

Project title

Frail old patients with *Clostridioides difficile* infection: improvement of quality in treatment and care

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Statistical considerations

Sample size calculation: 90-day mortality rate in CDI patients aged ≥ 70 years is 32% according to our cohort study (unpublished data) and another European study (1).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 control 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 (2) and the 20% mortality rate in geriatric patients receiving CGA (3). However, in Hocquart's study (2) a sixth of the patients are below the age of 70 years and therefore, the 12% mortality rate might be underestimated. Furthermore, Hansen et al. (3) only performed CGA 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 realistic and estimated to be 15%, and therefore, a mortality difference of 32-15 = 17%. 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.

Analyses of clinical treatment effect at 90 days of follow-up are divided into three parts: 1) intention-to-treat (ITT) analysis according to random allocation; 2) an as-treated analysis, taking cross-overs into account; 3) a per-protocol analysis including in the analysis only those patients who strictly adhered to the protocol. Differences will be examined with suitable statistics in relation to the distribution of data and data type. A statistical analysis plan will be performed before analysis of data. The statistical significance limit is 0.05. Subgroup analyses on primary and secondary efficacy measures are assessed for significance of sex, age, comorbidity, CDI number and number of FMT.

In interim analysis after inclusion of 60 patients, it is assessed whether the trial should be discontinued. Haybittle-Peto limits are used with a statistical significance level of 0.001. The analysis will be performed by an external reviewer.

References

1. Hensgens MP, Goorhuis A, Dekkers OM, van Benthem BH, Kuijper EJ. All-cause and disease-specific mortality in hospitalized patients with Clostridium difficile infection: a multicenter cohort study. *Clin Infect Dis.* 2013;56(8):1108-16.
2. Hocquart M, Lagier JC, Cassir N, Saidani N, Eldin C, Kerbaj J, et al. Early Fecal Microbiota Transplantation Improves Survival in Severe Clostridium difficile Infections. *Clin Infect Dis.* 2018;66(5):645-50.
3. Hansen TK, Pedersen LH, Shahla S, Damsgaard EM, Bruun JM, Gregersen M. Effects of a new early municipality-based versus a geriatric team-based transitional care intervention on readmission and mortality among frail older patients - a randomised controlled trial. *Arch Gerontol Geriatr.* 2021;97:104511.