

BMJ Open ATTIRE: Albumin To prevent Infection in chronic liver failure: study protocol for a single-arm feasibility trial

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ABSTRACT

Introduction: Circulating prostaglandin E₂ levels are elevated in acutely decompensated cirrhosis and have been shown to contribute to immune suppression. Albumin binds and inactivates this hormone. Human albumin solution could thus be repurposed as an immune restorative drug in these patients.

This feasibility study aims to determine whether it is possible and safe to restore serum albumin to >30 g/L and maintain it at this level in patients admitted with acute decompensated cirrhosis using repeated 20% human albumin infusions according to daily serum albumin levels.

Methods and analysis: Albumin To prevent Infection in chronic liver failure (ATTIRE) stage 1 is a multicentre, open label dose feasibility trial. Patients with acutely decompensated cirrhosis admitted to hospital with a serum albumin of <30 g/L are eligible, subject to exclusion criteria. Daily intravenous human albumin solution will be infused, according to serum albumin levels, for up to 14 days or discharge in all patients. The primary end point is daily serum albumin levels for the duration of the treatment period and the secondary end point is plasma-induced macrophage dysfunction. The trial will recruit 80 patients. Outcomes will be used to assist with study design for an 866 patient randomised controlled trial at more than 30 sites across the UK.

Ethics and dissemination: Research ethics approval was given by the London-Brent research ethics committee (ref: 15/LO/0104). The clinical trials authorisation was issued by the medicines and healthcare products regulatory agency (ref: 20363/0350/001-0001).

Results: Will be disseminated through peer reviewed journals and international conferences. Recruitment of the first participant occurred on 26/05/2015.

Trial registration number: The trial is registered with the European Medicines Agency (EudraCT 2014-002300-24) and has been adopted by the NIHR (ISRCTN 14174793). This manuscript refers to V.4.0 of the protocol; Pre-results.

INTRODUCTION

Liver disease is the only major cause of mortality currently increasing in the UK and is

Strengths and limitations of this study

- This study will demonstrate feasibility and safety of targeted albumin dosing in patients with acutely decompensated liver cirrhosis prior to a large randomised controlled trial (RCT).
- Biomarker end point provides validation of a novel biological assay for immune dysfunction.
- Outcomes will ensure optimal study protocol design for the RCT.
- Feasibility study therefore not randomised or powered to detect clinically relevant beneficial outcomes.

the fifth most common cause of death.¹ These deaths are predicted to double over the next 20 years.²

Patients with symptoms of liver failure secondary to cirrhosis are described as acute decompensation (AD) patients. They are highly prone to bacterial infection³ secondary to immune dysfunction,⁴ with nosocomial (hospital-acquired) infection rates of 35% compared to 5% in non-cirrhotic patients.^{5 6} Of those that develop infection with organ dysfunction, 60–95% die, often following prolonged intensive care unit (ICU) admission.⁷ There is, however, no medical strategy to restore immune competence.

It has been demonstrated that elevated circulating prostaglandin E₂ (PGE₂) levels contribute to immune suppression in AD patients.⁸ The plasma protein albumin binds and catalyses inactivation of PGE₂.⁹ Albumin is synthesised in the liver and levels fall as the synthetic function of the liver declines in advanced cirrhosis, making PGE₂ more bioavailable. In addition the binding capacity of endogenous albumin is known to be defective in cirrhosis.^{10 11} We found a serum albumin of <30 g/L predicted plasma-induced macrophage dysfunction in a small cohort of AD patients⁸ and this was reversed when albumin levels were increased to >30 g/L.

We propose a novel strategy to repurpose 20% human albumin solution (HAS) as an immune restorative drug in AD patients with the aim of maintaining serum albumin at near normal levels.

Albumin To prevent Infection in chronic liver failure (ATTIRE) incorporates a phase II single-arm multicentre feasibility trial (n=80) prior to a phase III randomised controlled trial (RCT) (n=866) assessing the impact of treatment on the incidence of nosocomial infections, organ dysfunction and mortality in patients admitted to hospital with AD of liver cirrhosis.

This feasibility trial aims to verify that daily intravenous human albumin infusions will restore serum albumin levels to near normal in AD patients, that this is safe and that there is physician equipoise prior to proceeding to a large RCT. Despite multiple studies, including systematic reviews,^{12 13} evaluating albumin in septic intensive care patients there is a lack of interventional RCTs in patients with liver cirrhosis in which the mechanism of albumin's action is different.^{14–16} To date there has not been an albumin dosing trial aimed at increasing serum albumin levels in this context therefore it was essential that this was completed before proceeding to a large, interventional RCT. We shall also examine the effects on patient plasma-induced macrophage dysfunction using assays developed within our laboratory⁸ which will validate the proposed mechanism of albumin's action in patients with chronic liver failure.

METHODS AND ANALYSIS

Primary objective

To determine whether it is possible to restore to and maintain serum albumin at >30 g/L in patients admitted with AD using repeated 20% HAS infusions according to daily measured serum albumin levels (figure 1).

Secondary objective

We shall assess patient plasma-induced macrophage dysfunction (as an indicator of immune suppression) in AD patients on the day of recruitment and during HAS treatment to determine whether this is substantially improved following albumin infusion.¹⁷

Trial design

This is a multicentre, open label single-arm feasibility trial in which all patients will be treated with 20% HAS to target levels above 30 g/L. Sequential patients admitted to 10 UK participating hospitals with a clinical diagnosis of cirrhosis and AD will be screened using the inclusion and exclusion criteria (table 1).

Clinical trial end points

The primary end point is daily serum albumin level for the duration of the treatment period (maximum of 14 days or when the patient is considered fit for discharge if less than 14 days).

The key secondary end point is patient plasma-induced macrophage dysfunction assessed by our

laboratory-based assays.⁸ Immune function is an extremely complex process for which there is no simple test or assay. During inflammation, monocytes move quickly to sites of tissue infection and differentiate into macrophages to elicit an immune response. Numerous studies have demonstrated the role of monocyte deactivation in cirrhosis associated immune suppression.^{18–20} It is, however, impractical to perform blinded, standardised, biological assays using fresh monocytes from 10 sites spread throughout the UK. As it has been demonstrated that circulating plasma mediators are responsible for monocyte and neutrophil dysfunction,^{21 22} we developed an assay in which stored plasma from AD patients is added to macrophages from healthy donors.⁸ This permits testing of patient samples from multiple sites at the same time in a controlled fashion.

We have selected macrophage production of the proinflammatory cytokine tumour necrosis factor α (TNF- α) as our immune-readout as this has been validated as a biomarker of monocyte function in critical illness. Reduced capacity to produce TNF- α is associated with adverse outcomes following sepsis.^{23 24}

We will stimulate human monocyte-derived macrophages with lipopolysaccharide (LPS) in the presence of 25% patient plasma pretreatment and post-treatment, measuring TNF- α production. LPS simulates a bacterial infectious stimulus. Improvement in macrophage function will be defined as an increase in LPS-induced TNF- α production. Plasma from healthy controls will also be used as a comparator.

Other secondary end points include rates of infection, organ dysfunction and mortality during the 14-day treatment period. Clinical data will also be collected regarding safety, type of infection, antibiotic prescribing, total amount of fluid administered, ICU admission and duration of hospital stay.

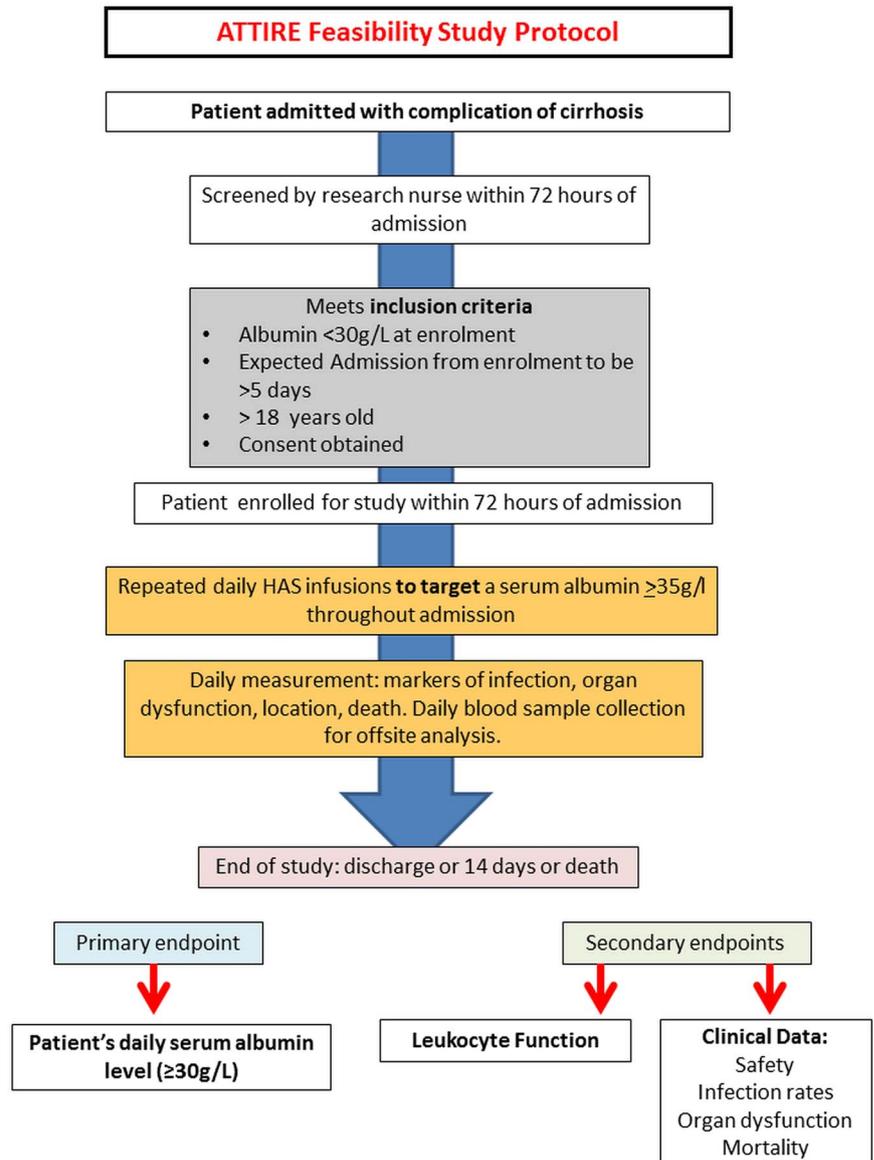
Patient population

This will include all patients admitted to hospital with complications of liver cirrhosis and serum albumin <30 g/L, aged over 18 years with anticipated hospital length of stay of five or more days at trial enrolment, which should be no later than 72 h from admission. This is subject to exclusion criteria as detailed in table 1. The diagnosis of cirrhosis will be performed by the clinical team as per standard UK practice and does not require liver biopsy or imaging.

Consent

Patient information sheets (see online supplementary appendix 1) will be given to and discussed with potential patients before consent is sought. Informed consent will be obtained from each participant or their legal representative. Patients who lack mental capacity, for any reason, are not excluded from the trial. An important subgroup of patients will have hepatic encephalopathy and these patients may lack capacity to consent. However, these patients may be among those that

Figure 1 Protocol for ATTIRE phase II feasibility trial. ATTIRE, Albumin To prevenT Infection in chronic liveR failurE.



receive maximum benefit from the intervention.^{25–27} In this case consent will be sought from an appropriate legal representative independent of the research team as per current UK clinical trials regulations.²⁸

Intervention

All patients will receive a daily infusion of 20% HAS intravenously (100mL/h) for a maximum of 14 days or until discharge (if less than 14 days). The volume of HAS prescribed each day will be determined by the patient's serum albumin level on that day.

Table 2 shows a suggested dosing protocol for albumin administration. This is based on the reported regimen used in the ALBIOS study²⁹ and clinical experience as there are no prior albumin dose-increment studies in cirrhosis patients. In ALBIOS²⁹ patients with a very low albumin (<20 g/L) incremented to a higher value within 4–5 days therefore we would expect 20% HAS requirements, as according to our trial protocol, to decrease after a few days with a subsequent decrease in

cost and time of administration. However, there may be a subgroup of non-responders. We expect these patients to be very unwell and careful monitoring of side effects with on-going albumin infusion may warrant cessation of the trial intervention in this group. If this is the case additional time-to-increment advice may be added to the RCT protocol.

Differing regimens may be used to cover large volume paracentesis (8 g of albumin/L of ascites drained) or treat hepatorenal syndrome (1 g of albumin/kg of body weight) as per international guidelines^{30 31} but HAS *must* be prescribed and given if serum albumin <35 g/L. All variations will be recorded in the patient's daily Case Report Form (CRF).

Evaluations during and after treatment

Clinical, biochemical and microbiological data will be collected daily during the trial treatment period (see online supplementary appendix 2) using information from hospital notes that is recorded as standard of care.

Table 1 Patient selection criteria

Patient inclusion criteria	Patient exclusion criteria
All patients admitted to hospital with acute onset or worsening of complications of cirrhosis	Advanced hepatocellular carcinoma with life expectancy of less than 8 weeks
Over 18 years of age	Patients who will receive palliative treatment only during their hospital admission
Predicted hospital admission >5 days at trial enrolment, which must be within 72 h of admission	Patients who are pregnant
Serum albumin <30 g/L at screening	Known or suspected severe cardiac dysfunction
Documented informed consent to participate (or consent given by a legal representative)	Any clinical condition which the investigator considers would make the patient unsuitable for the trial
	The patient has been involved in a clinical trial of Investigational Medicinal Products (IMPs) within the previous 30 days that would impact on their participation in this study
	Trial investigators unable to identify the patient (by NHS number)

NHS, National Health Service.

There is no follow-up beyond the treatment period. The blood samples collected for immune function tests will be analysed in a blinded fashion at a central site.

Statistical considerations

Sample size

The primary purpose of this Feasibility Trial is to demonstrate that repeated 20% HAS infusions can raise and maintain serum albumin at ≥ 30 g/L in liver cirrhosis patients presenting with AD.

Table 2 Dosing protocol for 20% HAS administration (amounts per day) as advised by measured serum albumin level on that day

Patient's serum albumin level (g/L)	Amount of 20% HAS to be administered (mL)
≥ 35	None
30–34	100
26–29	200
20–25	300
<20	400

HAS, human albumin solution.

Eighty patients will be recruited. Success would be demonstrated if 60% of patients were able to achieve and maintain serum albumin levels at or above 30 g/L on at least 1/3 of days in which the level is recorded. We believe that there will be a subgroup of patients with very low albumin levels who may not be able to achieve this end point which has influenced our definition of success. If our assumptions are correct these patients will be excluded from RCT recruitment. With 72 evaluable patients (allowing for 10% loss-to-follow-up/withdrawal) the probability of achieving 44 or more 'successes' is around 80% assuming that each patient has a 65% chance of attaining the required level.

The trial will be performed at 10 sites. 8–10 patients per site will allow identification of any variability in the delivery of the albumin-targeting dose protocol between centres. It will be compulsory to record reason for protocol variation in the daily CRF.

Statistical evaluation

As this is a feasibility trial the emphasis will be on producing relevant data summaries rather than on formal modelling or hypothesis testing. This will support the IDMC and TSC in deciding whether to recommend proceeding with the RCT.

Primary outcome

Serum albumin levels will be summarised for each of days 1–15 by table, mean \pm SD and graph (median level vs day with superimposed bars displaying IQR). The numbers of patients observed on each day will be noted. Day 1 will represent the baseline serum albumin level before the first administration of 20% HAS according to the protocol.

The number of patients on each day whose serum albumin level exceeds 30 g/L will be noted as a percentage of those evaluated, together with the overall percentage of patients whose serum albumin level exceeds 30 g/L on at least 1/3 of the days on which it is recorded.

Secondary outcomes

Albumin's ex vivo impact on immune function will be determined by comparing macrophage function in the presence of patient plasma using our laboratory assays when their albumin level is <30 g/L compared to ≥ 30 g/L. A substantial improvement in macrophage function is expected following treatment with albumin.

Information shall be summarised regarding the total volume of albumin infused and the total amount of fluid administered, days in ICU and duration of hospital stay, together with the rates of nosocomial infections, organ dysfunction and in-hospital mortality which are the component elements of the composite end point for the RCT. Safety will be assessed by consideration of the number of SAEs reported during the trial.

Data will be further summarised within 'groups' defined by baseline serum albumin levels (<20, 20–25 and 26–29 g/L) to investigate whether there are any

apparent differences in outcome by group. This subgroup analysis is exploratory, since we are not powered to detect differences, but may be useful in identifying whether any amendments are necessary to the protocol for the RCT.

DISCUSSION

ATTIRE is a UK multicentre trial that aims to evaluate the repurposing of HAS as an immune restorative drug. This protocol describes the feasibility trial which will determine if it is possible and safe to raise and maintain AD patients' serum albumin levels to >30 g/L.

In liver cirrhosis current evidence-based guidance^{31–33} advocates the use of HAS in large volume paracentesis,³⁴ hepatorenal syndrome³⁵ and spontaneous bacterial peritonitis.^{36 37} To date there has not been an albumin dosing trial aimed at increasing serum albumin levels. Therefore it was essential that this study was completed before proceeding to a large, interventional RCT.

Studies evaluating the safety of HAS infusions have generally shown it to be a safe treatment.^{12 13 29 34} The main concerns in the cirrhotic population are related to volume overload leading to pulmonary oedema and increase in portal pressure leading to variceal bleeding. A recent interventional trial in septic AD patients reported an 8.3% rate of pulmonary oedema in the albumin treatment group.³⁸ However, the weight based albumin dosing regimen in this study led to much larger daily volumes of albumin being prescribed than suggested in our protocol. This and other studies in cirrhosis have not reported an increased incidence in variceal bleeding.^{34 37 39}

We shall also correlate our primary end point of a numerical increase in albumin levels with a biological outcome measuring markers of immune function *ex vivo*. This aims to verify that increasing serum albumin above 30 g/L is associated with an improvement in patient plasma-induced macrophage dysfunction *ex vivo* in a much larger patient cohort than already shown.⁸ These outcomes will be used to move forward and if appropriate modify the protocol for the ATTIRE RCT.

Ethics and dissemination

This research group will involve a potentially vulnerable patient group that have hepatic encephalopathy and therefore lack the capacity to consent. However, patients with encephalopathy are at high risk of infection and could be those that potentially receive maximal benefit from the intervention and therefore should not be denied access to the trial treatment. We have undertaken steps to ensure these patients are appropriately recruited to the trial (described in 'Consent' section) and provided individual site training.

Research Ethics positive opinion was given by the London-Brent Research Ethics Committee (ref: 15/LO/0104) which specialise in trials involving patients who lack the capacity to consent.

The Clinical Trials Authorisation was issued by the Medicines and Healthcare products Regulatory Agency (MHRA, ref: 20363/0350/001-0001). The trial is registered with the European Medicines Agency (EudraCT 2014-002300-24) and has been adopted by the NIHR. Recruitment started in May 2015 and will finish by November 2015. Assuming feasibility milestones have been met a 866 patient phase III randomised control trial (ATTIRE stage 2) will start at the end of 2015 randomising patients to daily HAS infusion or routine standard of care.

Study findings will be disseminated through peer reviewed publications and international conference presentations. They will also be used to generate the study protocol for a large interventional RCT (ATTIRE stage 2).

Trial funding and sponsor

The work is supported by the Health Innovation Challenge fund (Wellcome Trust and Department of Health) award number 164699. The trial sponsor is UCL with trial management activities conducted by the UCL Comprehensive Clinical Trials Unit.

TRIAL MANAGEMENT AND MONITORING

Research Steering Group

The Research Steering Group (RSG) operates on behalf of the funders to ensure that appropriate milestones have been met in the delivery of the trial. It consists the CI, an independent expert and representatives of the Wellcome Trust and Department of Health.

Trial Management Group

The Trial Management Group (TMG) comprises the CI, Clinical Research Fellow, Clinical Project Manager, Trial Statistician, Trial Manager, Data Manager, Health Economist and five trial site PIs. The TMG is responsible for developing the design, co-ordination and strategic management of the trial.

Trial Steering Committee

The Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial in order to safeguard the interests of trial patients. The TSC provides advice to the CI, Clinical Trials Unit (CTU), funder and sponsor on all aspects of the trial through its independent chair.

Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) is responsible for safeguarding the interests of trial patients, monitoring the accumulating data and making recommendations to the TSC on whether the trial should continue as planned. It comprises a clinical chair (independent hepatologist), independent gastroenterologist and an independent statistician all with expertise in Clinical Trials.

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Contributors All authors read and approved the final manuscript. LC was involved in the protocol development, writing of this manuscript; NM was involved in the protocol development, manuscript review; ZS was involved in the protocol development, manuscript review; SS was involved in the protocol development, statistical input, manuscript review; AM: manuscript review, design of laboratory analysis; DG: manuscript review, design of laboratory analysis; AO was involved in the concept and design, protocol development, writing of this manuscript.

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Competing interests None declared.

Ethics approval London-Brent Research Ethics Committee (ref: 15/LO/0104).

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

- Health Service Quarterly. Vol. No. 40 (ed. Statistics, O.f.N.) p59–60 (Winter 2008).
- Williams R, Aspinall R, Bellis M, *et al.* Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. *Lancet* 2014;384:1953–97.
- Fernández J, Navasa M, Gómez J, *et al.* Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology* 2002;35:140–8.
- Rajkovic I, Williams R. Abnormalities of neutrophil phagocytosis, intracellular killing and metabolic activity in alcoholic cirrhosis and hepatitis. *Hepatology* 1986;6:252–62.
- Acevedo J, Fernández J. New determinants of prognosis in bacterial infections in cirrhosis. *World J Gastroenterol* 2014;20:7252–9.
- Fernández J, Acevedo J, Castro M, *et al.* Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. *Hepatology* 2012;55:1551–61.
- O'Brien AJ, Welch CA, Singer M, *et al.* Prevalence and outcome of cirrhosis patients admitted to UK intensive care: a comparison against dialysis-dependent chronic renal failure patients. *Intensive Care Med* 2012;38:991–1000.
- O'Brien AJ, Fullerton JN, Massey KA, *et al.* Immunosuppression in acutely decompensated cirrhosis is mediated by prostaglandin E2. *Nat Med* 2014;20:518–23.
- Yang J, Petersen CE, Ha CE, *et al.* Structural insights into human serum albumin-mediated prostaglandin catalysis. *Protein Sci* 2002;11:538–45.
- Klammt S, Mitzner S, Stange J, *et al.* Albumin-binding function is reduced in patients with decompensated cirrhosis and correlates inversely with severity of liver disease assessed by model for end-stage liver disease. *Eur J Gastroenterol Hepatol* 2007;19:257–63.
- Jalan R, Schnurr K, Mookerjee RP, *et al.* Alterations in the functional capacity of albumin in patients with decompensated cirrhosis is associated with increased mortality. *Hepatology* 2009;50:555–64.
- Patel A, Laffan MA, Waheed U, *et al.* Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality. *BMJ* 2014;349:g4561.
- Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *BMJ* 1998;317:235–40.
- Arroyo V, García-Martínez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. *J Hepatol* 2014;61:396–407.
- Domenicali M, Baldassarre M, Giannone FA, *et al.* Posttranscriptional changes of serum albumin: clinical and prognostic significance in hospitalized patients with cirrhosis. *Hepatology* 2014;60:1851–60.
- García-Martínez R, Andreola F, Mehta G, *et al.* Immunomodulatory and antioxidant function of albumin stabilises the endothelium and improves survival in a rodent model of chronic liver failure. *J Hepatol* 2015;62:799–806.
- Venet F, Lukaszewicz AC, Payen D, *et al.* Monitoring the immune response in sepsis: a rational approach to administration of immunoadjuvant therapies. *Curr Opin Immunol* 2013;25:477–83.
- Wasmuth HE, Kunz D, Yagmur E, *et al.* Patients with acute on chronic liver failure display “sepsis-like” immune paralysis. *J Hepatol* 2005;42:195–201.
- Antoniades CG, Wendon J, Vergani D. Paralysed monocytes in acute on chronic liver disease. *J Hepatol* 2005;42:163–5.
- Xing T, Li L, Cao H, *et al.* Altered immune function of monocytes in different stages of patients with acute on chronic liver failure. *Clin Exp Immunol* 2007;147:184–8.
- Lin CY, Tsai IF, Ho YP, *et al.* Endotoxemia contributes to the immune paralysis in patients with cirrhosis. *J Hepatol* 2007;46:816–26.
- Mookerjee RP, Stadlbauer V, Lidder S, *et al.* Neutrophil dysfunction in alcoholic hepatitis superimposed on cirrhosis is reversible and predicts the outcome. *Hepatology* 2007;46:831–40.
- Docke WD, Randow F, Syrbe U, *et al.* Monocyte deactivation in septic patients: restoration by IFN- γ treatment. *Nat Med* 1997;3:678–81.
- Ploder M, Pelinka L, Schmuckenschlager C, *et al.* Lipopolysaccharide-induced tumor necrosis factor alpha production and not monocyte human leukocyte antigen-DR expression is correlated with survival in septic trauma patients. *Shock* 2006;25:129–34.
- Bajaj JS, O'Leary JG, Reddy KR, *et al.* Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. *Hepatology* 2014;60:250–6.
- Bajaj JS, Ridlon JM, Hylemon PB, *et al.* Linkage of gut microbiome with cognition in hepatic encephalopathy. *Am J Physiol Gastrointest Liver Physiol* 2012;302:G168–175.
- Simón-Talero M, García-Martínez R, Torrens M, *et al.* Effects of intravenous albumin in patients with cirrhosis and episodic hepatic encephalopathy: a randomized double-blind study. *J Hepatol* 2013;59:1184–92.
- Medicines for Human Use (Clinical Trials Regulations) 2004 Informed consent in clinical trials. (ed. Authority, H.R.). 2008. <http://www.hra.nhs.uk/>
- Caironi P, Tognoni G, Masson S, *et al.* Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med* 2014;370:1412–21.
- Angeli P, Ginès P, Wong F, *et al.* Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol* 2015;62:968–74.
- European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010;53:397–417.
- Moore KP, Aithal GP. Guidelines on the management of ascites in cirrhosis. *Gut* 2006;55(Suppl 6):vi1–12.
- Runyon BA, AASLD. Introduction to the revised American association for the study of liver diseases practice guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology* 2013;57:1651–3.
- Bernardi M, Caraceni P, Navickick RJ, *et al.* Albumin infusion in patients undergoing large-volume paracentesis: a meta-analysis of randomized trials. *Hepatology* 2012;55:1172–81.
- Martin-Llahi M, Pépin MN, Guevara M, *et al.* Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. *Gastroenterology* 2008;134:1352–9.
- Fernández J, Navasa M, García-Pagan JC, *et al.* Effect of intravenous albumin on systemic and hepatic hemodynamics and vasoactive neurohormonal systems in patients with cirrhosis and spontaneous bacterial peritonitis. *J Hepatol* 2004;41:384–90.
- Sort P, Navasa M, Arroyo V, *et al.* Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999;341:403–9.
- Thévenot T, Bureau C, Oberti F, *et al.* Effect of albumin in cirrhotic patients with infection other than spontaneous bacterial peritonitis. A randomized trial. *J Hepatol* 2015;62:822–30.
- Guevara M, Terra C, Nazar A, *et al.* Albumin for bacterial infections other than spontaneous bacterial peritonitis in cirrhosis. A randomized, controlled study. *J Hepatol* 2012;57:759–65.

ATTIRE: Stage 1

Albumin To prevent Infection in chronic liver failure

The Problem

The most common cause of death in patients with liver disease is infection

→ this is because in liver disease the immune system does not work well, especially when you are unwell in hospital.

What we know

Albumin (a protein found in your blood) is lower in patients with liver disease. Research looking at blood samples has suggested that increasing the albumin levels in the blood can potentially improve the immune system in patients with chronic liver disease.

What question is this study trying to answer?

1. Does albumin actually stop patients admitted to hospital with chronic liver disease from getting infections? (or help them fight them)
2. How much albumin do we need to give to patients?

What additional treatment or investigations will occur if I take part?

1. You will be given albumin directly into your veins every day (for up to 14 days) whilst you are in hospital. Albumin is a very safe protein that is already commonly used in liver patients who have kidney problems or ascites (fluid in the abdomen).
2. A daily blood test (1 additional teaspoon of blood) will be taken along with your usual daily blood tests for up to 14 days of your hospital stay.

What are the possible advantages?

You may not have any direct benefit from taking part in the study, but you will be a part of a large study that will help gain a better understanding of treatment of patients with liver disease.

What are the possible disadvantages?

You will have to be connected to a drip for 1-2 hours a day (this can be when other drip medication is given). We will take an extra teaspoon of your blood every day. The side effects of albumin are very rare (listed in detail in the following pages).

ATTIRE

Stage 1: Patient Information Sheet

Full study title:

Albumin To prevent Infection in chronic liver failure.

A trial to investigate whether giving albumin to patients with advanced liver cirrhosis will reverse immune suppression and prevent nosocomial (hospital acquired) infection.

Invitation to take part in research study

We would like to invite you to take part in a research trial. Before you decide, we would like you to understand why the research is being done and what it involves. Please read this information sheet; one of the study team will answer any questions you may have. Talk to others about the study and ask us if there is anything that is not clear. Take time to decide whether or not you wish to take part.

The ATTIRE study is in two parts. The first stage will involve up to 80 patients and the second stage will include over 860 patients. They are very similar, but will look at slightly different outcomes.

This Patient Information Sheet is for Stage 1.

What is the purpose of the study?

Liver cirrhosis results in the liver tissue becoming scarred and developing lumps, these changes can prevent the liver from functioning properly. As the liver function worsens, symptoms such as fluid within the abdomen or legs, yellow skin, vomiting blood and confusion can develop. These are a result of advanced liver disease and are termed complications of cirrhosis. There are about 60,000 patient admissions to hospitals each year with such complications of liver cirrhosis. These patients are at higher risk of developing an infection during their hospital stay and this increase in risk is due to a weakened immune system. These hospital-acquired infections can be very serious.

Giving fluid directly into the veins (intravenous) is known to be very important to help kidney function in patients with advanced liver disease. However, how much to give or indeed what is the best fluid to give is currently unknown. We have shown in laboratory testing, that albumin might be a better option as it can strengthen the immune system. However, it is unclear whether this will reduce the number of infections in hospital and that is what our trial wishes to investigate.

Albumin is found in the blood and is made in the liver. Patients with liver cirrhosis cannot make albumin as easily due to the damage to their liver. In this stage of the study, patients will be given extra albumin to see if this can help return the albumin levels in the blood to near normal. Albumin is already used to treat patients with liver cirrhosis and is known to be safe.

Why have I been chosen?

You are being asked to take part in this study as you have been admitted to hospital with complications of liver cirrhosis. Your doctor believes that you could be eligible to take part.

Do I have to take part?

It is up to you whether or not to take part in the study. If you decide not to take part, this will not affect the treatment you would normally receive. If you take part, you are free to withdraw at any time without giving a reason; this will not affect the care you receive.

What will happen to me if I take part?

If you take part in this study you will be given albumin solution as an intravenous fluid. Albumin has been shown to be safe and is currently used in patients with liver disease. The amount of albumin that you are given will be decided by the amount that you already have in your blood. You will receive an infusion each day that you are in hospital, for a maximum of 14 days, until the levels in your blood have reached normal. You will have blood tests every day while you are in hospital (as part of your normal care). At this time an additional sample (about 1 teaspoon) will be collected for up to 15 days. You will also be asked to provide stool samples while on the study, however this is optional and you can still take part in the study without providing these samples.

The study will end either 14 days after the start of the study or when the doctor feels you are ready to go home.

What will I have to do?

If you agree to take part in the study you will be asked to sign a consent form. A member of the study team will then go through the initial assessments required to join the study including collecting details of your medical history. You will have tests (which will be part of your standard care) to look at your general health (e.g. heart rate and blood pressure), whether you have an infection, your liver function and the level of albumin already in your blood. Only if the level of albumin is below a certain level, will you be able to take part.

If you are a woman of childbearing potential, a pregnancy test will be carried out.

Starting Treatment

Once all of your tests have been completed and if you are still eligible to participate, treatment will be started.

The test for the amount of albumin in your blood will be used to work out how much albumin will be given, this will be given by a nurse or doctor. The albumin will be given directly into your blood through an intravenous cannula (a tube inserted into your vein to give fluid); the cannula will already be present as part of your standard care, an extra one will *not* be required. This will happen each day that you are on the study (a maximum of 14 days).

You will have blood tests each day for liver function and to look for infections. These would normally be taken during your hospital stay. Your extra blood sample (1 teaspoon) will be taken at the same time and will be used to look at your immune system. You will also be asked to provide stool samples while on the study, however this will be an optional sample. The stool samples and any samples left over will be stored for future research (for which further ethical committee review will be required).

If you do get an infection while on the study, you will be given the normal treatment for that type of infection that may include albumin. Taking part in the study will not affect the care that you normally get from your doctor.

End of study treatment

When you have taken part in the study for 14 days or you when your doctor feels you are ready to be discharged (if this is before 14 days of being on the study), you will stop your study treatments. This means that you will no longer be given albumin as part of the study or have any samples collected that are not part of your standard treatment.

If your doctor feels that you still need albumin, you will continue to receive it.

When should I contact the study team?

You should contact a member of the study team or staff on your ward if you feel unwell at any time or have any incidents that affect your physical wellbeing. If you become pregnant within 30 days of leaving hospital, please let a member of the study team know. Contact details of the study team at your hospital and the Chief Investigator are available at the end of this leaflet.

What happens if I become pregnant?

All women of child-bearing potential will have a pregnancy test before entering the study. If you do become pregnant during treatment or 30 days after treatment, you should inform your study team. It is not thought that albumin will affect pregnancy.

What are the alternative treatments if I don't take part?

If you do not take part in the study, standard treatment will be offered, which may include the use of albumin. Albumin is currently used for several reasons in patients with liver disease, for example those who require extra fluid to support their kidneys, or to replace fluid that has been drained from the abdomen, or in those who develop infections.

What are the possible disadvantages and risks of taking part?

There are some possible risks and disadvantages that you should consider before taking part in this study:

- Wherever possible we will ensure that the blood tests needed for the study are taken at the same time as those needed for your routine care, but you may be asked to have additional samples taken if this is not possible. The risks of having a blood test include local bruising and discomfort.
- You may experience discomfort and bruising from fluid infusion.
- As the albumin is taken from human blood, in theory there is chance that you could get an infection (virus) from the person who has donated the blood. However there are no reports of patients getting viral infections from albumin that is made following European manufacturing standards. The albumin given as part of the study is the same as that which would be given to you as part of your regular care by your doctor which you may have received as a treatment in the past.
- A cannula (very small plastic tube) will be used to give you the albumin. We would expect that you already will have one of these to give your other medications whilst in hospital and will use the same cannula. However if you don't have any medications or fluid that need to be given into the vein we will need to place a small cannula into the vein in order to give you the albumin. You will be connected to an albumin infusion for around 1-2 hours a day. You can still move around the ward with this but will need to have a drip stand with you.

What are the possible benefits of taking part?

There may be no benefit to you from taking part, however, intravenous albumin may help your kidneys and raise blood pressure that can be low in patients with liver problems. Taking part may also provide additional information about patients with liver disease.

What are the side effects of any treatment received when taking part?

The side effects of albumin are very rare, but can include: feeling sick, flushing, feeling feverish, itchy, raised bumps on the skin, shaking of the body (rigors), high blood pressure (hypertension), low blood pressure (hypotension), feeling cold, increased heart rate (tachycardia), tremor, shortness of breath, chest tightness, wheezing, noisy breathing from throat (stridor) and dizziness.

There is a small chance that you could have an allergic reaction to the albumin.

If any of the above reactions occur, you will be treated as you would in normal standard care.

What if relevant new information becomes available?

Sometimes we get new information about the treatments being studied. If this happens, your study team will tell you about it and discuss how this may impact you. They will discuss whether you want to or should continue in the study.

What happens when the research study stops?

If you still require any treatment once the study stops, your doctor will prescribe the treatment most suitable for you.

Expenses and payments

You will not receive any payments for participating in this study.

What if something goes wrong?

If you have any concerns about the study, you should discuss them with your local study team first. You can also contact the Chief Investigator for the study, Dr Alastair O'Brien, on 020 7679 6851 who will be happy to discuss any of your concerns.

If you would like to discuss your concerns with someone not involved in the study, please contact your local Patient Advice and Liaison Service (PALS). Information on how to contact your local PALS can be found at the end of this information sheet.

Every care will be taken during this clinical study. However in the unlikely event that you are injured by taking part, compensation may be available. If you suspect that the injury is the result of the Sponsor's (UCL) or the hospital's negligence then you may be able to claim compensation. After discussing it with your study team, please write to Dr Alastair O'Brien who is the Chief Investigator for the clinical study, about details of your claim. The Chief Investigator will then pass the claim to the Sponsor's Insurers, via the Sponsor's office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this. Contact details of the study team at your hospital and the Chief Investigator are available at the end of this leaflet.

You may also be able to claim compensation for injury caused by participation in this clinical study without the need to prove negligence on the part of University College London or another party. You should discuss this possibility with your study team in the same way as above.

Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff or about any side effects (adverse events) you may have experienced due to your participation in the clinical study, the normal National Health Service complaints mechanisms are available to you. Please ask your study team if you would like more information on this. Details can also be obtained from the Department of Health website: <http://www.dh.gov.uk>.

Will my taking part in this study be kept confidential?

Yes, it will. We will request your approval to contact and inform your GP in the consent form about your participation in the study. We will send information relating to this research to the Comprehensive Clinical Trials Unit at University College London (UCL), where the study is being managed. Relevant information about you and all other patients in the study will be stored on password protected computers and in locked filing cabinets and will only be available to the staff working on the study. The information stored by the Comprehensive Clinical Trials Unit will contain a unique code, your initials and month and year of birth. Your full name, address, contact details relevant medical history and relevant test results will be maintained at your local hospital. The information may be accessed by authorised personnel from UCL and the NHS hospital where you are being treated for auditing and monitoring purposes or by the regulatory authorities for inspection purposes to make sure the study is being carried out properly. Data collected during the study may be sent pseudo-anonymously (partially linked) to associated researchers in countries where the laws don't protect your privacy to the same extent as the law in the European Union (EU) but we will take all necessary steps to protect your privacy. Any data sent will only contain your unique code, your initials and month and year of birth. A data protection officer at UCL will be informed about any potential data transfer. You will be asked whether you agree to this when you sign the consent form.

If you withdraw consent from further study treatment, unless you object, your data and samples will remain on file and will be included in the final study analysis. In line with Good Clinical Practice guidelines, at the end of the study, your data will be securely archived for a minimum of 5 years. Arrangements for confidential destruction will then be made.

What will happen to the samples and results of the research study?

If you choose to take part in the study you will be given a unique trial identification code. All information collected from you for the study will be associated with this unique code, your initials and month and year of birth. No other personal information will be sent to personnel outside your hospital and no one outside your hospital care team will be able to identify you from this information.

The blood and optional stool samples collected for this study will be sent to the University College London, where they will be stored securely with your study specific identification number, initials, and month and year of birth. The blood samples will be analysed at UCL to look at your immune system. The stool samples will be stored securely at UCL to be used for future research. Any future research carried out on the samples will be subject to further ethical committee review. It may be possible that the samples, or part of the samples, will be sent to countries outside the EU where the laws for data protection differ from those in the UK. The stool samples are optional samples and will not affect your participation in the study.

The Comprehensive Clinical Trials Unit will analyse the data collected on the patients in the study after all 80 patients have completed their treatment. The results of the study will be presented at a scientific conference and will be published in a scientific journal which will be accessible to the public. None of the research participants will be identified in any report or publication. Should you wish to see the results, or the publication, please ask your study team.

Who is conducting and funding the research?

This study is being managed by the Comprehensive Clinical Trials Unit at the University College London. Funding for the research has come from the Department of Health and Wellcome Trust.

Who has reviewed the study?

All research in the NHS is reviewed by a Research Ethics Committee and an agency of the Department of Health called the MHRA (the Medicines and Healthcare products Regulatory Agency). Both of these groups have confirmed that they are content for the study to go ahead and are regularly updated on its progress by the Comprehensive Clinical Trials Unit.

Who to contact for further information?

You are encouraged to ask any questions you wish, before, during or after your treatment. If you have any questions about the study, please speak to a member of the study team. If you wish to read the research on which this study is based, please ask your study team. If you require any further information or have any concerns while taking part in the study please contact one of the following people at your study site:

Doctor

Name *add name of PI*

Tel. Number: *add Tel. number*

Study Nurse

Name *add name*

Tel. Number: *add Tel. number*

PALS Add local PALS contact details

Or contact the Chief Investigator for the study:

Dr Alastair O'Brien at University College London, Tel. Number: 020 7679 6851

Before you sign the informed consent form, you should ask questions about anything that you do not understand. The study staff will answer any questions before, during and after the study.

Thank you for taking the time to read this information sheet.

To be printed on hospital headed paper

ATTIRE

Stage 1: Patient Informed Consent Form

Albumin To prevent Infection in chronic liver failure (ATTIRE)

PATIENT ID: - -

SITE:

MONTH AND YEAR OF BIRTH: -
M M M - Y Y Y Y

PATIENT INITIALS:

This Informed Consent Form is intended for consenting patients into Stage 1 of the ATTIRE study.

Please insert your **initials** in the boxes to confirm consent:

	Initials
1. I confirm that I have read and understood the Patient Information Sheet version 3.0 dated 14Jul2015 for the ATTIRE study and have had the opportunity to consider the information and ask questions, which have been answered to my satisfaction.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason and without my medical care or legal rights being affected.	
3. I understand that sections of my medical records may be looked at by properly authorised personnel involved in the running of the study or from regulatory authorities, where it is relevant to my taking part in this study. I give permission for these individuals to have access to my records.	
4. I understand that my taking part in this study will mean that I have additional blood tests taken.	
5. I understand that some of my samples will be stored at the hospital and then transferred to University College London.	
6. I agree to be contacted by the research team, should the need arise, after my hospital discharge.	
7. I agree to take part in the ATTIRE study.	

Optional Consent:

The following is optional. Declining any of the below will not prevent you from taking part in the trial. Please initial in the boxes to confirm consent:	Initials
8. I give permission for my study data and samples to be sent to an associated researcher outside of the EU.	
9. I give permission for my GP to be informed of my participation.	
10. I agree to my remaining blood samples, not used in this study, being used in future, ethically approved, research.	
11. I agree to provide stool samples and I agree to my samples being used in future, ethically approved, research.	

Patient/Legal Representative's Name (score through as applicable) Signature Date

Person Taking Consent Signature Date

Witness (if applicable) Signature Date

Appendix 2

Patient timeline for Stage 1 Feasibility Trial:

	Screening/Day 1 <i>(within 72hrs of admission)</i>	Treatment Period <i>(up to day 14)</i>	Day 15 or discharge <i>(if prior to Day 15)</i>
Eligibility screen	X		
Informed consent	X		
Medical history	X		
Blood tests and sample collection*	X	X	X
Administration of Human Albumin solution (HAS)	X ^a	X ^a	
Clinical observations measured	X	X	X
Infection/initiation of antibiotics clinical record	X	X	X
Patient location recorded	X	X	X
Urine pregnancy test (β hCG) (women of child bearing potential only)	X		

*Blood tests include: Full Blood Count, Urea & Electrolytes, Liver Function Tests, C-reactive Protein, Serum Albumin concentrations and daily plasma saved for immune function analysis. An optional stool sample will be requested at baseline (within 72hrs of enrolment) and an additional sample at least 72hrs following the initial sample.

^a Volume of HAS given will be determined by the Serum Albumin results