

## **Primary Antibiotic Prophylaxis using Cotrimoxazole to Prevent Spontaneous Bacterial Peritonitis in Cirrhosis**

### **ACRONYM: ASEPTIC - Antibiotic SpontanEous PeritonITIs Cirrhosis**

Our proposed research is a double blind placebo controlled trial to determine whether primary antibiotic prophylaxis with Cotrimoxazole (Trimethoprim/Sulfamethoxazole or Septrin) substantially reduces the incidence of spontaneous bacterial peritonitis (SBP) in people with advanced liver disease. SBP is the most common infection in these people and has very severe health-related consequences even when effectively treated, therefore we believe that a strategy of prevention may be beneficial.

### **Summary of Research**

**Research question:** We will determine the efficacy of antibiotic prophylaxis for adults with cirrhosis & ascites but no previous spontaneous bacterial peritonitis (SBP) to prevent development of SBP, “primary prophylaxis”.

**Background:** Bacterial infections are a leading cause of death in cirrhosis and SBP is the most common cause. A strategy of prevention with antibiotic prophylaxis may be beneficial. This is established for those with prior SBP but not for primary prophylaxis yet importantly >90% of SBPs have no previous episode. Antibiotic prophylaxis appears to prevent infection but there is a risk of anti-microbial resistance (AMR) and *Clostridium difficile* associated diarrhoea (CDAD). With liver disease set to overtake heart disease as the leading cause of lost working life years, there is huge necessity for this trial.

The choices are quinolones, cotrimoxazole or rifaximin. In view of likely equivalent efficacy, low cost and less concern of CDAD & AMR compared to quinolones, we will use cotrimoxazole. As rifaximin may be beneficial and is prescribed for encephalopathy, participants will be stratified according to its use.

**Methods:** We plan a multicentre placebo controlled randomised doubled blind trial to assess efficacy, cost-effectiveness and safety of cotrimoxazole for 2 years to prevent SBP in 548 participants with cirrhosis, ascites and a low ascitic fluid (AF) protein count (<1.5g/dl) from 30 NHS sites. The primary outcome will be event free survival with time to first incidence of SBP compared between arms. Sample size calculation used 90% power and 2-sided 5% significance level with 20% loss-to-follow-up. Secondary outcomes include mortality, AMR & CDAD incidence and cost effectiveness. Patients will be stratified by liver disease severity and active alcohol use.

Patients >18 years with cirrhosis, ascites and low AF protein count will be eligible. They will have 3 monthly follow-up visits to collect medication, bloods. A case report form (CRF) will document SBP admissions. Patients will stop treatment if ascites resolves, undergo transplant or complete 2 years follow-up.

A detailed statistical analysis plan will be approved before analysis of unblinded data, including health economics, quality of life & serious adverse events.

**Timelines for delivery:** We anticipate 6 month setup for protocol development, CRFs and organising contracts with sites. Recruitment will be 24 months with anticipated recruitment rate of 1 patient per site per month with a staggered initiation of 30 sites over 12 months. A 9 month GO/NO GO internal pilot will demonstrate deliverability based on anticipated recruitment. We estimate recruiting 320 patients from first 15 sites & 230 from the second 15 giving 548 participants required to demonstrate a 55% relative reduction in cumulative event probabilities of SBP. Treatment duration is 24 months. Close out, cleaning, analysis & dissemination will be 6 months

**Anticipated impact and dissemination:** This will be the largest study of SBP prophylaxis ever and if successful we will update international guidance.

**For further information,** please contact Alastair O'Brien ([a.o'brien@ucl.ac.uk](mailto:a.o'brien@ucl.ac.uk)) or Louise China ([louise.china@ucl.ac.uk](mailto:louise.china@ucl.ac.uk)).