and 40 imputed datasets were constructed.25,27 Data were imputed according to treatment allocation. The imputation model variables included baseline and follow-up HrQoL measurements along with age, gender, WHO performance score and the number of previous CDIs at inclusion. A complete list of missing data and details on the imputation model is available in Supplementary file 1.

Analytic methods
For baseline characteristics, continuous variables are presented as medians with ranges, while categorical variables are presented as the number of patients with percentages. For HrQoL, results are reported for imputed (base-case analysis) and complete data. The mean and standard errors or the medians and interquartile ranges (IQRs) for measurements at baseline, week 8 and week 26 are presented for both the EQ-VAS and the utility weights derived from the EQ-5D-3L descriptive system. Differences between baseline and follow-ups measurements were calculated for each patient and presented as means with standard errors or medians with IQR. A univariable linear regression analysis based on these differences (corresponding to a paired t-test) was used to assess statistical significance (p < 0.05). Supplemental analyses using multivariable linear regression were performed to compare the increase in HrQoL between baseline and follow-ups among the three treatment groups included in the RCT. The results were presented as unadjusted estimates as well as estimates adjusted for differences in baseline utilities. All statistical analyses were performed in STATA version 16.1 (StataCorp LLC, College Station, TX, USA).

Ethical considerations
The RCT was approved by the Central Denmark Region Ethics Committee (j.no. 1-10-72-2577-15), the Danish Medicines Agency (j.no. 2015092214) and the Danish Data Protection Agency (j.no. 1-16-02-15-16). Patients that were included in the RCT signed written informed consent for participation.

Results
Baseline characteristics of the 64 patients included in the RCT are presented in Table 1.21 Patients were randomised to either vancomycin (n=16),
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fidaxomicin (n=24), or initial vancomycin followed directly by FMT (n=24). At the 26-week follow-up, a total of 13 (81%) patients treated with vancomycin, 12 (50%) patients treated with fidaxomicin and 3 (13%) patients treated with FMT had a subsequent recurrence after the primary allocated treatment and received a rescue FMT. Thus, a total of 49 (77%) patients were treated with FMT before the treatment was considered effective in attaining rCDI resolution.

Table 1. Baseline characteristics of the patients included in this study based on previously published data from the RCT conducted by Hvas et al.21

| Parameter | Overall (n = 64) |
|-----------|----------------|
| Age [years], median [range] | 68 [21–92] |
| Women, n [%] | 44 [69] |
| Charlson comorbidity index score, median [range] | 1 [0–7] |
| WHO performance score, median [range] | 1 [0–4] |
| Previous CDIs [n], median [range] | 4 [2–10] |
| Previous CDI treatments, n [%] | |
| Metronidazole | 48 [75] |
| Vancomycin | 64 [100] |
| Fidaxomicin | < 5 [<10] |
| Ribotype 027, n [%] | 0 [0] |
| Hospital admission at inclusion, n [%] | 6 [10] |
| Intensive care admission < 1mo before inclusion, n [%] | 0 [0] |
| Liquid stools per 24h [n], median [range] | 6 [3–31] |
| Duration of symptoms during the current CDI [days], median [range] | 13 [1–152] |
| Duration since onset of the first CDI [days], median [range] | 136 [25–963] |

CDI, Clostridioides difficile infection; RCT, randomised controlled trial; WHO, World Health Organization.

HrQoL

The HrQoL, expressed by EQ-5D values, in patients with rCDI before treatment and at 8- and 26-week follow-up are presented in Table 2. In the base-case analysis, patients with untreated rCDI had a mean utility weight of 0.675. The average utility weight increased after effective treatment for rCDI to an average utility weight of 0.813 at week 8 (p < 0.001) and 0.773 (p = 0.003) at week 26. For EQ-VAS, the values increased from 52.1 at baseline to 68.7 at week 8 (p < 0.001) and 70.8 (p < 0.001) at week 26. The tendencies were similar for the data with imputations and complete data.

For the patients with complete data, 80% experienced an increase in HrQoL between baseline and week 8 and 75% showed an increase in HrQoL between baseline and week 26. Some variations were observed between weeks 8 and 26, as 35% of patients experienced an increase while 32.5% experienced decreased HrQoL between the two follow-ups (Supplementary file 2). At baseline, before treatment, patients with complete data reported ‘no problems’ (level 1) in 54% of the answers to the EQ-5D-3L descriptive system. In comparison, ‘moderate problems’ (level 2) and ‘extreme problems’ (level 3) were reported in 38% and 8% of the answers, respectively. At week 8, these values improved, as patients reported ‘no problems’ (level 1) in 72% of the answers, ‘moderate problems’ (level 2) in 26.5% of the responses, and ‘extreme problems’ (level 3) in 1.5% of the answers. At baseline, patients were mainly affected by pain/discomfort and their ability to perform usual activities; ‘moderate problems’ (level 2) or ‘extreme problems’ (level 3) were reported by 67.5% and 62.5% of patients, respectively. This was followed by problems with mobility (42.5%), anxiety/depression (35%) and self-care (22.5%). While 22.5% still reported self-care problems at week 8, other domains were improved from baseline: 32.5% reported problems with either pain/discomfort, usual activities or mobility, while 20% reported problems with anxiety/depression. Distributions of answers to the EQ-5D-3L descriptive system are presented in Supplementary file 2.

No statistically significant differences were found among the three treatment groups when evaluating the development of HrQoL between baseline and follow-ups at weeks 8 and 26 (Supplementary file 3). The data showed a trend towards patients being randomised to FMT having a larger increase in HrQoL at week 8 compared with patients randomised to fidaxomicin and vancomycin. Conversely, at week 26 week of follow-up, patients randomised to either fidaxomicin or vancomycin had a larger increase in HrQoL compared with patients randomised to FMT (Supplementary file 3).
This study indicates that rCDI has a substantial negative impact on patients’ HrQoL. The average utility weight for untreated patients with rCDI was 0.675. After receiving effective treatment with antibiotics or FMT, this value increased by 0.139 to 0.813 ($p < 0.001$) at week 8 and by 0.098 to 0.773 ($p = 0.003$) at week 26 of follow-up. Our findings can be compared with population norms to assess the differences in HrQoL between the general population and patients cured of rCDI. In a Danish study based on a representative sample of the general population in the North Denmark Region, the average HrQoL among men and women aged 65–74 years was found to be 0.84 and 0.82, respectively. The average HrQoL of patients cured of rCDI in this study is slightly lower but seems to approach the HrQoL in the general Danish population. This indicates that it may be possible to increase patients’ average quality of life to near normal with close monitoring of patients and the availability of effective treatments.

In this study, most patients (77%) were treated with FMT before they attained a sustained cure. A high rate of recurrence was observed among patients in both the vancomycin group (81%) and the fidaxomicin group (50%). Equivalent high rates of recurrence have been reported in other RCTs comparing vancomycin with FMT for rCDI. All patients had received vancomycin for treatment of CDI prior to inclusion but consequently experienced a recurrence. This might suggest a limited susceptibility to vancomycin for attaining a sustained cure among these patients. In addition, the use of pulsed/tapered treatment regimens of vancomycin or fidaxomicin could potentially have been more effective in attaining cure without recurrence and are recommended in guidelines for the treatment of rCDI. Patients included in the RCT had a median of 4 CDIs, but the number ranged from 2 to 10. This is in accordance with recent Danish guidelines, in which FMT may be considered for the first recurrence that is, second CDI and is the first choice of treatment for the second and subsequent recurrences. Readers should, however, be aware that other guidelines recommend awaiting treatment with FMT until appropriate antibiotic treatment has been tried for at least two recurrences, that is, at least three CDI episodes.

### Table 2. Health-related quality of life measured by the EQ-5D-3L and EQ-VAS at baseline and at weeks 8 and 26 of follow-up.

|                      | Baseline | Week 8 | Week 26 | Difference between baseline and week 8 | Difference between baseline and week 26 |
|----------------------|----------|--------|---------|----------------------------------------|----------------------------------------|
| **EQ-5D-3L index**   |          |        |         |                                        |                                        |
| Base case (n = 64)   |          |        |         |                                        |                                        |
| Mean (SE)            | 0.675 (0.028) | 0.813 (0.026) | 0.773 (0.032) | 0.139 (0.030) | 0.098 (0.032) |
| Median (IQR)         | 0.756 (0.637 to 0.824) | 0.824 (0.717 to 1.000) | 0.796 (0.692 to 1.000) | 0.142 (0.009 to 0.243) | 0.079 (-0.003 to 0.227) |
| Complete case (n = 40) |         |        |         |                                        |                                        |
| Mean (SE)            | 0.684 (0.033) | 0.841 (0.027) | 0.820 (0.030) | 0.156 (0.031) | 0.136 (0.027) |
| Median (IQR)         | 0.756 (0.645 to 0.824) | 0.833 (0.755 to 1.000) | 0.824 (0.723 to 1.000) | 0.167 (0.038 to 0.277) | 0.162 (0.009 to 0.244) |
| **EQ-VAS**           |          |        |         |                                        |                                        |
| Base case (n = 64)   |          |        |         |                                        |                                        |
| Mean (SE)            | 52.1 [2.6] | 68.7 [2.7] | 70.4 [2.6] | 16.5 [3.2] | 18.3 [3.4] |
| Median (IQR)         | 52.0 [40.0 to 65.2] | 70.3 [55.5 to 85.0] | 70.8 [59.3 to 89.3] | 15.6 [2.7 to 30.3] | 19.0 [3.3 to 35.1] |
| Complete case (n = 40) |         |        |         |                                        |                                        |
| Mean (SE)            | 53.2 [3.4] | 69.3 [3.0] | 73.7 [2.5] | 16.1 [3.4] | 20.5 [3.5] |
| Median (IQR)         | 54.0 [41.0 to 67.0] | 73.0 [56.0 to 85.0] | 73.0 [65.0 to 90.0] | 15.0 [5.0 to 30.0] | 20.0 [10.0 to 32.0] |

EQ-5D-3L, EuroQol 5-Dimensions 3-Levels; EQ-VAS, EuroQol visual analogue scale; IQR, interquartile ranges; SE, standard error.
Our study found that the average HrQoL of 0.675 reported by patients is substantially higher than the HrQoL of CDI described in other studies. Wilcox et al.\textsuperscript{16} examined the HrQoL in patients hospitalised with CDI in the United Kingdom using the EQ-5D-3L questionnaire and found that CDI was associated with a utility weight of 0.42. Similarly, Barbut et al.\textsuperscript{17} investigated the HrQoL in hospitalised patients with CDI in France using the EQ-5D-3L questionnaire. Patients were asked to fill in the questionnaires for their current state of health and perform a retrospective assessment of their health before the infection, resulting in estimates of 0.050 and 0.542, respectively.\textsuperscript{17} Heinrich et al.\textsuperscript{18} used cross-sectional survey data from several countries to estimate the HrQoL based on the Short-Form Six-Dimension (SF-6D) in patients with current CDI, previous CDI and people who had never experienced CDI, resulting in adjusted utility weight estimates of 0.58, 0.64 and 0.71, respectively. Several differences between the studies may explain the different values. Wilcox et al.\textsuperscript{16} and Barbut et al.\textsuperscript{17} carried out their research in hospitalised patients, while only 9.5% of patients in our study were hospitalised at the time of inclusion. Furthermore, as we based our analyses on data from an RCT, the eligibility criteria were stricter than those applied in Wilcox et al.\textsuperscript{16} and Barbut et al.\textsuperscript{17} Here, it seems especially important to point out that patients who could not tolerate inclusion in the RCT, for example, due to the risk of additional recurrences, were excluded from the study. Moreover, compared with Barbut et al.,\textsuperscript{17} patients included in this study had substantially lower Charlson comorbidity scores, reflecting that the patients may also be less comorbid. Variations might, furthermore, emerge due to the use of different generic questionnaires, that is, the EQ-5D-3L \textit{versus} the SF-36 and the use of different value-sets, for example, from Denmark, the UK or France.\textsuperscript{14,33,34}

Previous health economic evaluations investigating the cost-effectiveness of alternative treatments for rCDI have mainly applied utility weights from other related diseases, for example, inflammatory bowel disease or non-infectious diarrhoea, in their analyses.\textsuperscript{19,20} In a previous systematic review, we reported that the differences between utility weights applied for health states with current CDI and previous CDI (healthy state) ranged from 0.06 to 0.36.\textsuperscript{20} In the present study, we found a difference between 0.098 and 0.139 depending on follow-up time. Applying these utility weights for rCDI in future economic evaluations could potentially increase the confidence in the results.

To our knowledge, this is the first study to prospectively investigate the HrQoL of patients with rCDI before initiation of treatment and after effective treatment of the disease. We acknowledge several limitations. First, missing data on HrQoL were found at follow-ups with at least some data missing for 24 (37.5%) of the 64 patients. We found no statistically significant predictors for missing data, indicating that data may be missing completely at random. However, in our base-case analyses, we chose to handle the missing data as if it was missing at random, a less restrictive assumption of the missing data mechanism. Therefore, we included variables that were believed to be correlated with the missing variables on HrQoL in our imputation model. Second, we found differences in the average HrQoL seen between weeks 8 and 26 of follow-up (0.813 versus 0.773). We cannot explain this difference based on the available data. It is possible that changes in patients’ underlying health impacted their responses over time. Third, because a large part of patients allocated to vancomycin or fidaxomicin received rescue FMT, leading to statistical censoring, the supplemental analyses cannot be used to make inferences on the different treatments. Instead, the analyses might indicate whether awaiting FMT for one more recurrence might have impacted patients’ HrQoL at 8 and 26 weeks after successful treatment. No significant differences were found between the groups, with an important note that the study was not powered to show statistical significance for this comparison. Furthermore, the trends observed in the data might be due to the differences in the timing of follow-up assessments as these were made 8 and 26 weeks after successful treatment was attained, that is, the length of follow-up measured from randomisation increased if a rescue FMT were needed. The results of these analyses, therefore, need further investigation. Fourth, our data were related to a subsample of patients with rCDI and might not be generalisable to patients who are more severely affected by rCDI or have multiple comorbidities. Future research could benefit from investigating the HrQoL of patients CDI divided into groups of disease severity.
Conclusion
We found that patients’ HrQoL were adversely affected during an active episode of rCDI but increased substantially after receiving an effective treatment algorithm in which rescue FMT was provided in case of primary treatment failure. This finding highlights the importance of close monitoring and the availability of effective treatments for patients with rCDIs. The results from this study can potentially be applied in future economic evaluations of treatments for rCDI.

Author contributions
Lianna H. Hammeken: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.
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Lars H. Ehlers: Conceptualization; Investigation; Methodology; Writing – review & editing.

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Availability of data and materials
Additional data supporting the findings of this study are presented in the supplementary material. Other requests can be made to the corresponding author.

Supplemental material
Supplemental material for this article is available online.

References
1. Leffler DA and Lamont JT. Clostridium difficile infection. N Engl J Med 2015; 372: 1539–1548.
2. Napolitano LM and Edmiston CE Jr. Clostridium difficile disease: diagnosis, pathogenesis, and treatment update. Surgery 2017; 162: 325–348.
3. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. N Eng J Med 2014; 370: 1198–1208.
4. Kuipers EJ and Surawicz CM. Clostridium difficile infection. Lancet 2008; 371: 1486–1488.
5. McFarland LV, Elmer GW and Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent Clostridium difficile disease. Am J Gastroenterol 2002; 97: 1769–1775.
6. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Eng J Med 2011; 364: 422–431.
7. Lee C, Louie TJ, Weiss K, et al. Fidaxomicin versus vancomycin in the treatment of Clostridium difficile infection: Canadian outcomes. Can J Infect Dis Med Microbiol 2016; 2016: 8048757.
8. Baunwall SMD, Lee MM, Eriksen MK, et al. Faecal microbiota transplantation for recurrent Clostridioides difficile infection: an updated systematic review and meta-analysis. EClinicalMedicine 2020; 29–30: 100642.
9. Garey KW, Aitken SL, Gschwind L, et al. Development and validation of a Clostridium difficile health-related quality-of-life questionnaire. J Clin Gastroenterol 2016; 50: 631–637.
10. Lurienne L, Bandinelli PA, Galvain T, et al. Perception of quality of life in people experiencing or having experienced a Clostridioides difficile infection: a US population survey. J Patient Rep Outcomes 2020; 4: 14.
11. Guillemin I, Marrel A, Lambert J, et al. Patients’ experience and perception of hospital-treated Clostridium difficile infections: a qualitative study. Patient 2014; 7: 97–105.
12. Vergel YB and Sculpher M. Quality-adjusted life years. Pract Neurol 2008; 8: 175–182.
13. Haraldstad K, Wahl A, Andenæs R, et al. A systematic review of quality of life research in medicine and health sciences. Qual Life Res 2019; 28: 2641–2650.

14. Brazier J, Ara R, Azzabi I, et al. Identification, review, and use of health state utilities in cost-effectiveness models: an ISPOR good practices for outcomes research task force report. Value Health 2019; 22: 267–275.

15. Drummond MF, Sculpher MJ, Claxton K, et al. Methods for the economic evaluation of health care programmes. 4th ed. Oxford: Oxford University Press, 2015.

16. Wilcox MH, Ahir H, Coia JE, et al. Impact of recurrent Clostridium difficile infection: hospitalization and patient quality of life. J Antimicrob Chemother 2017; 72: 2647–2656.

17. Barbut F, Galperine T, Vanhems P, et al. Quality of life and utility decrement associated with Clostridium difficile infection in a French hospital setting. Health Qual Life Outcomes 2019; 17: 6.

18. Heinrich K, Harnett J, Vietri J, et al. Impaired quality of life, work, and activities among adults with Clostridium difficile infection: a multinational survey. Dig Dis Sci 2018; 63: 2864–2873.

19. Le P, Nghiem VT, Mullen PD, et al. Cost-effectiveness of competing treatment strategies for Clostridium difficile infection: a systematic review. Infect Control Hosp Epidemiol 2018; 39: 412–424.

20. Hammeken LH, Baunwall SMD, Hvas CL, et al. Health economic evaluations comparing fecal microbiota transplantation with antibiotics for treatment of recurrent Clostridiodes difficile infection: a systematic review. Health Econ Rev 2021; 11: 3.

21. Hvas CL, Dahl Jørgensen SM, Jørgensen SP, et al. Fecal microbiota transplantation is superior to fidaxomicin for treatment of recurrent Clostridium difficile infection. Gastroenterology 2019; 156: 1324–1332.

22. Jørgensen SMD, Erikstrup C, Dinh KM, et al. Recruitment of feces donors among blood donors: results from an observational cohort study. Gut Microbes 2018; 9: 540–550.

23. EuroQol Research Foundation. EQ-5D-3L user guide, https://euroqol.org/publications/user-guides/ (2018, accessed 12 April 2021).

24. Wittrup-Jensen KU, Lauridsen J, Gudex C, et al. Generation of a Danish TTO value set for EQ-5D health states. Scand J Public Health 2009; 37: 459–466.

25. Faria R, Gomes M, Epstein D, et al. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. Pharmacoconomics 2014; 32: 1157–1170.

26. National Research Council. Panel on Handling Missing Data in Clinical Trials: Committee on National Statistics Division of Behavioral and Social Sciences and Education. The prevention and treatment of missing data in clinical trials. Washington, DC: The National Academies Press, 2010.

27. White IR, Royston P and Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Stat Med 2011; 30: 377–399.

28. The North Denmark Region. Hvordan har du det? Sundhedsprofil for Nordjylland 2017 [How are you? Health profile for the North Denmark Region 2017], https://rn.dk/sundhed/til-sundhedsafgivene-og-samarbejdspartnere/samedele/sundhedsafgivne/om-sundhedsprofil/om-sundhedsprofillen/hvordan-har-du-det/resultater-2017 (2018, accessed 12 April 2021).

29. Van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med 2013; 368: 407–415.

30. Cammarota G, Masucci L, Ianiro G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection. Aliment Pharmacol Ther 2015; 41: 835–843.

31. Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on Management of Clostridiodes difficile infection in adults. Clin Infect Dis 2021; 73: e1029–e1044.

32. Baunwall SMD, Dahlerup JF, Engberg JH, et al. Danish national guideline for the treatment of Clostridium difficile infection and use of faecal microbiota transplantation (FMT). Scand J Gastroenterol 2021; 56: 1056–1077.

33. Brazier J, Roberts J, Tsuchiya A, et al. A comparison of the EQ-5D and SF-6D across seven patient groups. Health Econ 2004; 13: 873–884.

34. Lien K, Tam VC, Ko YJ, et al. Impact of country-specific EQ-5D-3L tariffs on the economic value of systemic therapies used in the treatment of metastatic pancreatic cancer. Curr Oncol 2015; 22: e443–e452.