1. Full title of project

Palliative Long-term Abdominal Drains Versus **RE**peated **D**rainage in **U**ntreatable Ascites Due To Advanced **C**irrhosis: A Randomised Controlled Trial (REDUCe 2 Study).

2. Research abstract

Research question: Do palliative long-term abdominal drains (LTADs) result in better health related quality of life (HRQoL) in patients with refractory ascites due to end-stage liver disease (ESLD) compared with standard of care (large volume paracentesis, LVP)?

Background: Palliative care is suboptimal in ESLD. Refractory ascites confers a median transplant-free survival of six months and needs repeated hospitalisation for drainage (LVP). LTADs allow home drainage but are not routinely used in ESLD due to effectiveness/safety concerns. Our feasibility REDUCe study (LVP vs. LTADs in ESLD) demonstrated feasibility to proceed with a definitive trial. It also informed the recent national ascites guidelines recommending trials assessing LTADs in ESLD.

Aims/objectives: To assess whether LTADs result in better HRQoL compared to LVP in patients with refractory ascites due to ESLD.

Methods: This multicentre trial will recruit patients with ESLD and refractory ascites, randomised 1:1 to either LTADs or LVP. Community nurses will visit LTAD patients at home, 2-3 times a week to perform drainage (1-2 litres per visit). LVP patients will attend hospital every 10 -14 days with 5-15 litres of ascites drainage and receive intravenous albumin. Research staff will visit ALL participants at home fortnightly for 3-months for safety monitoring and questionnaire-based assessments (Ascites Q, SFLDQoL, EQ-5D-5L, CRRS). The primary outcome will be HRQoL assessed by the SFLDQoL questionnaire. An embedded qualitative study will explore perspectives on both LTADs and LVP by patients (n=30), caregivers (n=20) and health care professionals (n=30).The minimal clinically important difference (MCID) is the mean change in HRQoL score for patients reporting a minimal yet perceptible change in HRQoL between baseline and follow-up assessments. We have selected an MCID of 8 points. REDUCe study data showed the pooled baseline mean across SFLDQoL domains (excluding sexual function) was 56.4 (SD=26.1). With 93 participants in each group, we will have 90% power for 5% significance to detect an adjusted difference in mean SFLDQoL scores of 8 points between the LTAD and LVP groups at the end of 3-months (effect size 0.31). We will assume a correlation between baseline and follow-up measurements of 0.48 (lower bound of 95% confidence interval, REDUCe study data). With an expected 40% attrition, we will recruit 310 patients in total for the trial. Statistical analysis will follow intention-to-treat principles, performing for the primary outcome, a longitudinal analysis of covariance by fitting a mixed effects linear regression model. Qualitative data will be analysed using thematic analysis and triangulation. A probabilistic cost effectiveness analysis will be conducted.

Delivery timelines: Study duration will be 57-months: 6-months' set up; 18-months' internal pilot with STOP/GO criteria; 29-months' main trial and 4-months data analysis/dissemination. The pilot will recruit 84 patients from 24 sites. Assuming a successful pilot, 11 further sites will be opened over 5 months', recruiting the remaining 226 patients from 35 sites.

Impact: This will be the largest palliative interventional trial in the UK with the potential to improve end of life care for an underserved group.