Supplementary file 1. The protocol article entitled "Clostridioides difficile infection in frail older patients, quality in treatment and care: the CLODIFRAIL study protocol for a multicentre randomised controlled trial"

Clostridioides difficile infection in frail older patients, quality in treatment and care: the CLODIFRAIL study protocol for a multicentre randomised controlled trial

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Running title: *Clostridioides difficile* infection and frailty, the CLODIFRAIL study

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Abstract

Background: *Clostridioides difficile* infection (CDI) is complex and associated with adverse clinical outcomes in older patients, including increased mortality rates. Effective transition of care for patients with CDI is critical to improve survival and health outcomes and to reduce recurrence rates. This study aimed to investigate the effect of a geriatric intervention on the survival of older patients with CDI compared with those receiving standard care.

Methods and analysis: This is a quality improvement study comparing two organisational pathways. We plan to include 216 patients aged 70 years or more diagnosed with CDI. Patients with a positive *Clostridioides difficile* toxin polymerase chain reaction (PCR) test are randomised 1:1 to either 1) a geriatric assessment and intervention (the CLODIFRAIL intervention) or 2) standard care at the treating physician's discretion. The intervention has three main parts: 1) a clinical geriatric assessment; 2) a clinical evaluation of indication for and treatment with faecal microbiota transplantation (FMT); 3) weekly clinical assessments during eight weeks. The follow-up period is 90 days. The primary outcome is 90-day survival from the date of positive CDI PCR test.

Ethics and dissemination: The trial is conducted in accordance with the Declaration of Helsinki and poses no project-related risks, experimental treatments, or invasive biological sample collection. The study is conducted as a quality improvement study, embedded in two parallel and fundamentally different routine clinical care pathways. The study design and its categorisation as a quality improvement study is approved by the Central Denmark Region Committees on Health Research Ethics. This study will provide new knowledge on the effects of a geriatric intervention for older patients with CDI, incorporating an early assessment of the indication for FMT on patient survival and clinical outcomes.

Trial registration: The study was pre-registered at ClinicalTrials.gov on 28 June, 2022. Study identifier: NCT05447533.

Keywords: *Clostridioides difficile*; Frailty; Aged; Faecal microbiota transplantation; Gastroenterology

Strengths:

- The project is innovative in aiming to improve care and treatment for all older patients with *Clostridioides difficile* infection in a real-life setting
- All patients with a positive *C. difficile* test are included and therefore, the population is representative of a broad range of older patients with *Clostridioides difficile* infection.

Limitations:

- Standard care may include elements of the intervention during the follow-up period (geriatric care and FMT), making it less likely that the intervention will produce any effects.
- Component disaggregation for geriatric intervention is challenging, hindering replication precision.

Introduction

Clostridioides difficile infection (CDI) has a poor prognosis, and mortality rates increase dramatically with age.[1] Treatment and care are managed across multiple healthcare settings, and this challenges the overall health care management process.[2] Preventive strategies and effective therapeutic approaches are warranted to reduce older patients' risk of dying from CDI.

CDI primarily affects older patients.[3] Older patients with severe CDI are characterised by a high comorbidity burden, low functional status, high degree of polypharmacy, malnutrition and a need for support in everyday life.[4-6] Collectively, these factors indicate frailty. Frailty is a framework used in geriatrics to describe older patients' risk of a poor prognosis. It develops due to age-related decline in physiological functions,[7] collectively increasing vulnerability to stressors.[8] Previous studies indicate that CDI affects frail patients.[9] Frailty indicators, rather than age alone, are therefore important determinants of CDI risk in an older adult population.[10]

Frail older patients present with atypical symptoms[11], and typical symptoms of illness may change or be absent.[12-14] The traditional CDI severity markers are not necessarily present in older patients.[15] This challenges the CDI severity assessment and may delay appropriate treatment initiation.[16]

Geriatricians are trained in the assessment and planning of care for multimorbid older patients. The Comprehensive Geriatric Assessment (CGA) is considered the gold standard of multidisciplinary assessment and care planning for this group.[17] It is a diagnostic process intended to determine an older person's medical, psychosocial, and functional capacities and problems to create an overall treatment plan with short- and long-term follow-up, ultimately guiding intervention.[18] Frailty identification and assessment are important constituent parts of the CGA. The Multidimensional Prognostic Index (MPI) is a systematic CGA-based assessment tool for prediction of short- and long-term mortality in older hospitalised patients.[19,20]

Systematic reviews have affirmed the clinical utility of CGA-guided interventions for older patients compared with standard care, including improved functional ability,[21-23] reduced mortality[22,24] and increased survival at home after discharge.[25] This was documented in the setting of in-hospital medical patients in dedicated ageing and health wards and across different departments and medical conditions.[25,26] In a Danish older adult inpatient population, early geriatric follow-up conducted by outgoing geriatric teams after discharge reduced readmission rates[27-29] and mortality rates in such patients living in their own homes.[30]

The need for transition of care for patients with CDI has been emphasized by others.[2] Older patients with CDI are often diagnosed and managed across multiple health care settings and discharged prior to completion of

CDI therapy without follow-up, which increases their risk of recurrence, readmission and death. There is currently no existing literature regarding CGA and geriatric follow-up treatment at home for older patients with CDI.

Faecal microbiota transplantation (FMT) has emerged as a life-saving treatment in patients with CDI. For first and recurrent CDI, it is effective in achieving sustained resolution,[31,32] and it tends to reduce mortality rates compared with vancomycin treatment alone.[33] Limited data support that FMT has a similar effect and safety profile in patients aged ≥ 65 years.[34-37] Despite its benefits to this population at risk of recurrence and severe disease, [37] access to this treatment remains limited for older patients. In most settings, FMT requires hospital attendance. Older patients who are too frail to tolerate transportation may therefore be withheld treatment. We previously proposed that FMT may be conducted as a hospital-at-home treatment, but this has yet to be confirmed in larger scale.[38]

Aim

The aim of this study is to investigate the effect of a geriatric intervention on the survival of older patients with CDI compared with those receiving standard care.

Methods

Study design

This is a multicentre randomised controlled trial (RCT) named *CLOstridioides Difficile* Infection in FRAIL older patients (CLODIFRAIL). Outcomes are assessed after 90 days of follow-up. The patient flow is illustrated in Figure 1; the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT),[39] in Figure 2. The SPIRIT checklist is included in Additional file 1.

Roles and responsibilities

The study is conducted at Aarhus University Hospital, Denmark, and at four affiliated regional hospitals in the Central Denmark Region (CDR). The study compares two well-known organisations of care and does not involve experimental treatments or sampling of biological material beyond material obtained as part of routine care. It is therefore classified as a quality improvement project and does not require patient consent before randomisation. The project is anchored in the Geriatric Research Unit, which has experience in conducting clinical research on frailty, and in cooperation with the Centre for Faecal Microbiota Transplantation that holds expertise

on research and development of FMT.[40] The geriatricians in the medical departments in the CDR are responsible for patient treatment and clinical contacts to patients**.** The organisation chart is illustrated in Additional file 2.

Patient and public involvement

Two members of the Danish Council of senior citizens are engaged in the project steering group as patient representatives (Additional file 2). The patient representatives have actively participated in the initial idea phase, study planning, protocol review, development of information materials and offering assistance in securing funding for the study (Additional file 3).

Study population

Eligible patients are consecutively included from a complete list of all patients in the CDR diagnosed with a positive *Clostridioides difficile* (CD) toxin polymerase chain reaction (PCR) test. The list is maintained at the Department of Clinical Microbiology at Aarhus University Hospital and is sent to the project manager every weekday. Patients are identified via the national identification number-based Civil Registration Register, collected and managed using REDCap electronic data capture tools hosted at Aarhus University.[41]

Patient inclusion criteria

- Patients aged ≥ 70 years and living in the CDR
- Positive PCR toxin test for CD
- Not previously included in the study during the study period

Patient exclusion criteria

- Patients already receiving geriatric assessment of CDI within 8 weeks from positive PCR test, defined as follows: affiliated with the ageing and health wards (in- or outpatient activity) at the time of the positive PCR test for CDI
- FMT treatment 8 weeks before date of positive PCR test for CDI
- > 4 episodes of CDI
- End-of-life care defined as follows: end-of-life care treatment has been initiated before positive PCR test for CDI and the patient has a life expectancy less than days/few weeks, based on investigator consensus.

Patients included are patients not already receiving parts of the intervention, including geriatric assessment and/or FMT treatment. Only a few patients survive 4 or more episodes with CDI (unpublished data). Patients

with multiple recurrent CDI are refractory to any treatment and would therefore pose a special challenge. We have chosen to exclude these patients as clinical experience indicates that these patients differ from the rest of the population with CDI.

Randomisation and blinding

Eligible patients are identified consecutively from the reporting system by the project manager and will be randomised within the first weekday from a positive CD test. When the patient is allocated for geriatric intervention, the project manager will contact the regional ageing and health wards who will contact the department that ordered the PCR test and plan a visit to the patient. Randomisation allocation will be performed in REDCap. Allocation lists are generated for the treatment groups at a 1:1 ratio. Proper randomisation concealment was obtained by use of an external randomisation service (Clinical Trial Unit, Department of Clinical Medicine, Aarhus University, Denmark).

The research assistant, who provides all the assessments at follow-up, is blinded with respect to allocation. Given the nature of the intervention, it is not feasible to blind either the patients or the clinicians.

Geriatric intervention

The geriatric intervention is called the CLODIFRAIL intervention. It includes a systematic assessment of both the patient's geriatric problems (CGA) and a systematic assessment of CDI-related symptoms, including an early assessment of indication for FMT. The intervention will be performed at the time of CDI diagnosis and includes an organised set of contacts to ensure close evaluation of clinical status and early intervention in case of exacerbation (Figure 3).

The CLODIFRAIL intervention consists of the following components:

1. CGA, including frailty assessment by the bedside MPI[19]
2. Geriatric CDI check list, including geriatric evaluation of indication for FMT
3. Treatment with FMT if this is indicated
4. Clinical contacts, weekly or more, if necessary during 8 weeks or until cured

1. Comprehensive geriatric assessment and frailty assessment

Within five weekdays from the date of randomisation, the patients receive a visit by a physician trained in geriatric medicine. A CGA with a tailor-made intervention will be conducted at the location where the patient is situated at the time of positive PCR test, i.e., in the allocated ward or at home. Relevant blood analyses are ordered if not already available (electrolytes, renal function, nutritional indicators, infectious parameters and haematological tests). Bedside evaluation of frailty will be conducted, using the MPI[19] and registered in the Electronic Medical Record (EMR). The MPI is a systematic CGA-based aggregate risk score based on comorbidity, habitation status, number of daily prescription drugs used, activities of daily living, cognitive status, wound pressure score and nutritional risk. The MPI provides a tripartite score, categorising patients into groups of non-frail (MPI score 0.0-0.3; MPI=1), moderately frail (MPI score 0.34-0.66; MPI=2) and severely frail (MPI score 0.67-1.0; MPI=3)[19]. An individualised intervention will be performed according to the clinical issues identified.

2. Geriatric CDI checklist and early assessment of FMT indication

The geriatric CDI checklist (Figure 4) will be performed by the geriatrician at the first visit to secure early CDI assessment and prepare a treatment strategy. The checklist will be uploaded to the electronic archive of the EMR. The procedure implies a geriatric evaluation of indication for FMT and treatment planning. CDI-related symptoms are reported in the EMR using standardised headlines (Additional file 4). The checklist recommends to start vancomycin treatment 125 mg x 4 on the same day as the positive PCR test for CDI has been received, if indicated. Next, the checklist recommends to revise the medication list, in particular by discontinuing antibiotics and proton pump inhibitors, if possible, as well as optimising the patient's nutritional and hydration status according to our national guidelines.[42] FMT will be considered if the patient fulfils one of the following criteria:

1) Severe index, recurrent or refractory CDI as defined by national clinical guidelines[43]

or

2) High-risk patient defined as frailty grade MPI-2 (moderate) or MPI-3 (severe).

If FMT is indicated, a date for the FMT procedure will be scheduled. Information material (Additional file 5) targeting CDI and treatment will be delivered to the patient. Targeted CDI information for primary health care will be ensured through corresponding letters, using standardised headlines (Additional file 4).

3. Treatment with faecal microbiota transplantation

When the patient meets the indication for FMT, FMT will be performed at hospital or at home. FMT will be delivered as 15-25 capsules (~ 50 grams of donor faeces from one thoroughly screened healthy donor [44]). If the patient has dysphagia diagnosed by dysphagia screening or carries a nasogastric tube, vancomycin and FMT can be delivered by naso-jejunal tube (Bengmark 10 Fr, Nutricia), requiring referral to the Radiology Department for verification of duodenal/jejunal tube placement. If the patient cannot come to the hospital for control of placement of the naso-jejunal tube, FMT can be delivered by a nasogastric tube under close clinical monitoring. Each FMT component is accompanied by a treatment leaflet and a patient consent form. The treatment leaflet ensures traceability between each unique FMT component and recipient. It contains the recipient's name and national identification number-based Civil Registration Register, FMT information and anonymised donor data. It is completed by the attending physician at each FMT. If the patient is not admitted to hospital, FMT can be delivered as home treatment via a regional geriatric team or the project manager and project nurse (Additional files 6 and 7).

4. Clinical contacts

Physicians arrange weekly telephone contact and schedule the necessary clinical contacts within the project period. Clinical contacts can encompass a clinical evaluation, further drug adjustments, blood tests, etc., and can be conducted by a geriatrician and/or a geriatric nurse or through telephone contacts with the patient, a relative or the home nursing service. To secure clinical symptom feedback on treatment, patients and/or relatives or home nursing service personnel are asked to fill out stool diary, including Bristol scale (Additional file 8) and return the answers in a standardised form (Additional file 4, "Corresponding letter for primary health care"), which is documented in the EMRs. The ageing and health wards remain responsible for CDI treatment for a minimum of 8 weeks from the last FMT or start of antibiotic CDI treatment and until CDI resolution. A control stool PCR test for CDI will be performed upon treatment termination.

Upon FMT treatment termination, we will ensure continued cooperation with the primary sector by incorporating standardised headlines in the discharge summary describing the treatment status and any precautionary principles for future treatment (Additional file 4).

Procedures for monitoring intervention adherence

To secure adherence to the intervention, all activities will be logged in the patient's EMR, including the MPI, the CDI checklist and FMT.

Standard care group

Patients are not contacted by the geriatric team until after 90 days of follow-up but can be admitted and/or referred to ageing and health wards by their patient care team during the entire period. They receive usual treatment at the treating physician's discretion. The Danish healthcare system is tax-financed and available to all Danish residents on a free and equal basis. The general practitioner functions as a gatekeeper to the secondary sector. In the CDR, Aarhus University Hospital and the four main regional hospital units provide secondary care (outpatient, inpatient and intensive care). Standard care includes assessment of CDI and treatment with CDI-related antibiotics and FMT if the physician finds that this is indicated. All patients can be referred to FMT as an outpatient clinic activity or during admission. Standard care for patients with CDI in Denmark is described in the national clinical guideline.[42]

Outcome measures

All outcome measures are predefined and will be registered at 90 days (± 7 days) from the date of positive PCR test for CDI.

The primary outcome is 90-day survival from the date of positive PCR test for CDI.

Secondary outcomes include quality improvement-related and patient-related outcomes:

1. Quality- related outcome measures
    a. Time-to-treatment with FMT. Time frame: from date of positive PCR test for CD to date of FMT.
    b. Time-to-treatment with vancomycin. Time frame: from date of positive PCR test for CD to date of start treatment with vancomycin.
    c. CDI recurrence within a 90-day follow-up period. Recurrent CDI is defined as a new CDI episode after ended CDI treatment with treatment response. New episode of diarrhoea (≥3 loose stools, Bristol 6-7) and a positive CD toxin test.
    d. Readmission defined as any unplanned, acute rehospitalisation (elective or planned admissions and outpatient procedures excluded) at any hospital within the CDR, occurring within four hours and up to 30 days after hospital discharge.[45]
    e. Days in hospital: number of days in hospital from date of first positive PCR/inclusion in study and until 90 days. Both dates are included.
2. Patient related outcomes

a. Quality of life measured by the European Quality of Life (EuroQol) measurement of health-related quality of life[46] (version of the European Quality of Life-5 Domain (EQ-5D-5L) Interviewer Administration and EQ-5D-5L proxy 2) and by the Overall Quality of Life Depression List (OQoL-DL)[47]

b. Functional status is measured by the Functional Recovery Score (FRS)[48]

Mortality is chosen as the primary outcome and quality of life and functional capacity as a secondary outcome by consensus in the project steering group. Overall QoL is assessed by the OQoL-DL because of its acceptable level of agreement and reliability in frail older persons with moderate cognitive impairment [47]. The OQoL-DL is supplemented by the EQ-5D,[46,49] which is intended to complement other QoL measures and to facilitate collection of a common data set for reference purposes. It is a generic health-related QoL instrument that has been used to describe population health and health outcomes in clinical trials. Five dimensions are mapped: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The version EQ-5D-5L paper interviewer administration and the EQ-5D-5L proxy version will be performed.

The FRS[48] consists of a refined Katz Index[50] and Lawton Scale[51] and includes mobility assessment (Activities of Daily Living (ADL)+ I-ADL), resulting in an instrument that has five (ADL) and six (I-ADL) options for assessing each item. ADL and mobility comprise 77% of the FRS score; I-ADL, 23%. It has predictive and discriminant validity and is responsive to changes.

Data collection, management and analysis

Baseline variables

The following descriptive variables are registered at baseline:

- Demographic data
- Charlson Comorbidity Index[52]
- Frailty level measured by record-based MPI[53]
- CDI diagnosis, site (primary healthcare, outpatient, inpatient)
- CD toxin profile
- CDI definition[54] Healthcare facility-onset, Community-onset, Healthcare facility-associated, Community-associated
- Faecal chart consistency and frequency will be registered for the intervention group
- Habitation status (Living in own home, Nursing home resident)

- Use of antibiotics (other than CDI related antibiotics) at time of positive PCR test for CDI and within one month before date of positive PCR test for CDI
- Use of proton-pump inhibitors at time of positive PCR test for CDI

Measuring QoL and functional capacity at baseline is not feasible because this could possibly affect the standard care group, which is intended to receive no interaction from the geriatric team until the follow-up date.

Data collection

Data are collected and managed using REDCap electronic data capture tools hosted at Aarhus University to secure data security and storage.[41] The database includes range checks for data values. To avoid double data entries, the national identification number-based Civil Registration Register is checked before data entrance. Baseline characteristics are obtained from the EMRs only, and will be collected before randomisation. Primary outcome and quality-related outcome measures will be obtained from the EMRs. The project manager will collect all data from the EMRs. Collection of data on primary outcome will also be checked by a specialist in either geriatric or gastrointestinal diseases to avoid errors. The project manager has access to all EMRs in the CDR.

FRS, OQoL-DL and EQ-5D-5L tests will be performed on both groups by a trained project assistant during planned home visits. Additionally, the FRS will be performed retrospectively on both groups, including recording of functional capacity before CDI at the date of positive CDI PCR test.

Sample size calculation

Sample size calculation: 90-day mortality rate in CDI patients aged ≥ 70 years is 32% according to our cohort study (unpublished data) and another European study.[1] Hence, the 90-day mortality rate for the standard care group was set to 32%. The assumed effect of the intervention was calculated on the basis of the 12% 90-day mortality rate among CDI patients receiving FMT[55] and the 20% mortality rate in geriatric patients receiving CGA.[29] However, in Hocquart' s study,[55] a sixth of the patients are below the age of 70 years. Therefore, the 12% mortality rate might be underestimated. Furthermore, Hansen et al.[29] performed CGA only on moderate to severely frail patients. As we will include patients also with mild frailty, the 90-day mortality rate of 20% might be overestimated. Assuming an additive effect of CGA on FMT interventions, a mortality rate between 12% and 20% is considered realistic, with an estimated rate of 15%. Consequently, the expected mortality difference would be 17% (32%-15%). With a power of 80% and an alpha of 5%, 108 patients are needed in each group;

which is the final number of patients, not taking into account drop-outs. We have predetermined an interim analysis to be conducted after enrolling 108 randomised patients, with predefined stopping rules based on the Haybittle-Peto limits, which require statistical significance levels below 0.001.[56] The analysis will be performed by a blinded external reviewer.

Statistical analysis plan

The statistical analysis will be performed by the project manager and members of the team when the last patient has completed the follow-up period and all data have been entered into REDCap. Patients' baseline characteristics will be compared using chi-square test or Fisher's exact tests for categorical variables and Wilcoxon Rank Sum test or Student's t-test for continuous variables, as appropriate.

Primary outcome analyses of 90-day mortality will be performed according to the intention-to-treat and per-protocol principles. The per-protocol analysis will include all patients who have undergone their first visit, which includes assessment of the multidimensional prognostic index and completion of the CDI checklist. The binary primary outcome will be tested for significance in a binary regression model and presented as an odds ratio (OR) estimate with 95% confidence intervals (CIs). Estimates will be provided with 95% exact confidence intervals and medians with interquartile ranges or ranges, as applicable. Precision will be performed by adjusting for age ≥ 85 years (yes/no) and diagnosed during hospital admission (yes/no). Furthermore, subgroup analysis of the two stratified groups (age ≥ 85 years (yes/no) and diagnosed during hospital admission (yes/no)) will be performed according to binary primary outcome and presented as OR. The OR for patients diagnosed during hospital admission will be compared with the OR of patients diagnosed outside hospital. Likewise, the RR of patients aged ≥ 85 years will be compared with the OR of patients < 85 years. We will conduct an as-treated-analysis of the primary outcome, comparing patients receiving FMT within 90 days from positive PCR test for CDI compared with those who did not. The primary outcome will be tested for significance using chi-square test, and OR will be estimated using the binary regression model.

Secondary outcomes: Recurrent CDI and readmission will be tested for statistical significance in a binary regression model. Functional status (estimated by FRS sum score) and overall QoL (estimated by EQ-5D-5L and OQoL-DL sum scores) in the survivors on day 90 will be compared in a linear regression model. Precision will be assessed by adjusting for age ≥ 85 years (yes/no) and diagnosed during hospital admission (yes/no). Likewise, days in hospital within 90 days from positive PCR test for CDI and time-to-treatment with vancomycin and FMT in all randomised patients will be compared in a linear regression model. Precision will be assessed by adjusting

for age ≥ 85 years (yes/no) and diagnosed during hospital admission (yes/no) by performing linear regression analysis. If data are non-normally distributed, data will be logarithm-transformed in the regression model.

There will be no missing data on the primary outcome as these data are available from the EMRs. The number of missing follow-up data on the secondary outcomes will be presented and we will perform a dropout analysis of the data.

All analyses will be performed in Stata version 17 (Stata Corp, Texas, USA).[57] The data will be monitored by an independent external monitoring institution.

Discussion

CDI constitutes a major health risk for frail older patients. The key challenge lies in conducting a personalised early assessment and treatment approach for CDI. For this purpose, clinical evaluations and close monitoring of the patient's condition are necessary.

In designing the CLODIFRAIL study, we prioritise investigating real-life scenarios. While the treatment will be individualised, our intention is to evaluate the intervention using stringent scientific methods. The project is innovative in aiming to improve care and treatment for all older patients with CDI in a real-life setting disregarding their mental or physical capability. This includes evaluating FMT in older frail patients who would otherwise be ineligible or unwilling to participate in randomised controlled trials of microbe-based therapeutics.[58]

There are important limitations to the study. First, the participants will be old and multi-morbid and therefore prone to experience new illnesses during the study period. This might make the intervention less effective. Second, the standard care may include elements of the intervention during the follow-up period (geriatric care and FMT), making it less likely that the intervention will produce any effects. The patients and their relatives are not blinded. Therefore, there is a risk that the research assistant might be unblinded if the participants reveal their group allocation. Nor are the geriatricians participating in the study blinded, and those administering the intervention to patients may exhibit heightened attention their patients' treatment throughout the study period. Finally, it is possible to validate the CDI diagnosis according to clinical symptoms only from data in the EMR as it is not possible to contact the standard care group.

Because our intervention will address the concurrent frailty and clinical issues of each patient, it is important to note that the intervention is not completely standardised. Interventions for geriatric patients are often complex.[59,60] Describing the intervention with sufficient precision as to facilitate replication is a major challenge.[61] The CLODIFRAIL intervention includes several components. We chose the multi-component intervention as we found it unethical and clinically questionable to assess patients for FMT without also giving them a CGA. For that reason, we do not envisage these components to be disaggregated. It therefore makes sense to evaluate the whole package of intervention. Consequently, pinpointing the specific components of the intervention that are most effective may pose a challenge. To address this, we intend to compensate for this challenge by providing a detailed description of the interventions that were implemented.

The geriatric intervention is extensive. Still, if it is effective, we argue that it can be conducted within the existing framework of an outgoing and multidisciplinary geriatric clinic. Alongside performing the study, we will

gain clinical knowledge on challenges in the treatment of older patients with CDI and implement a clinical framework for home treatment with FMT in the ageing and health wards.

Trial status

The approved protocol with amendment number 4 was issued on 28 June 2022. The first patient was included on 01 September 2022. The study has finished recruiting patients at 3 May 2023.

List of abbreviations

CDI, *Clostridioides difficile* infection; CD, *Clostridioides difficile*; CDR, Central Denmark Region; CGA, Comprehensive Geriatric Assessment; EMR, Electronic medical record; EQ-5D-5L, 5-level EQ-5D version; FMT, Faecal microbiota transplantation; FRS, Functional Recovery Score; MPI, Multidimensional Prognostic Index; OQoL-DL, Overall Quality of Life Depression List; SPIRIT, Standard Protocol Items, Recommendations for Interventional Trials

Declarations

Ethical statement

This study is conducted in accordance with the Helsinki Declaration.[62] All patients receive, as a minimum, established standard medical care according to national clinical guidelines.[42] In the study, we compare two established organisational care pathways, i.e., a geriatric team assessment and the standard care of the attending team. The study is conducted as a quality improvement study, embedded in two parallel and fundamentally different routine clinical care pathways. It does not include experimental procedures or collection of biological specimens other than those needed for clinical diagnostics and care planning. No patients will be exposed to any project-related risk or experimental treatments. Participants may decline parts of or the entire plan or treatment at any time. According to Danish law, the study does therefore not fall under the jurisdiction of the Scientific Ethics Committees. The study protocol was approved by the hospital board of directors at all participating hospitals. Approval was obtained 14 March 2021. The study design and its categorisation as a quality improvement study was approved by the Central Denmark Region Committees on Health Research Ethics (j.no. 1-10-72-1-21, 2 February 2021), following review of the complete study protocol. On publication, only anonymised and summarising data will be presented.

Permission to assess and transmit personal data from the EMRs relevant for quality improvement for patients with CDI was obtained from the hospital boards at Aarhus University Hospital and all attending regional hospitals in the CDR. CD tests, conducted at the Department of Clinical Microbiology, AUH, are a part of the EMRs. Thus, the project manager's permission to access the microbiological lists was granted via the same permission. The CDR is the data protection responsible party. Personal data from the EMRs for quality improvement are transferred to the research project at Aarhus University with a legal basis according to law, viz. the Data Protection Act §10. Data will be managed via REDCap according to a cooperation agreement between Aarhus University and the CDR.

By Danish law, consent to routine clinical treatment is given by oral and not written consent. All examinations and treatments in the study are conducted according to routine clinical practice and following obtaining informed oral consent, as required by the Danish Health Authority, under Danish law. In patients who do not have the capacity to provide oral consent, consent is given on behalf of the patient by a next of kin. All patients in the study are contacted by the geriatric team at 12 weeks of follow-up. Oral consent to perform QoL and functional status assessments is obtained and documented in the EMRs.

FMT treatment is provided following informed written consent, using a standardised FMT consent form (Additional file 9). The patient's consent concerns permission for record access and data storage to allow full traceability according to the Tissue Act. Before FMT, the patient is informed orally and through a written information leaflet about the effect and possible side effects.

Consent for publication

No personal information is published.

Availability of data and materials

No study data are available at the protocol stage of the project process. A code book for data entry databases and all other project-related raw material are available upon reasonable request to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TR*, HV*, MG*, MA*, IB*, JJ*, MR*, JR*, MØ*, RV*, CK*, CS*, SB*, CH* and ED* contributed to the design and planning of the study and have critically revised the manuscript. HV, RV and CS contributed to developing patient material. MG and CS provided statistical expertise. TR is responsible for the daily running of the study, data collection and wrote the manuscript. All authors have approved the final manuscript. The authors follow the ICMJE authorship guidelines. We made no use of professional writers.

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Figures and Tables legends

Figure 1. CONSORT diagram. Patient flow.

Abbreviations: CDI: *Clostridioides difficile* infection; PCR: Polymerase chain reaction

Figure 2. Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) flow diagram figure

* All examinations and treatments in the intervention group are conducted according to routine clinical practice and following obtaining informed oral consent, as required by the Danish Health Authority, in accordance with Danish law.

**All patients in the intervention and standard care group are contacted by the geriatric team at 90 days of follow-up, and oral consent to perform overall quality of life and functional status assessment is given and registered in the electronic medical journal.

Figure 3. CLODIFRAIL intervention, flowchart.

Abbreviations: PCR: Polymerase chain reaction; CGA: Comprehensive geriatric assessment; MPI: Multidimensional Prognostic Index; FMT: Faecal microbiota transplantation

Figure 4. *Clostridioides difficile* infection, geriatric checklist

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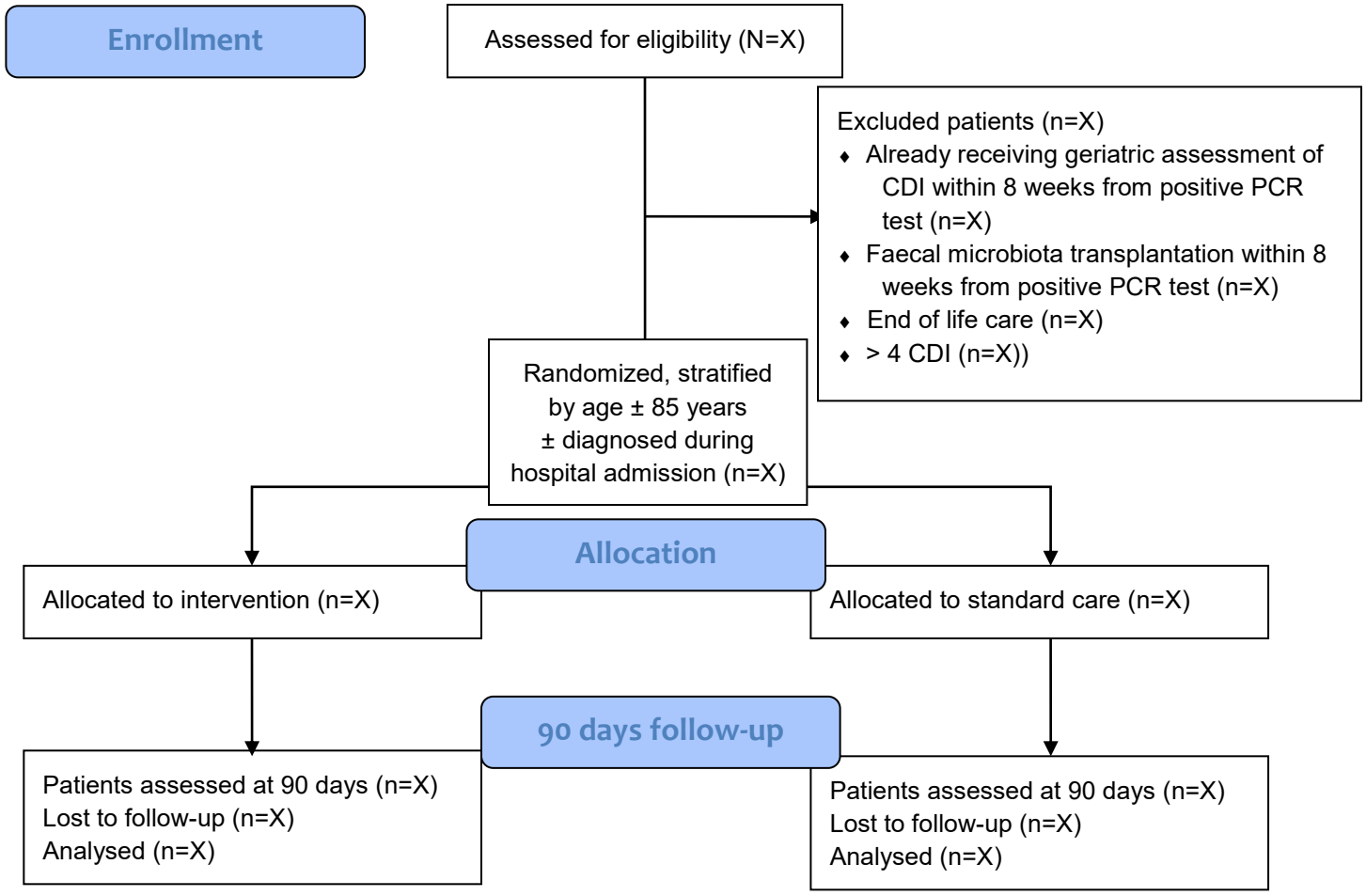
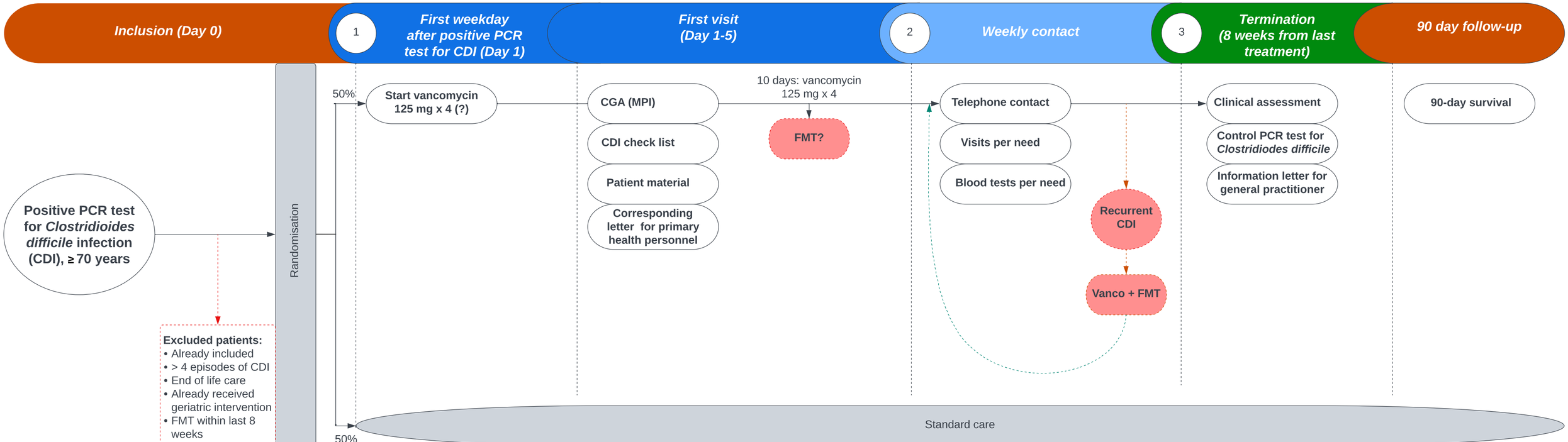

Enrollment
Assessed for eligibility (N=X)
Excluded patients (n=X)
♦ Already receiving geriatric assessment of CDI within 8 weeks from positive PCR test (n=X)
♦ Faecal microbiota transplantation within 8 weeks from positive PCR test (n=X)
♦ End of life care (n=X)
♦ > 4 CDI (n=X))
Randomized, stratified by age ± 85 years ± diagnosed during hospital admission (n=X)
Allocation
Allocated to intervention (n=X)
Allocated to standard care (n=X)
90 days follow-up
Patients assessed at 90 days (n=X)
Lost to follow-up (n=X)
Analysed (n=X)
Patients assessed at 90 days (n=X)
Lost to follow-up (n=X)
Analysed (n=X)

	STUDY PERIOD				
	Enrolment	**Allocation**	**Post-allocation**		**Close-out**
TIMEPOINT**	***-t_1***	**0**	***Intervention***	***90 days***	***90 days***
ENROLMENT:					
Eligibility screen	X				
Informed consent intervention		X		X	
Informed consent control*				X	
Non blinded randomisation	X				
Allocation		X			
INTERVENTIONS:					
Intervention group (geriatric assessment)		X	X		
Standard care group		X			
ASSESSMENTS:					
Electronic medical records:					

Baseline variables		X				
90 day survival				X		X
Time to treatment with FMT (FMT date)				X		X
Time to treatment with vancomycin (date of start treatment with vancomycin)				X		X
CDI recurrence				X		X
Readmission rate				X		X
Days in hospital				X		X
Trained research assistant						
Overall Quality of Life Depression List (OQoL-DL)				X		X
Overall Quality of Life EuroQol measurement (version EQ-5D-				X		X

5L Interviewer Administration						
Overall Quality of Life EuroQol measurement (version EQ-5D-5L proxy 2)				X		X
Functional status: Functional recovery score (FRS)				X		X


Inclusion (Day 0)
1
First weekday after positive PCR test for CDI (Day 1)
First visit (Day 1-5)
2
Weekly contact
3
Termination (8 weeks from last treatment)
90 day follow-up
Positive PCR test for Clostridioides difficile infection (CDI), ≥ 70 years
Excluded patients:
• Already included
• > 4 episodes of CDI
• End of life care
• Already received geriatric intervention
• FMT within last 8 weeks
Randomisation
50%
Start vancomycin 125 mg x 4 (?)
CGA (MPI)
CDI check list
Patient material
Corresponding letter for primary health personnel
10 days: vancomycin 125 mg x 4
FMT?
Telephone contact
Visits per need
Blood tests per need
Recurrent CDI
Vanco + FMT
Clinical assessment
Control PCR test for Clostridiodes difficile
Information letter for general practitioner
90-day survival
50%
Standard care

Patient label_____

Figure 4. Geriatric Clostridioides difficile infection – check list

Patients with Clostridioides difficile infection (CDI) during hospital admission or at home.

Clostridium difficile infection (CDI) - definition: ≥ 3 watery stools daily (Bristol stool chart ≥ 6) + positive Clostridioides difficile PCR toxin test.		
	Done	Not relevant
1) CDI treatment care planning		
Describe CDI clinical status – use standard headlines (cdi1)	☐	☐
Blood analyses (electrolytes, renal function, albumin, infectious parameters and haematological tests)	☐	☐
Start vancomycin peroral or bactocin oral suspension (probe) 125 mg x 4. Continue vancomycin at least 10 days or until day before faecal microbiota transplantation (FMT).	☐	☐
Perform the Multidimensional Prognostic Index	☐	☐
Geriatric assessment of indication for Faecal Microbiota Transplantation (FMT) and treatment care planning.	☐	☐
Deliver information material to the patient	☐	☐
Deliver stool diary to the patient and/or primary caregivers.	☐	☐
Corresponding letter to general practitioner, use standard headline (cdi2) + primary health care (cdi3)	☐	☐
2) Medication review		
Antibiotics (other than vancomycin): discontinue if possible	☐	☐
Antibiotics: consider preventive initiatives to avoid future use of antibiotics (e.g. Positive Expiratory Pressure device, vagifem treatment, sterile intermittent cathetherization etc.)	☐	☐
Laxative: discontinue	☐	☐
Proton pump inhibitor: discontinue if possible	☐	☐
Diuretics: consider reduction during active diarrhoea (renal function)	☐	☐
3) Rehydration and nutrition		
Nutrition: consider need for nutrition therapy and monitoring	☐	☐
Rehydration therapy: consider need for rehydration therapy and monitoring	☐	☐
Consider other reasons for diarrhoea! (e.g. inflammatory bowel disease, cancer, microscopic colitis)	☐	☐
All patients have clinical contact to geriatric department during 8 weeks from date of last FMT or completed vancomycin treatment.		
4) At termination (8 weeks)		
Clinical resolution: number of daily stools + Bristol scale.	☐	☐
Stool PCR test for Clostridioides difficile	☐	☐
Discharge summary for general practitioner – use standard headlines (cdi4)	☐	☐

All activities are registered in the electronic medical journal.

Additional file 1. SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	16
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 5,7,18
	5b	Name and contact information for the trial sponsor	n/a
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5-6
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5,7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	17
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-9, Figure 3
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12-13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a

Methods: Data collection, management, and analysis

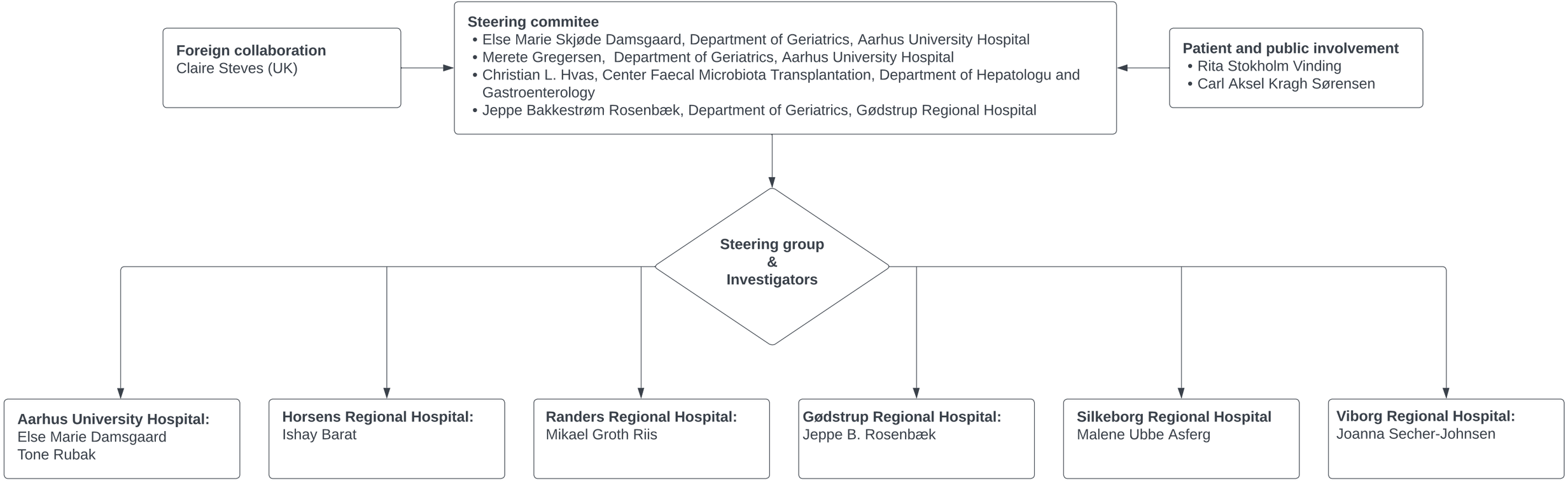
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13-14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			

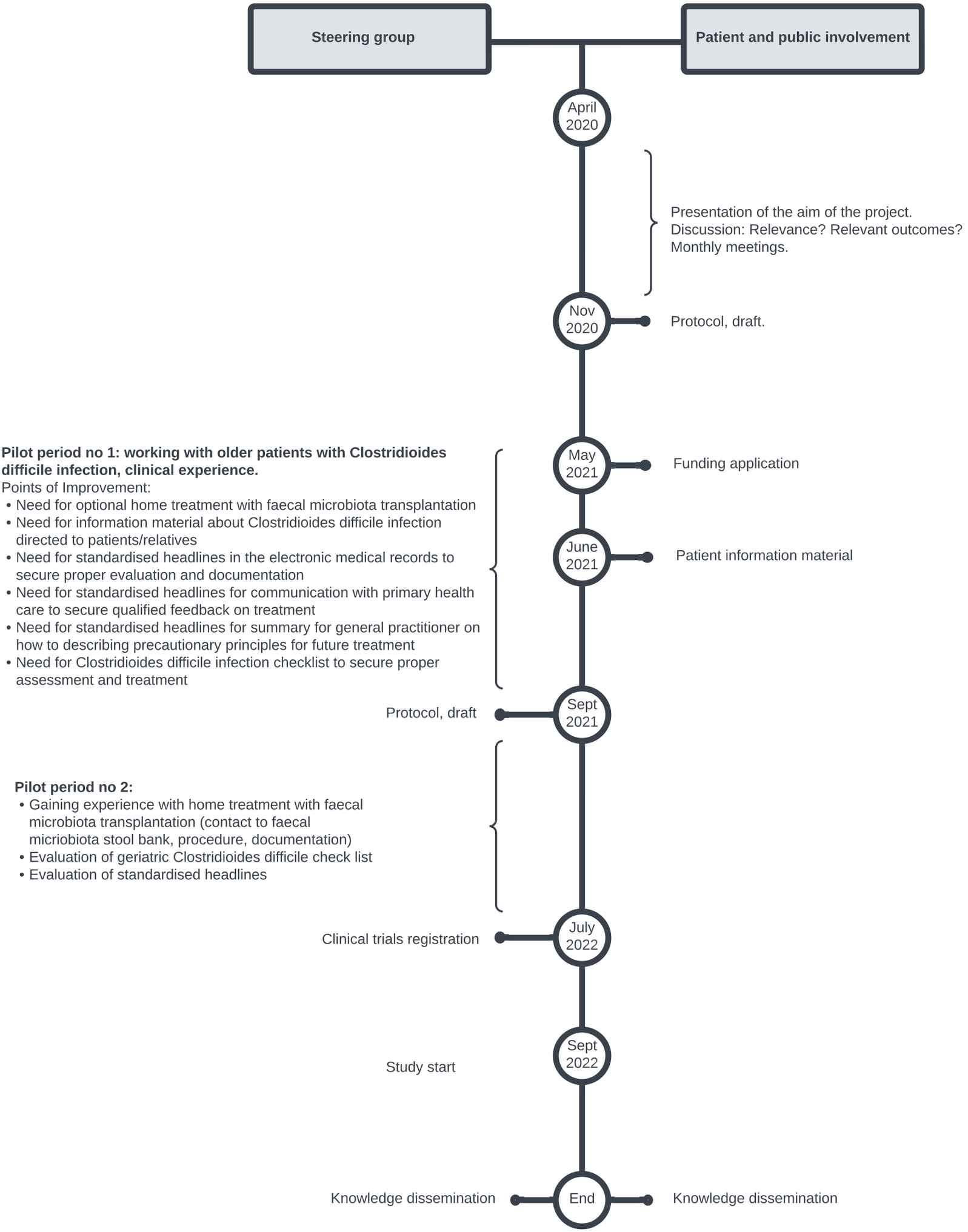
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___17-18_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____n/a_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___17-18_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____n/a_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____17_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____18_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____18_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____n/a_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____n/a_____ _
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____19_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____n/a_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___17-18_____

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____n/a_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

Additional file 2. Organisation chart for the study




Steering group
Patient and public involvement
April 2020
Presentation of the aim of the project.
Discussion: Relevance? Relevant outcomes?
Monthly meetings.
Nov 2020
Protocol, draft.
Pilot period no 1: working with older patients with Clostridioides difficile infection, clinical experience.
Points of Improvement:
• Need for optional home treatment with faecal microbiota transplantation
• Need for information material about Clostridioides difficile infection directed to patients/relatives
• Need for standardised headlines in the electronic medical records to secure proper evaluation and documentation
• Need for standardised headlines for communication with primary health care to secure qualified feedback on treatment
• Need for standardised headlines for summary for general practitioner on how to describing precautionary principles for future treatment
• Need for Clostridioides difficile infection checklist to secure proper assessment and treatment
May 2021
Funding application
June 2021
Patient information material
Protocol, draft
Sept 2021
Pilot period no 2:
• Gaining experience with home treatment with faecal microbiota transplantation (contact to faecal micriobiota stool bank, procedure, documentation)
• Evaluation of geriatric Clostridioides difficile check list
• Evaluation of standardised headlines
Clinical trials registration
July 2022
Study start
Sept 2022
Knowledge dissemination
End
Knowledge dissemination

Additional file 4. Standardised headlines for documenting *Clostridioides difficile* infection

Name (code)	**Standard headlines**
CDI clinical status at first contact (cdi1)	Abdominal pain? Number of stools per day? Bristol type? Faecal incontinence? Loss of appetite? Is the patient candidate for faecal microbiota transplantation according to a geriatric assessment? Plan: The patient is affiliated with the Department of Geriatrics the following 8 weeks because of gastrointestinal infection with *Clostridioides difficile.* Please contact Department of Geriatrics if indication for antibiotics other than CDI related antibiotics. Please contact Department of Geriatrics in case of recurrent CDI. Contact information (…)
Corresponding letter for primary health care (cdi2)	The patient is affiliated with the Department of Geriatrics the following 8 weeks because of gastrointestinal infection with *Clostridioides difficile.*

	Please send weekly status of the following (corresponding letters/telephone contact): Abdominal pain? yes/no Number of daily stools Bristol type Appetite? Is the patient overall improving, status quo or clinically worsening? Please contact Department of Geriatrics if indication for antibiotics other than CDI related antibiotics. Please contact Department of Geriatrics in case of increasing diarrhoea, abdominal pain or waning general condition. Contact information (…)
Corresponding letter for general practitioner (cdi3)	The patient is affiliated with the Department of Geriatrics the following 8 weeks because of gastrointestinal infection with *Clostridioides difficile.* Please contact Department of Geriatrics if indication for antibiotics other than CDI related antibiotics. Please contact Department of Geriatrics in case of increasing diarrhoea, abdominal pain or waning general condition. Contact information (…)

Discharge summary for general practitioner (cdi4)	The patient has been affiliated with the Department of Geriatrics because of gastrointestinal infection with *Clostridioides difficile*. The infection has been treated with vancomycin and faecal microbiota transplantation (date). Bowel movement has normalised (?). The patient has an increased risk of recurrent *Clostridioides difficile* infection, especially when treated with antibiotics other than CDI related antibiotics and/or treatment with proton pump inhibitors. In case of unexplained diarrhoea, we recommend PCR toxin test for *Clostridioides difficile*. If positive toxin test we recommend to start vancomycin as soon as possible and referral to faecal microbiota transplantation. Feel free to contact us if in doubt. Contact information (…)
Faecal microbiota transplantation procedure (cdi5)	The patient takes (number) of capsules within (minutes). Experiences no discomfort (?) and is

	observed in 30 minutes without acute complaints (?). Complications to treatment: (?) Clinical contact and follow-up via Department of Geriatrics. The patient and/or relatives and/or healthcare staff are informed of test stool kit which should be delivered as control test 8 weeks from today. Informed to continue to note stool frequency and gastrointestinal symptoms via stool diary. During the day after faecal microbiota transplantation procedure the patient may experience abdominal pain and loose stools. If fever or clinical worsening the patient is informed to contact the Department of Geriatrics (contact information).

Additional file 5. Patient information material regarding *Clostridioides difficile* infection and treatment

Clostridioides Difficile infection and faecal microbiota transplantation

Clostridioides difficile is a bacterium that can cause serious infection of the intestine. In the elderly patient, where other illness has caused weakness, an infection with *Clostridioides difficile* can become serious. The infection tends to come back. What is typically experienced is numerous diarrhoea, nausea, reduced appetite, dehydration, fever, fatigue, weight loss and increased sadness. Some patients lose the will to live because of loss of energy.

We identify the infection using a stool sample supplemented with blood tests. Treatment is started with an antibiotic targeting the *Clostridioides difficile* bacterium following supply of healthy intestinal bacteria.

Faecal microbiota transplantation

Supply of healthy intestinal bacteria is also called faecal microbiota transplantation (FMT). There are no known side effects or late effects of FMT in patients who do not have other bowel disease. The healthy intestinal bacteria come from donors affiliated with the Department of Hepatology and Gastroenterology, Aarhus University Hospital. Strict requirements are placed on the donors equally to the Danish blood donor system. Donors are anonymous.

Faecal microbiota transplantation can take place in three ways:

1. via capsules taken orally over 30-45 minutes
2. via tube to the intestine
3. via endoscopy of the intestine (colonoscopy)

Regardless of which type you are offered, there will be clinical follow up contacts via the Department of Geriatrics.

Clinical follow-up contacts

Many older patients with *Clostridioides difficile* infection are severely weakened and need supportive treatment with fluids and nutrition including close monitoring of gastrointestinal symptoms. We offer clinical follow-up by staff trained in diseases in older patients. The purpose is to ensure an evaluation of the gastrointestinal symptoms and early start of treatment if indication for this.

How does the follow-up take place?

The follow-up involves a visit from the outgoing ageing and health ward team when you have received the diagnosis and a weekly telephone contact regarding evaluation of the gastrointestinal related symptoms. If there is a need for further visits, treatment or supportive therapy this will take place in your own home via the outgoing ageing and health ward teams.

What should I be aware of?

In case of changes in bowel movements, abdominal pain, nausea, reduced fluid intake/nutrition you/your relatives should contact Department of Geriatrics. In need of antibiotics other than the antibiotics used to treat CDI you must contact the Department of Geriatrics regarding treatment strategy because antibiotics can trigger a relapse of the infection. Transmission of the infection occurs with faeces and bacterial spores in the surroundings close to the patient. Handwash followed by hand disinfection must be carried out before leaving the patient. It important to use water/soap or

chloring alcohol. We recommend that health personnel ware plastic aprons and gloves to reduce infection transmission.

What are my responsibilities?

At termination we will ask you to deliver a stool sample to test for *Clostridioides difficile*. We will hand out a faeces kit and ask you to send/deliver it to Department of Microbiology.

Contact information

(…).

Additional file 6. Faecal microbiota transplantation home treatment – check list

Clostridium difficile infection (CDI) - definition: ≥ 3 watery stools daily (Bristol stool chart ≥ 6) + positive Clostridioides difficile PCR toxin test
1) FMT – treatment planning
Plan date for FMT and hand out patient preparation information material
Patient consent form is to be completed by the patient
Contact Center for Faecal Microbiota transplantation for capsules preparation
2) FMT Procedure
On the day of FMT collect capsules in freezer bag. The capsules must be used within 4 hours from start of thawing.
The patient takes the FMT capsules within one hour with apple juice/ cola. Observe for 30 minutes after last capsule has been taken.
3) FMT documentation
Complete treatment leaflet and send copy to Center for Faecal Microbiota transplantation, auh.cefta@rm.dk
Document FMT procedure in the electronic medical record using standard headline (cdi5)
All patients have clinical contact to geriatric department during 8 weeks from date of last FMT.
4) At termination (8 weeks)
Clinical resolution: number of daily stools + Bristol scale.
Stool PCR test for Clostridioides difficile

All activities are registered in the electronic medical journal.

Dear (patient label) _____

You have been offered and accepted treatment with faecal microbiota transplantation. The treatment consists of 15-25 capsules to be taken with apple juice or cola within one hour.

The treatment is performed by: (name of nurse/doctor) _____

on the (date)_____/_____ time _____

Following preparations are needed:

Fast from (time)_____ on the (date)_____/_____.

You are allowed to take liquids, but not dairy products until (time)_____ on the (date)_____.

Vancomycin is terminated at (time)_____ at (date)_____/_____.

You have received tablet of Metoclopramide 10 mg which you are to take at (time)_____ on the (date) _____/_____.

After the treatment (name of doctor/nurse) _____, we will be there for half an hour. After one hour you are allowed to eat/drink as usual. Some patients find that it takes a few hours before they feel hungry. You may experience loose stools, abdominal pain

within the first day. This is harmless and should resolve spontaneously. In case fever we advise you to contact us.

If you have any questions you are welcome to contact us: (contact info).

Additional file 8. Stool diary

Please write down daily.
We will contact you and ask to your gastrointestinal symptoms to take stock of your clinical status.

Date	Abdominal pain (yes/no)	Number of stools per day	Bristol type	Loss of appetite? (yes/no)	Do you feel better? (yes/no)

Additional file 9. Faecal microbiota transplantation consent form

Information on fecal microbiota transplantation (FMT)
Center for Fecal Microbiota Transplantation (CEFTA)

Consent to quality assurance and research
You have agreed with your doctor to receive treatment with fecal microbiota transplantation (FMT). In order to investigate the quality and effects of the treatment, we need your consent. The aim is to gain a better understanding of how FMT works and to investigate the long-term consequences of treatment. The purpose is fulfilled through quality assurance and research. We ask for your consent to three things:

Consent to disclose health information
Information about your course is passed on to a database at Aarhus University. Only the researchers associated with the treatment have access to the database. All data is kept confidential and complies with the Personal Data Act and the European Personal Data Directive.

Consent to lookup in your patient record
After your treatment has ended, we would like to look up in your patient record to investigate any long-term consequences of the treatment. If we become aware that the treatment may pose a risk to you, we will contact you.

Consent for storage of samples for future research
There is still a lot we do not know about FMT. We therefore perform quality assurance and research to learn. All research projects are approved by the local Ethics Committee.

About the treatment
You will receive separate written patient instructions about the treatment. The written leaflet contains information on how the treatment takes place and the expected effect and any side effects.

About donor
Healthy faecal donors are found among blood donors. In order to be able to donate feces, a donor must undergo a study program
- Personal inquiry about medical history, previous or hereditary diseases, medication consumption
Questionnaire on risk of transmission of contagious diseases: travel abroad, tattoos, risk of infection with sexually transmitted diseases, etc.
- Blood tests with examination for infectious diseases and chronic diseases
- Stool sample with examination for infectious diseases and antibiotic resistance
A physician reviews all test results, and only approved donors provide stool for treatment.

Responsible for the treatment
Chief physician Christian Lodberg Hvas, Department of Hepatology and Gastroenterology, Aarhus University Hospital.
www.levermavetarm.auh.dk

Consent for fecal microbiota transplantation (FMT)
Center for Fecal Microbiota Transplantation (CEFTA)

Name and cpr
1. Consent to transfer gut-related health information to a database
2. Consent to follow-up by posting in your patient record at a later date
3. Consent for storage of samples for future research

"I hereby confirm that, having received the above written information, I know sufficiently about the purpose, advantages and disadvantages of giving this consent.
I know that participation is voluntary and that I can withdraw my commitment to participate at any time, after which my data will be deleted without affecting my current or future treatment options."
You have the right to a reflection period before you sign the consent form
Information about your health conditions is subject to a duty of confidentiality and will only be available to doctors and nurses at the Department of Hepatology and Gastroenterology and the Blood Bank at Aarhus University Hospital. If data are passed on, it only happens in anonymised form.

_____ _____
Date Signature (patient)

Name of responsible doctor:

_____
Name (responsible doctor)

_____ _____
Date Signature (responsible doctor)