Position Paper

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Endpoints and design of clinical trials in patients with decompensated cirrhosis: Position paper of the LiverHope Consortium

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Summary

Management of decompensated cirrhosis is currently geared towards the treatment of complications once they occur. To date there is no established disease-modifying therapy aimed at halting progression of the disease and preventing the development of complications in patients with decompensated cirrhosis. The design of clinical trials to investigate new therapies for patients with decompensated cirrhosis is complex. The population of patients with decompensated cirrhosis is heterogeneous (*i.e.*, different etiologies, comorbidities and disease severity), leading to the inclusion of diverse populations in clinical trials. In addition, primary endpoints selected for trials that include patients with decompensated cirrhosis are not homogeneous and at times may not be appropriate. This leads to difficulties in comparing results obtained from different trials. Against this background, the LiverHope Consortium organized a meeting of experts, the goal of which was to develop recommendations for the design of clinical trials and to define appropriate endpoints, both for trials aimed at modifying the natural history and preventing progression of decompensated cirrhosis, as well as for trials aimed at managing the individual complications of cirrhosis.

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Background

The natural history of cirrhosis is characterized by an asymptomatic or minimally symptomatic phase defined by the absence of overt clinical manifestations of the disease, followed by a decompensated phase, characterized by the occurrence of complications, typically ascites, gastrointestinal (GI) bleeding, hepatic encephalopathy (HE), and/or jaundice. Such patients are at risk of bacterial infections and acute kidney injury (AKI). The occurrence of decompensated cirrhosis is associated with reduced survival.[1,2] Management of decompensated cirrhosis is based on treatment of individual complications once they occur. Most drugs and therapeutic interventions used in the management of complications of cirrhosis were introduced decades ago and merely control symptoms; thus, complications tend to recur after treatment is discontinued. In fact, with the possible exception of non-selective beta-blockers (NSBBs) and transjugular intrahepatic portosystemic shunts (TIPS) in selected populations,[3–5] there is no therapeutic approach that has shown efficacy in slowing the progression of disease. In this regard, a number of studies have been performed to investigate new therapeutic strategies for the management of specific complications of cirrhosis or the prevention of disease progression.[6–11] The design, methodology, study population and endpoints of these trials have been variable and sometimes difficult to interpret or apply widely. This is partly due to the complexity of defining target populations and endpoints in clinical trials for decompensated cirrhosis. The population of patients with decompensated cirrhosis is quite heterogeneous, in terms of etiology, variety of complications, severity of liver failure, comorbidities and access to liver transplantation. Therefore, the populations of patients with decompensated cirrhosis included in clinical trials are often diverse, as varied inclusion and exclusion criteria are used. In addition, primary endpoints are frequently heterogeneous and sometimes not appropriate. This leads to difficulties in the interpretation and comparison

of results from different studies. Although there have been a number of initiatives to provide recommendations for the design and endpoints of clinical trials in other areas of hepatology, especially in non-alcoholic fatty liver disease,[12–14] these initiatives are lacking in the field of decompensated cirrhosis.

Therefore, there is an unmet need to standardize the design and definition of endpoints in clinical trials in patients with decompensated cirrhosis. The aim of this document is to provide expert recommendations to meet that need. The first part of the document summarises the recommendations for trials aimed at modifying the natural history of decompensated cirrhosis and preventing its progression, whereas the second part summarises the recommendations for trials targeting individual complications of cirrhosis. The document focuses on all complications of cirrhosis with the exception of portal hypertension-related bleeding, because recommendations for clinical trials in this specific area have been reported recently.[15–17]

Methods

Literature review

A literature review was performed by a task force of 10 young investigators from hospitals involved in the LiverHope Consortium. This task force systematically searched PubMed from Jan 1, 1980 to Jan 1, 2019, for clinical trials on decompensated cirrhosis. Search terms used were “decompensated” and “cirrhosis”, and a filter for clinical trials was used. Only English articles were considered. Of the 311 search results, the task force selected the clinical trials that were considered most relevant based on the following criteria: published in the first decile high-impact journals; selected trials investigating specific therapies or interventions aimed at modifying the natural history of decompensated cirrhosis; and a clear experimental design targeting the population of patients with decompensated cirrhosis. The initial search was reviewed by a senior investigator (PG) and a final selection was made. These studies were used as a framework for the meeting and to develop the first part of this document on trials assessing interventions to modify the natural history of decompensated cirrhosis. The same procedure was followed for every specific complication of cirrhosis presented in this document.

Literature evidence was summarized and reviewed in groups of 2 in a 2-day meeting. Following this, a working document was prepared and later discussed in depth by all members of the conference during a 2-day face-to-face meeting in June 2019.

Meeting of the LiverHope consortium

The meeting was organized by the LiverHope consortium with the objective of proposing recommendations for the design and selection of study populations for clinical trials in decompensated cirrhosis. LiverHope is a 7-nation consortium composed of 9 European hospitals with extensive experience in hepatology that is aimed at exploring new therapies for cirrhosis (www.liverhope-h2020.eu). The Consortium is funded by the European Commission under the Horizon 20/20 program. Within the consortium, patients are represented by the European Liver Patients Association (ELPA). The LiverHope consortium convened a group of experts including a body of investigators, members of ELPA, pharmaceutical industry representatives, medical statisticians, and health economists, as well as members of the LiverHope external advisory board to participate in a special workshop. The current position document summarises the areas of discussion and consensus among members of the conference.

Methodological aspects for the design of clinical trials in decompensated cirrhosis

Careful planning and reporting of the design of clinical trials is essential to achieve robust and comparable results. Important issues that need to be considered and detailed when designing and reporting results from clinical trials include aspects such as characteristics used to define the target population, selection and definition of adequate endpoints and adequate statistical analysis planning (Table 1). A detailed description of the methodological and statistical aspects that need to be considered when designing clinical trials in patients with decompensated cirrhosis is included in the supplementary material.

Trials assessing interventions aimed at modifying the natural history of decompensated cirrhosis

Recommendations on the population to be included in these studies should be a balance between including a homogeneous population and not being too restrictive, so that the results can be translated into a large proportion of patients with decompensated cirrhosis.

In this setting, when defining the target population, there is often controversy regarding whether to include specific patient characteristics, such as advanced age, severity of liver failure or specific comorbidities, as part of the exclusion criteria. The next section includes recommendations for defining specific characteristics of the target population. A summary of the recommendations for the target population and endpoints is provided in Table 2.

Target population

Child-Turcotte-Pugh score

The concept of decompensated cirrhosis refers to patients with cirrhosis and complications of the

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Table 1. Important information when reporting results of clinical trials in patients with decompensated cirrhosis.

Baseline characteristics of patients	• Include demographic data, previous complications of cirrhosis, etiology and characteristics of liver disease and liver function tests. • Prognostic scores such as MELD, MELD-Na and/or CTP (consider CLIF-C AD or CLIF-C ACLF) • Important to include comorbidities such as obesity, diabetes mellitus, arterial hypertension, cardiovascular disease or chronic kidney disease
Confounding factors	• It is important to include data on variables that may act as confounding factors in this population, such as alcohol consumption/abstinence during study period, presence or placement of TIPS, etiologic treatment (*i.e.*, antivirals, corticosteroids for autoimmune hepatitis).
Endpoints	• Primary and all secondary endpoints should be carefully detailed and defined. • Report absolute numbers and proportions of patients with response in each treatment arm • Describe both absolute changes and percent changes for efficacy-related endpoints
Statistics	• Planning of statistical analysis should be performed before starting the trials. • Description of expected and timing of interim analysis and stopping rules should be defined. • Consider the need for competing-risk or time-dependent analysis according to the trial design.
Safety data	• Treatment-related adverse events should always be included • Complications of cirrhosis and any other adverse events • Any other specific adverse events related to the characteristics of the study treatment

CLIF-C ACLF, EASL-CLIF consortium acute-on-chronic liver failure; CLIF-C AD, EASL-CLIF consortium acute decompensation; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; MELD-Na, MELD-sodium; TIPS, transjugular intrahepatic portosystemic shunt.

Table 2. Recommendations on characteristics of the target population and endpoints for the design of clinical trials aimed at investigating new strategies to modify the natural history of decompensated cirrhosis.

Target population	
Inclusion criteria	• Patients with cirrhosis defined by standard clinical criteria, ultrasonographic findings and/or histology. - Decompensated cirrhosis with CTP score B or C up to 12 points (a subgroup of CTP A patients may have decompensated cirrhosis; in particular those with moderate ascites and preserved hepatic function). • No upper limit for age • Patients on the waiting list for liver transplantation should be included
Exclusion criteria	• Active alcohol consumption expected to preclude correct adherence to study procedures • Patients with a history of significant non-hepatic diseases with impaired short-term prognosis (heart failure NYHA Grade III/IV, COPD GOLD C or above). • Patients with current non-hepatic malignancies including solid tumours and hematologic disorders. • Patients with hepatocellular carcinoma, except for patients with early HCC (BCLC-0 or BCLC-A) or patients with previous history of HCC and absence of recurrence 2 years after treatment. • Patients on antiviral therapy for HCV or those who have received it within the last 12 months. Patients with antiviral therapy for HBV for less than 12 months. • Patients under treatment with corticosteroids for autoimmune hepatitis for less than 6 months. • TIPS insertion within 6 months prior to study inclusion.
Endpoints – phase III trials	
Primary endpoint	• Survival (90-day, 1-year)
Secondary endpoints	• Composite endpoint of complications of cirrhosis • Development of ACLF • Hospital readmissions • Treatment-related adverse events
Endpoints – phase II trials	
Primary endpoint	• Surrogate markers with known association with survival (*i.e.*, changes in CTP or MELD score)
Secondary endpoints	• Biomarkers of disease progression known to correlate with hard clinical endpoints (*i.e.*, cytokines, oxidized albumin, NGAL or other biomarkers). • Treatment-related adverse events

ACLF, acute-on-chronic liver failure; COPD, chronic obstructive pulmonary disease; CTP, Child-Turcotte-Pugh; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; NGAL, neutrophil gelatinase-associated lipocalin; NYHA, New York Heart Association; TIPS, transjugular intrahepatic portosystemic shunt.

disease, namely ascites, GI bleeding, HE or jaundice. These patients are also at risk of bacterial infections or AKI.[18,19] Patients with decompensated cirrhosis usually belong to Child-Turcotte-Pugh (CTP) class B or C, corresponding to a CTP score ≥7 points (Table 3). However, there are exceptions to this rule. First, a subgroup of patients rated as CTP class A may have decompensated cirrhosis if they have moderate ascites or grade I-II HE with preserved liver function. Another exception to this classification is patients with significantly impaired liver function (*i.e.* serum bilirubin 2–3 mg/dl) without clinical complications, that may be classified as CTP class B but would strictly fit in the category of compensated cirrhosis.

CTP classification has pitfalls because of the subjective nature of assessment of ascites and HE. It is also a categorical classification for a clinical continuum. On the other hand, the CTP classification is a widely used, easy to calculate and validated tool that can be applied for classification and stratification of patients with decompensated cirrhosis in clinical trials.[20] In order to minimise subjectivity, it is recommended to strictly follow the original CTP classification to grade the clinical and laboratory variables adequately.[21] Another aspect that should

Table 3. Child-Turcotte-Pugh scoring system.

	1	2	3
Hepatic encephalopathy	None	Mild to moderate (grade 1–2)	Severe (grade 3–4)
Ascites	None	Mild to moderate (diuretic-responsive)	Severe (refractory)
Bilirubin (mg/dl)	1–2 mg/dl	2–3 mg/dl	>3 mg/dl
Albumin (g/dl)	>3.5 g/dl	2.8–3.5 g/dl	<2.8 g/dl
PT prolongation	1–4 s	4–6 s	>6 seg

PT, prothrombin time.
The table is based on the original Child-Turcotte-Pugh scoring system except for the grading of ascites. Assessment of ascites severity is based on subsequent modifications that are currently widely used and lead to more objective assessment of this complication.*
*see refs.[20,21]

be considered for the design of clinical trials is that cirrhosis is a dynamic and bidirectional disease, and that a number of patients with previous decompensations may "recompensate" after etiological treatment or specific interventions. In these cases, it is important to note that the evaluation of clinical decompensations and CTP calculation should be performed at the time a patient is evaluated for inclusion in a clinical trial, and only current decompensations should be considered.

Data derived from cohorts describing the prognosis of patients with cirrhosis according to CTP class do not provide specific information on mortality according to CTP score (points).[1,22–25] That is, CTP class is used to stratify patients, but cannot be used to calibrate risk of mortality. However, clinical experience and evidence from published studies show that patients with very high CTP scores (≥13 points) have a poor short-term prognosis. In this regard, one could argue that those patients may not benefit from the intervention tested and that this group might unbalance the study cohort. Recently published or ongoing randomized controlled trials (RCTs) including patients with decompensated cirrhosis have addressed the issue of the inclusion of CTP C patients differently. Some trials do not exclude patients based on CTP score,[7–9,11] whereas others have excluded patients with high CTP scores.[6,26,27] In this regard, we recommend excluding patients with CTP scores ≥13 from trials due to their markedly impaired prognosis. However, exceptions could be made for short-term studies. Stratification of study cohorts according to the CTP score should always be considered.

Age

As a result of the aging of the general population in the last decades and the improvement of the management and survival of patients with cirrhosis, patients with decompensated cirrhosis tend to be older than in the past. The exclusion of patients from clinical trials based on an upper limit of age is a controversial topic. To date, some published RCTs in cirrhosis include an upper limit for age,[6–8] but others do not include this age restriction.[9,11,26] Although age influences prognosis and excluding older patients may seem reasonable, there is no objective data to decide which is the best cut-off to use as an upper limit of age. On this background and considering the current demographic and clinical characteristics of patients with decompensated cirrhosis, we suggest that exclusion criteria should be based on severe comorbidities rather than an upper limit of age.

This position is also supported by the National Institutes of Health (NIH) policy that states that individuals of all ages must be included in all human research conducted or supported by the NIH, unless there are scientific or ethical reasons not to include them.

Comorbidities

Because the population of patients with cirrhosis is getting older and given the rising incidence of non-alcoholic steatohepatitis (NASH)-related cirrhosis, it is expected that an increasing number of patients with comorbidities will be evaluated for inclusion in clinical trials of decompensated cirrhosis in the coming years.[28] A reasonable recommendation for this scenario is to exclude patients with severe comorbidities unrelated to liver disease that are associated with high short-term mortality, such as severe heart failure defined by the New York Heart Association (NYHA) classification III and IV[29]; patients with severe chronic obstructive pulmonary disease, defined by a Global Initiative for Chronic Obstructive Lung Disease (GOLD) score of C or above[30]; and patients with extrahepatic malignancies with expected high short-term mortality. Inclusion and exclusion criteria for patients with chronic kidney disease will be discussed later in this document (see section hepatorenal syndrome-acute kidney injury).

HIV infection

In the past, patients with HIV infection were excluded from clinical trials in cirrhosis because of their poor prognosis and the risk of opportunistic infections as well as contraindications to many drugs and interventions because of interactions with HIV treatment. Nowadays, patients with chronic HIV infection under control on treatment have a life expectancy similar to that of the general population.[31,32] Therefore, the general recommendation is that these patients can be included in RCTs of decompensated cirrhosis if HIV infection is well controlled (defined as CD4 >250/

mm^3 and undetectable viral load[33]), and no significant interactions are expected between the tested drug and HIV treatment.

Active alcohol consumption

Alcohol is the most frequent cause of cirrhosis in Europe and the US.[34–36] In patients with alcohol-related cirrhosis, alcohol consumption is a major prognostic factor for survival.[37,38] However, a significant number of patients with alcohol-related cirrhosis are active drinkers. Excluding such patients from clinical trials would create a study population quite different from what is seen in clinical practice in many countries. Exclusion of patients with active alcohol consumption should be based on the amount of alcohol that is considered by the investigator to preclude adherence to the study protocol, as well as factors such as psychiatric comorbidities or personality or social issues that may affect adherence to the study protocol. Conversely, if patients become abstinent while on a therapeutic trial this may result in improved survival *per se* and act as a confounding factor. Therefore, it is essential to periodically record alcohol consumption in all patients with alcohol-related cirrhosis included in clinical trials to enable the correct interpretation of results.

The use of biomarkers of alcohol consumption is recommended, if possible, to provide a more objective assessment of alcohol consumption. Biomarkers, which are products of the metabolism of alcohol are highly specific and have a longer detection window than measurement of alcohol in body fluids or exhaled air. Among the alcohol consumption biomarkers available, it may be preferable to use those that are not affected by liver disease, such as ethyl glucuronide (EtG), ethyl sulfate or phosphatidylethanol.[39–41] Urine EtG is the most widely used marker of alcohol consumption in alcohol addiction programmes and on waiting lists for liver transplantation. Moreover, its use is recommended for confirmation and monitoring of alcohol consumption by the European and the American scientific society guidelines for the management of alcohol-related liver disease. Therefore, using biomarkers such as EtG seems a good option for clinical trials of decompensated cirrhosis that include patients with alcohol-related liver disease.[42,43]

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) influences the natural history of cirrhosis *per se* and represents a confounding factor in trials evaluating survival. However, exclusion of all patients with current or previous HCC might restrict recruitment into studies. The probability of progression of early HCC (BCLC-0 and BCLC-A) within 6–12 months is very low.[44,45] Therefore, patients with BCLC-0 or BCLC-A HCC may be included in clinical trials that require 6–12 months follow-up, as HCC is not expected to impact survival during that period in patients with decompensated cirrhosis. When considering patients with a previous history of treated HCC, absence of recurrence for 2 years following completion of treatment is generally considered as complete response. The prognosis of these patients is good with low HCC-related mortality over the mid to long term.[46,47] Thus, these patients may also be included, as HCC would likely not influence outcomes.

Regarding patients with intermediate stage HCC (BCLC-B), the expected median survival without treatment is 16 months[44,48] and the presence of impaired liver function is an accepted contraindication for locoregional therapies[49] and an independent predictive factor of poor outcome.[50] Finally, in patients with severely impaired liver function, HCC is categorized as terminal.[44,49] Accordingly, patients with HCC who are BCLC stages B-D have an unacceptable competing mortality risk and their inclusion in clinical trials of decompensated cirrhosis should not be supported.

Etiologies of cirrhosis with specific treatment: autoimmune and viral hepatitis

Specific therapies, such as corticosteroids and azathioprine for autoimmune hepatitis (AIH) or antiviral drugs for HBV and HCV, may modify the natural history of decompensated cirrhosis by improving liver function. There is more evidence available on this in patients with HCV-related cirrhosis than in patients with HBV or AIH. In this regard, although most studies have focused on the effect of antiviral therapy on clinical decompensations at 6 months after treatment, there are also studies indicating that a positive effect on clinical decompensations may be seen after an even longer period of time (1 or 2 years) following antiviral treatment in a proportion of patients. Nonetheless, improvement in portal pressure and clinical decompensations after sustained virological response (SVR) are less frequent in patients with previous ascites, compared to those without previous ascites.[51–53]

A period of at least 6 months after SVR in the case of HCV or after suppression of viral replication in the case of HBV may be sufficient to avoid the interference of the effect of the etiological treatment in clinical trials. However, in light of these recent results, we currently propose waiting a 12-month period after SVR in patients with HCV or after control of infection in HBV before including these patients in clinical trials. In the case of AIH there is less evidence of favourable response and resolution of clinical decompensations after immunosuppressive therapy; however, a period of at least 6 months after obtaining clinical and biochemical remission under immunosuppressive therapy seems reasonable before including these

patients in clinical trials of decompensated cirrhosis. It is important to note that a number of patients may experience resolution of their clinical decompensations after removal of the cause of cirrhosis. In this regard, the evaluation of the clinical status and stage of the disease of patients with cirrhosis must be performed when patients are considered for inclusion in the clinical trial. Patients in whom ascites resolves after cure of HCV should not be considered as candidates for trials of decompensated cirrhosis. The same holds true for patients with alcohol-related cirrhosis with ascites resolution after alcohol abstinence.[37,54,55]

Patients awaiting liver transplantation

Patients on the waiting list for liver transplantation should not be excluded from clinical trials of decompensated cirrhosis because this would represent a selection bias by excluding patients with the most advanced liver disease. However, some aspects should be considered when including this type of patient, because liver transplantation represents a competing event. One solution is to consider liver transplantation and death as competing-risk events (see below). However, it should be mentioned that time to liver transplantation in patients with decompensated cirrhosis varies in different countries based on the organ allocation systems, donor availability and other factors independent of the severity of liver disease.[56,57] Therefore, consideration of liver transplantation as a competing risk in clinical trials may cause some unavoidable biases in the analysis of the primary endpoint of the studies. A country-based stratification may help alleviate this issue.

Transjugular intrahepatic portosystemic shunt

TIPS has been shown to improve survival and reduce decompensation episodes in a proportion of patients with decompensated cirrhosis.[10,58–60] There are 2 major concerns regarding the inclusion of patients with TIPS in clinical trials of decompensated cirrhosis: (i) TIPS placement changes the natural history of cirrhosis; and (ii) access to TIPS is strongly dependent on physician preference and centre's expertise. However, excluding all patients who have received TIPS may greatly restrict the selection of the study population, and results of RCTs may not be applicable to a significant proportion of patients with decompensated cirrhosis. A balanced solution would be to include patients that still meet the criteria for decompensated cirrhosis a minimum of 6 months after TIPS placement. When included in such studies, patients may be stratified according to the presence or absence of TIPS.

Endpoints

The distinction between phase II and phase III trials is important to define the best primary endpoints for clinical trials of patients with decompensated cirrhosis.

Phase III trials

Primary endpoint: Considering the poor prognosis of patients with decompensated cirrhosis, transplant-free survival is recommended as the primary endpoint for these studies. Transplant-free survival is a hard and objective primary endpoint. Moreover, it is the most valuable result that can be expected of a specific intervention or drug therapy. For this reason, survival has been the primary endpoint in some previous clinical trials in patients with decompensated cirrhosis.[7,9,11] In addition, overall survival should always be assessed in these trials, and patients should be followed up to the end of the trial regardless of protocol adherence. Although survival is the ideal primary endpoint in these types of studies, it is not always feasible because of the requirement for a large sample size. In this situation we recommend a composite endpoint of complications of cirrhosis or development of ACLF as a "surrogate" primary endpoint.

If either transplant-free survival or another "surrogate" primary endpoint is used, overall survival may be used as a co-primary endpoint. In this case, if the results of transplant-free survival or the surrogate endpoint are positive, there would likely be no detrimental effect derived from an overall survival analysis.

Secondary endpoints: A composite endpoint should include all complications that are known to influence the quality of life and prognosis of patients with cirrhosis, such as ascites or refractory ascites, HE, GI bleeding, bacterial infections, AKI and jaundice. There are some pitfalls when using this composite endpoint because each complication of cirrhosis confers a different prognosis. This is not to say that some of these complications are not clinically meaningful. We recommend including these complications as secondary endpoints; they might also represent a surrogate for poor survival. Therefore, if a composite endpoint of complications of cirrhosis is used, worsening of a current decompensation or the onset of a new decompensation needs to be well defined to minimise possible subjectivity in the interpretation of outcomes. We propose a summary of the definitions of each decompensation event that should be included in this composite endpoint (Table 4).

ACLF development is another possible secondary endpoint that can be used in this setting because of its association with mortality. Although there is no global consensus on the definition of ACLF, based on criteria of the different international societies (EASL, NACSELD, APASL),[61–63] overall ACLF is characterized by a clinical decompensation of cirrhosis that is severe enough to be associated with organ failures and poor prognosis. If ACLF development is used as a secondary endpoint, the possible bias of using a composite endpoint of complications could be

Table 4. Definition of the decompensations to be included in a composite endpoint of complications of cirrhosis.

Complication	Definition
Ascites	New onset ascites, development of refractory ascites or worsening of ascites (defined as need for large-volume paracentesis).
Hepatic encephalopathy	Development of acute episode of HE grade 2 or greater, according to West Haven criteria.
Gastrointestinal bleeding	Portal hypertension-related bleeding requiring hospital admission.
Bacterial infections	Proven infections using standard definitions*
Acute kidney injury	Development of AKI stage 1B or greater or HRS-AKI**

AKI, acute kidney injury; HE, hepatic encephalopathy; HRS-AKI, hepatorenal syndrome-acute kidney injury.
*see Table S4.
**see reference.[82]

avoided. However, using ACLF as an endpoint in clinical trials might also have some pitfalls. First, ACLF may not always be easily identified and diagnosed if it is not specifically looked for. Second, advances in palliative care in decompensated cirrhosis currently enable a significant percentage of patients to receive medical or nursing care at home or in nursing homes. In these cases, it may be difficult to obtain the information required to diagnose ACLF in these patients. Therefore, we propose using onset of ACLF as an endpoint when data are available to make the diagnosis; or liver-related death when patients with decompensated cirrhosis die in terminal care facilities.

Hospital readmissions *per se* should not be considered as a primary endpoint or part of a composite endpoint in trials assessing the natural history of the disease because of susceptibility to multiple biases. Readmission criteria are different across countries and health systems and depend on the social support of the patient and other factors not necessarily related to the severity of liver disease. Nonetheless, readmissions *per se* should be considered as part of the secondary endpoints as they are clinically meaningful and reflect the effect of a specific intervention on the recurrence of complications. However, elective readmissions (*i.e.*, HCC therapy, large-volume paracentesis [LVP], endoscopic band ligation, among others) should be excluded.

Phase II trials

In phase II trials, the primary endpoint should focus on finding some specific signals of the effect of the drug or intervention under investigation. In proof-of-concept studies, it is important to include robust surrogate markers closely associated with hard clinical endpoints (ideally with survival). To this end, prognostic scores for survival in cirrhosis can be useful, *i.e.* changes in MELD, MELD-Na or CTP scores.[64–66] Although there is less evidence available, changes in the CLIF-C score could also be considered.[67]

In this scenario, change in hepatic venous pressure gradient (HVPG) is a useful endpoint in phase II trials in decompensated cirrhosis, as previous longitudinal studies have shown that HVPG reductions in response to therapy are predictive of clinically relevant outcomes, such as development of ascites, GI bleeding, encephalopathy and death.[68–70] However, the use of this tool as an endpoint in phase II trials may be limited to centres with specialized hepatic haemodynamic units.

In addition, biomarkers of disease progression can be considered as possible candidate endpoints in this type of studies. In this context, biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) correlate with hard clinical endpoints.[71–73] However, more information is required before accepting biomarkers as surrogate endpoints of disease progression/impairment.

Phase IIa clinical trials are pilot studies performed in a relatively small number of patients in order to obtain efficacy signals and determine safety of the investigational drug. A placebo group is not required for this phase of the study. Phase IIb clinical trials are pivotal well-established controlled trials performed on a larger number of patients in order to judge the efficacy and safety of the investigational drug. A placebo or control arm is desirable in phase IIb trials. Whenever feasible, depending on the nature of the intervention, treatment arms should be blinded to minimise possible bias.

It is necessary to comment on the importance of safety analysis of investigational agents in patients with decompensated cirrhosis. As cirrhosis is associated with abnormalities in drug metabolism, proof-of-concept studies should consider including pharmacokinetic analysis of the interventional drug, as well as recording information about possible interactions with other drugs. Adverse events related or unrelated to the study medication should always be assessed. Drug-induced liver injury and drug-induced kidney injury may be more difficult to diagnose in patients with decompensated cirrhosis with underlying hepatic and renal dysfunction.

Trials assessing interventions for the management of specific complications of cirrhosis

Ascites

Based on data from previous clinical trials[10,74–81] patients require a different therapeutic approach depending on the phenotype of ascites. When designing trials to assess new interventions for the management of ascites, patients should be divided based on 2 major phenotypes: i) diuretic-responsive ascites, and ii) refractory or recurrent

Table 5. Recommendations on characteristics of the target population and endpoints for the design of clinical trials evaluating interventions for the management of ascites.

Diuretic-responsive ascites	
Target population	
Inclusion criteria	• Stable, outpatients with either persistent grade 2 ascites or patients with grade 2 ascites responding to diuretic treatment (no specific diuretic dose required).
Exclusion criteria	• Patients with TIPS • Consider all other exclusion criteria described in Table 2.
Endpoints	
Primary endpoint	• Worsening of ascites defined as the need for LVP.
Secondary endpoints	• Survival • Time to LVP • Number of patients evolving from grade 2 to grade 3 ascites and development of refractory ascites • Hospitalizations for ascites • Diuretic-related complications or development of other complications of cirrhosis (SBP, AKI, hyponatremia) • Health-related quality of life • Treatment-related adverse events
Refractory ascites	
Target population	
Inclusion criteria	• Patients with refractory ascites as defined by currently accepted definition*
Exclusion criteria	• Patients with TIPS • Consider all other exclusion criteria described in Table 2.
Endpoints	
Primary endpoint	• Total number of LVP over a certain period of time or time to first LVP
Secondary endpoints	• Survival • Development of other complications of cirrhosis (SBP, AKI, hyponatremia) and/or sarcopenia • Health-related quality of life • Treatment-related adverse events

AKI, acute kidney injury; LVP, large-volume paracentesis; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunt.
*see Table S1 and reference.[82]

ascites. The characteristics and endpoints of these trials will depend on the target population (Table 5).

Diuretic-responsive ascites

Target population. Based on the rationale for the management of uncomplicated ascites[82,83] and data derived from previous clinical trials in the field,[76,78–81] we recommend including outpatients with diuretic-responsive ascites. A point of debate is whether a minimum diuretic dose should be required for patients to be included in these trials as this has been used as an inclusion criterion in some but not all trials.[8,11] There is no evidence to support using a minimum threshold of diuretic dose as an inclusion criterion. However, considering that guidelines do not recommend diuretic treatment for patients with grade 1 ascites and that the natural history of these patients is not well known,[82] patients with grade 1 ascites should not be included in trials. Therefore, we recommend a target population that includes patients with persistent grade 2 ascites responding to diuretic treatment, who do not require LVP. Finally, considering that TIPS modifies the pathophysiology of portal hypertension, increases renal sodium excretion and may improve prognosis,[84–86] patients with TIPS should be excluded from trials assessing interventions for the management of ascites. In this regard, there is some controversy about the possibility of including patients with ascites who had previous TIPS that is occluded or has failed. Although this could be a possibility, we believe the best option is to exclude these patients to completely rule out a possible residual effect of TIPS on the control of ascites.

Endpoints. Previous trials have used response to treatment as the primary endpoint, defined as either an improvement or worsening of ascites.[76,78–81] We recommend worsening of ascites as the most clinically relevant and unbiased primary endpoint. However, the definition of this endpoint is challenging as there are no homogeneous criteria and it may introduce some degree of subjectivity. The primary endpoint should be defined in such a way that it reflects a clinical deterioration leading to the need for a change in the management of ascites. Among all definitions of worsening of ascites used in the past,[76,78–81,87] there was an agreement that this endpoint should be defined as "need for LVP to relieve intense abdominal discomfort".

Finally, other data such as survival, health-related quality of life (HRQOL) and cost-effectiveness are recommended as the most important secondary endpoints in these trials. Other secondary endpoints that should also be assessed are time to LVP; number of patients progressing from grade 2 to grade 3 ascites; development of refractory ascites; hospitalizations for ascites; diuretic-related complications; development of other complications of cirrhosis (spontaneous bacterial peritonitis

Table 6. Recommendations on characteristics of the target population and endpoints for the design of clinical trials evaluating interventions for the management of hypervolemic hyponatremia.

Target population	
Inclusion criteria	• Patients with decompensated cirrhosis and hypervolemic hyponatremia defined as serum sodium <130 mmol/L, irrespective of the presence of symptoms.
Exclusion criteria	• Hypovolemic hyponatremia • Diseases that may induce hyponatremia other than cirrhosis (*i.e.*, hypothyroidism, heart failure, chronic kidney disease, SIADH) • Drug-induced hyponatremia • AKI stage 1B* or above • Patients with hepatic encephalopathy grade 2 or above • Consider all other exclusion criteria described in Table 2.
Endpoints	
Primary endpoint	• Improvement of hyponatremia defined as increase in serum sodium levels of at least 5 mmol/L.
Secondary endpoints	• Pre and post liver transplant survival • Occurrence of hepatic encephalopathy • Health-related quality of life • Treatment-related adverse events

AKI, acute kidney injury; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
*AKI 1B: patients with AKI stage 1 and serum creatinine at diagnosis >1.5 mg/dl (reference[82]).

[SBP], AKI, hyponatremia); or treatment-related adverse events.

Refractory or recurrent ascites

Target population. Trials should include patients with refractory ascites as defined by the currently accepted definition (see Table S1).[82] However, because the diagnostic criteria for refractory ascites may be too stringent, the target population of these studies may be modified by adding patients who, despite not meeting the criteria for refractory ascites, develop recurrent large-volume ascites requiring LVP (more frequently than 3 times a year). Patients with TIPS should be excluded.

Endpoints. Although survival is a strong primary endpoint it should probably not be the primary endpoint of choice in these trials. Interventions for the management of refractory ascites may not increase survival, particularly in patients who are not candidates for liver transplantation, but may improve the control of ascites or HRQOL,[88–90] which are clinically meaningful endpoints in this population.

Most previous clinical trials that have assessed interventions for the management of refractory ascites have used either total number of LVP/total volume of ascites removed over a certain period of time, or time to first LVP, to assess response to treatment.[10,58,74,75,77,91] There is agreement that these are the most appropriate primary endpoints to use in trials. In addition, other relevant endpoints such as survival, HRQOL, other complications of cirrhosis (SBP, AKI, hyponatremia, hepatic hydrothorax) and sarcopenia are recommended as secondary endpoints. A summary of recommendations for refractory ascites is provided in Table 5.

Hyponatremia

There is a large body of evidence showing that hyponatremia is not just a laboratory abnormality, but is associated with relevant clinical outcomes such as increased risk of HE and impaired quality of life in patients with decompensated cirrhosis.[92,93] In addition, hyponatremia is associated with increased mortality both before and after liver transplantation.[65,94–96] Thus, hyponatremia is considered a relevant complication of cirrhosis that has an important impact on patient outcomes and, therefore, should be included as a complication requiring therapy.

The distinction between hypovolemic and hypervolemic hyponatremia in patients with cirrhosis is crucial, not only from a theoretical point of view but also from a therapeutic perspective. In this consensus document, we focus only on studies that include patients with cirrhosis and hypervolemic or dilutional hyponatremia (Table 6).

Target population

Although the threshold for defining hyponatremia in the general population is established as serum sodium below 135 mmol/L,[97] classically, in patients with cirrhosis, hyponatremia has been arbitrarily defined as serum sodium <130 mmol/L.[98,99] Nonetheless, studies investigating therapeutic strategies for the management of hyponatremia and the impact of hyponatremia on clinical outcomes have used heterogeneous criteria. Some have included patients with serum sodium <130 mmol/L, while others have mainly included patients with serum sodium <135 mmol/L.[93,100] To use homogeneous criteria in future trials evaluating therapeutic options for the management of hypervolemic hyponatremia it may be appropriate to include patients with serum sodium <130 mmol/L, irrespective of the presence of symptoms. We suggest that clinical trials should stratify patients according to the severity of hyponatremia by using <125 mmol/L as a cut-off level, as it has been defined in previous studies.[100–102]

Exclusion criteria. It is essential to rule out the presence of hypovolemic hyponatremia. In addition, we recommend that patients with diseases other than cirrhosis that may induce hyponatremia should be excluded (*i.e.*, hypothyroidism, heart failure, chronic kidney disease, syndrome of

Table 7. Recommendations on characteristics of the target population and endpoints for the design of clinical trials evaluating interventions for the management of HRS-AKI.

Target population	
Inclusion criteria	• Patients with HRS-AKI defined according to the definition included in current clinical practice guidelines*
Exclusion criteria	• Consider all other exclusion criteria described in Table 2. • Patients with baseline CKD should not be excluded.
Endpoints	
Primary endpoint	• Complete response to treatment defined according to current guidelines: decrease in SCr to a value within 0.3 mg/dl (≤26.5 mmol/L) of the baseline value
Secondary endpoints	• Partial response to treatment: reduction by at least 1 AKI stage with decrease of SCr to ≥0.3 mg/dl (≥26.5 mmol/L) above the baseline value. • Decrease in serum creatinine values: 30% decrease in SCr with respect to pre-treatment value • Survival (in-hospital, 28-day and 90-day) • Need for renal replacement therapy • Recurrence of HRS-AKI after treatment

AKI, acute kidney injury; CKD, chronic kidney disease; HRS-AKI, hepatorenal syndrome-acute kidney injury; SCr, serum creatinine concentration.
*Reference.[82]

inappropriate antidiuretic hormone secretion). Moreover, other clinical conditions that can cause or modify the course of hyponatremia should be ruled out (*i.e.*, use of psychotropic drugs). Finally, patients with significant AKI (AKI 1B or greater, defined as AKI stage 1 with creatinine at diagnosis ≥1.5 mg/dl, see definition in section 2.3) and patients with HE grade 2 or above according to the West Haven criteria[103] should be excluded from these trials.

Endpoints

Based on criteria used in previous trials,[104–106] we recommend that the primary endpoint should be resolution of hyponatremia. Nonetheless, there is no accepted definition for resolution of hyponatremia in clinical trials including patients with cirrhosis. Previous clinical trials, either in the general population or in patients with cirrhosis, have based the definition of resolution of hyponatremia on: i) changes in serum sodium concentration with respect to baseline; and/or ii) achieving normal serum sodium concentration.[79,100,105–107] Considering that baseline serum sodium concentration may be very low in some patients with decompensated cirrhosis (*i.e.* <125 mmol/L) we believe using a final sodium threshold of ≥135 mmol/L for resolution of hyponatremia may be too stringent. We propose the concept of partial response, to refer to those patients with an increase of serum sodium levels of at least 5 mmol/L irrespective of the final value of serum sodium, and complete response for those who achieve levels of serum sodium >130 mmol/L.

Secondary endpoints. Hyponatremia is an important risk factor for increased morbidity and mortality in cirrhosis. There is a large amount of data showing that hyponatremia is a risk factor for the development of HE and that it is also associated with impaired quality of life and pre- and post-transplant mortality.[65,92,95] Based on this evidence, we recommend that studies aimed at assessing the efficacy of different therapies for improvement of hyponatremia should include pre- and post-liver transplant survival, improvement of quality of life and occurrence of HE as secondary endpoints. Time-to-correction of hyponatremia may also be included as a secondary endpoint. Importantly, it is well known that correcting hyponatremia too rapidly may lead to severe neurological disorders in patients with cirrhosis[108] (*i.e.*, osmotic demyelination syndrome – formerly known as central pontine myelinolysis or CPM). Therefore, including treatment-related adverse events as secondary endpoints in these trials is mandatory.

Hepatorenal syndrome-acute kidney injury

Patients with cirrhosis may develop different types of AKI.[107,109] Hepatorenal syndrome-acute kidney injury (HRS-AKI) is a characteristic type of AKI in patients with decompensated cirrhosis and is the only type of AKI that has a specific treatment.[82,110] For the purposes of this document we focus only on trials assessing interventions for the management of HRS-AKI (see Table 7).

Target population

The definition of AKI and, consequently, the definition of HRS-AKI has recently been modified.[111,112] Therefore, patients included in clinical trials of HRS-AKI should meet the definition included in current clinical practice guidelines[82] (see Tables S2 and S3).

Before including patients into clinical trials, the presence of AKI due to causes other than HRS must be ruled out. Recently, novel kidney biomarkers have emerged in this setting to help differentiate between HRS-AKI and acute tubular necrosis, with NGAL being the most promising.[73,82,113–117] Although biomarkers are still not widely available, we believe there is sufficient evidence supporting kidney biomarkers, particularly NGAL, to warrant discussion about their incorporation into the algorithm for the differential diagnosis of HRS-AKI.[82] They may also be recommended as inclusion criteria in future clinical trials.

Considering the current definition of AKI, HRS-AKI can develop in patients with baseline chronic kidney disease (CKD). In addition, given the increasing number of patients with NASH-related cirrhosis, there has been a progressive increase in the prevalence of patients with cirrhosis and CKD. Since the frequency of patients with CKD may be high, we recommend not excluding these patients from clinical trials evaluating HRS-AKI. Moreover, several studies have shown that baseline serum creatinine (SCr) levels are a predictive factor for response to treatment.[118] We recommend stratifying patients at randomization according to baseline CKD or by baseline SCr levels.

Finally, a recent study reported that the presence and severity of ACLF has a negative impact on response to treatment in patients with HRS-AKI.[119] In fact, patients with the most severe ACLF, namely ACLF grades 2 and 3 (2 or 3+ organ failures, respectively), had a lower probability of response to terlipressin and albumin compared to patients with ACLF grade 1. We suggest that in future clinical trials that include patients with HRS-AKI, patients should be stratified according to the presence and severity of ACLF at randomization.

Endpoints

It should be noted that, to date, none of the clinical trials evaluating the efficacy of treatment for HRS have included patients with HRS-AKI according to the new definition. Therefore, all recommendations are based on previous trials including patients with classical type-1 HRS.[109,120–124]

The primary endpoint for trials evaluating new strategies for the management of HRS-AKI should be complete response to treatment, which is the primary endpoint that has been widely used in previous trials in the field.[109,120–124] According to guidelines, treatment should be maintained until complete response or for a maximum of 14 days in the case of partial response or non-response.[82]

Complete response should be defined according to current guidelines as the decrease in SCr to a value within 0.3 mg/dl (≤26.5 μmol/L) of the baseline value. Partial response to treatment should be included as a secondary endpoint and be defined as regression of at least 1 AKI stage with a reduction of SCr to ≥0.3 mg/dl (≥26.5 μmol/L) above the baseline value.[82] Previous clinical trials evaluating the efficacy of treatment for type-1 HRS have used a percentage decrease in SCr as a secondary endpoint.[124] This variable has been shown to be associated with mortality. Therefore, it is suggested that a 30% decrease in SCr with respect to pre-treatment value may be included as a secondary endpoint.

Survival should also be included as a secondary endpoint (in-hospital, 28-day and 90-day survival). It is important to note that in the setting of patients with HRS-AKI, renal replacement therapy (RRT) and liver transplant influence short-term survival. Therefore, a survival assessment which accounts for these competing events (RRT, liver transplant) is necessary for such trials. Other variables that we recommend including as secondary endpoints are need for RRT and recurrence of HRS-AKI after treatment.

Bacterial infections

As far as trials specifically evaluating strategies for the management of bacterial infections are concerned, two types of trials with different patient populations can be considered: prophylactic trials and therapeutic trials. A summary of the recommendations is provided in Table 8.

Prophylactic trials

Target population. Prophylactic trials should include patients at high risk of developing bacterial infections. Currently, there is evidence of different populations at high risk of developing bacterial infections: i) patients with ascites and low protein content in ascitic fluid (<1.5 g/dl) and CTP class B or C[7]; ii) patients with variceal bleeding[125]; iii) patients surviving an episode of spontaneous bacterial peritonitis[126]; iv) patients with ACLF[127]; v) hospitalized patients at risk of nosocomial infections.[128]

Endpoints in prophylactic trials. The most appropriate primary endpoints for prophylactic trials are: i) time to the development of bacterial infections or ii) total number of infections during study period. The former would be more appropriate for short-term studies, while the latter would be appropriate for long-term studies. Death or liver transplant during follow-up should be considered as a potential competing risk for the development of infections.

Bacterial infections should be identified and diagnosed according to international standardized diagnostic criteria[129] (Table S4). Ideally, suspected but unproven infections should not be counted as endpoints in this setting.

The severity of infections, as defined by the occurrence of sepsis and/or septic shock, may be included as a secondary endpoint in prophylactic trials. The criteria for sepsis have recently been modified and are based on the sepsis-3 and quick sequential organ failure assessment (qSOFA) criteria, which have been validated in some groups of patients with cirrhosis. A diagnostic algorithm for the application of Sepsis-3 and qSOFA has been suggested[130] and is recommended for use in this setting (Fig. S1). We recommend diagnosing septic shock according to Sepsis-3 criteria.

Other clinically relevant information that we recommend analysing as secondary endpoints in prophylactic trials include: i) survival, and ii) development of organ failures and ACLF.

Table 8. Recommendations on characteristics of the target population and endpoints for the design of clinical trials evaluating interventions for the management of bacterial infections.

Prophylactic trials	
Target population	
Inclusion criteria	• Patients at high risk of developing bacterial infections: - patients with ascites and low protein content in ascitic fluid (<1.5 g/dl), - patients with variceal bleeding, - patients surviving an episode of spontaneous bacterial peritonitis, - patients with acute-on-chronic liver failure, - hospitalized patients surviving an episode of bacterial infection (at risk for nosocomial infections)
Exclusion criteria	• Consider exclusion criteria described in Table 2.
Endpoints	
Primary endpoint	• Time to the development of infections or total number of infections during study period
Secondary endpoints	• Survival • Development of sepsis or septic shock • Development of organ failures • Treatment-related adverse events
Therapeutic trials	
Target population	
Inclusion criteria	• Patients with decompensated cirrhosis and bacterial infections*
Exclusion criteria	• Consider all other exclusion criteria as described in Table 2.
Endpoints	
Primary endpoint	• Resolution of infections defined as clinical cure ± microbiological cure*
Secondary endpoints	• Survival (30-day, 90-day) • Development of sepsis or septic shock • Development of AKI and other organ failures • Number of further hospitalizations during follow-up • Treatment-related adverse events

AKI, acute kidney injury.
*see Table S4.

Therapeutic trials

Target population. According to the type of trial, the population may include a single type of infection; patients with different types of infection but with a high risk of mortality (such as sepsis or ACLF); and/or patients at high risk of treatment failure. Standard criteria should be used to diagnose infections (see Table S4). Patients with suspected but unproven infections could be included in trials while awaiting results of cultures. Thereafter, if cultures are negative, two different options are possible: i) exclude these patients from the analysis, or ii) stratify the final analysis by suspected/culture-negative infections *vs.* proven/culture-positive infections.

Endpoints for therapeutic trials. The optimal primary endpoint for therapeutic trials aimed at treating infections (such as those assessing new antibiotics) is the resolution of infection. The definition of infection resolution can rely on two concepts: clinical cure and microbiological cure.[131]

Clinical cure is defined as the investigator's assessment of clinical response and is based on the resolution of signs and symptoms of infection and clinical improvement. However, there is no consensus definition of clinical cure, which can lead to potential bias and lack of reliability. The use of an adjudication committee with pre-specified criteria may reduce this bias. The sequential use of biomarkers such as CRP or procalcitonin may be useful. Data on the evolution of CRP levels during the course of infections in patients with cirrhosis suggests that it could be a useful tool to guide adjudication.[132]

Microbiological cure is defined by negative cultures. It is more objective than clinical cure, but it is limited by the low rate of culture positivity in patients with cirrhosis and bacterial infections (particularly in SBP and pneumonia – 50–65%). Thus, microbiological cure may be a good endpoint for urinary tract infections and bloodstream infections, while clinical cure may be more suitable for pneumonia. Suggested definitions for resolution of infection based on current guidelines or FDA recommendations are shown in Table S5. Specific time points for the assessment of clinical cure and/or microbiological cure should be pre-specified according to the characteristics of the study treatment. Time to clinical/microbiological cure can also be used as a secondary endpoint.

Other secondary endpoints should include 28-day and 90-day mortality, development of AKI and other organ failures (ACLF) and number of further hospitalizations during follow-up.

Studies aimed at preventing or treating infections with antibiotics in patients with cirrhosis could potentially select multidrug resistant (MDR) bacteria, a particularly relevant concern in some parts of the world.[133,134] We suggest considering the development of infections due to MDR bacteria a potential secondary endpoint for both prophylactic and therapeutic trials.[9] Studies in the general hospital population indicate that the acquisition of carrier status could be relevant for

the spread of MDR bacteria; however, due to the paucity of studies in patients with cirrhosis there is not enough evidence to suggest that MDR carriage could be considered as a secondary endpoint.

Hepatic encephalopathy

RCTs evaluating HE should take into account that this complication is heterogeneous and dynamic, making classification difficult.[135,136] Clinical trials in HE may be categorized as: i) therapeutic trials to reverse episodes of overt HE (OHE); ii) trials to prevent OHE; and iii) trials in covert HE.[137] Covert HE will not be covered in the current position paper. A summary of recommendations for clinical trials on HE is provided in Table 9.

Therapeutic trials focused on reversing episodes of overt HE

Target population. To have an homogeneous population we recommend including patients with OHE, that is patients with grade 2 (with temporal disorientation or asterixis) to grade 4 (coma) HE, according to West Haven criteria.[103,138,139] Because of the need for sufficient time to exclude other conditions that resemble HE and also to correct for precipitating events, we recommend including only patients with an overt episode of HE lasting for a minimum of 24 hours. In addition, it is recommended that trials should include only hospitalized patients to allow for a complete assessment of the intervention on HE.

As for the exclusion criteria, a careful examination of the patient should be performed to exclude specific neurological conditions such as other metabolic encephalopathies or neuropsychiatric diseases unrelated to liver disease.[140,141]

There was agreement that patients with TIPS or spontaneous shunts should not be excluded. Nevertheless, as their clinical course and complications may have specific characteristics, we recommend stratifying the population according to presence or absence of TIPS or large spontaneous shunts. Large spontaneous portosystemic shunts have been defined arbitrarily as a shunt with a transversal diameter greater than 8 or 10 mm, in different studies, or as a total shunt area greater than 83 mm^2.[142–144] Although the information on this issue is still limited, we propose using the cut-offs of 10 mm of transversal diameter or 100 mm^2 (10×10 mm) of total shunt area for patient stratification in clinical studies on HE.

Finally, we recommend excluding patients with ACLF grade 3, with 4 or more organ failures, due to the poor short-term prognosis.[61,145] Nonetheless, because of the heterogeneity of patients with ACLF, we suggest that patients should be stratified according to presence and severity of ACLF in future clinical trials.

Endpoints. Complete resolution of HE defined as the absence of OHE after a specific period of time (*i.e.*, 72 hours) should be the primary endpoint. Most recent trials use time to resolution of HE as the primary endpoint. However, we consider that the frequency of patients achieving complete resolution of HE is more suitable as a primary endpoint because it is more clinically relevant from the patient perspective.

Secondary endpoints. Time to resolution of HE may be considered as a secondary endpoint. Other secondary endpoints that we recommend considering include: i) improvement of at least 2 grades in the severity of HE according to West Haven score; ii) length of hospital stay; iii) 28-day and 90-day survival. Finally, changes in ammonia levels and in neuropsychiatric test measures could also be considered, but only as a secondary endpoint.

Clinical trials focused on prophylaxis of HE

Target population. Two different populations can be defined within this category: i) patients who have recovered from the first bout of OHE, for whom standard of care is non-absorbable disaccharides; ii) patients with recurrent HE (2 or more bouts of OHE within 6 months), for whom the current standard of care is non-absorbable disaccharides plus rifaximin.[103,139]

Endpoints. Recent clinical trials in this setting use either time to next episode of HE or number of episodes of HE as a primary endpoint (see Table 9). We consider the number of episodes of OHE requiring hospital admissions in a defined period of time as the most appropriate primary endpoint for prophylactic trials. Time to the next episode of HE and the severity of episodes of HE according to West Haven criteria grade could be considered as secondary endpoints.

Acute-on-chronic liver failure

One of the major issues to be addressed when designing trials on ACLF is the lack of consensus on diagnostic criteria. Indeed, various definitions of ACLF have been developed worldwide,[61,62,146] thus leading to differences in the patient populations included across studies.

Before a common definition of ACLF is arrived at, we recommended using the most up-to-date local definition when designing clinical trials, according to the recommendations or consensus of the main international scientific societies. Nevertheless, in our opinion, taking into consideration all definitions, it seems advisable to use diagnostic criteria based on the combination of acute decompensation of cirrhosis and at least 1 organ failure.

In the setting of ACLF, studies may be divided according to the type of intervention: i) therapeutic trials or ii) prophylactic trials aimed at preventing

Table 9. Recommendations on characteristics of the target population and endpoints for the design of clinical trials evaluating interventions for the management of HE.

Therapeutic trials (OHE)	
Target population	
Inclusion criteria	• Patients with persistent episodes of overt hepatic encephalopathy (≥24 hours) grade 2 or above according to West Haven classification.
Exclusion criteria	• Other neurological conditions (metabolic encephalopathies, neuropsychiatric diseases). • Patients with previously known neurological or psychiatric disorders • Normal serum ammonia levels. • Patients with ACLF with ≥4 organ failures. • Patients with GI bleeding within the last 5 days. • Consider other exclusion criteria as described in Table 2. ***Patients with TIPS or spontaneous shunts should not be excluded, except if TIPS has been performed within the last 3 months.*
Endpoints	
Primary endpoint	• Complete resolution of HE defined as the absence of overt hepatic encephalopathy.
Secondary endpoints	• Time to resolution of HE • Survival (28-day, 90-day). • Improvement of at least 2 grades in the staging of HE • Length of hospital stay • Treatment-related adverse events
Prophylactic trials	
Target population	
Inclusion criteria	• Patients who have recovered from the first acute episode of OHE or patients with recurrent HE (≥2 episodes of acute HE in 6 months)
Exclusion criteria	• Consider same exclusion criteria as for therapeutic trials.
Endpoints	
Primary endpoint	• Number of episodes of OHE requiring hospital admission (in a predefined period of time).
Secondary endpoints	• Time to next episode of OHE • Severity of episodes of OHE • Survival (28-day, 90-day). • Health-related quality of life. • Treatment-related adverse events

ACLF, acute-on-chronic liver failure; GI, gastrointestinal; HE, hepatic encephalopathy; OHE, overt hepatic encephalopathy; TIPS, transjugular intrahepatic portosystemic shunt.

the development of ACLF in patients at risk. A summary of the recommendations for ACLF is provided in Table 10.

Therapeutic trials

Target population. ACLF is a very dynamic syndrome and is associated with high short-term mortality. In this regard, considering the short time frame that must be considered and the subsequent need for large cohorts of patients, we suggest being *inclusive* when selecting patients. We suggest not excluding comorbidities or clinical conditions that potentially only modify the long-term prognosis of patients in the setting of ACLF.

The severity of ACLF and the number of concomitant organ failures lead to high heterogeneity within study populations, with different prognoses and mortality rates. Patients with 4 or more organ failures have very high short-term mortality rates, ranging from 50 to 80%.[61,147,148] It should be noted that mortality also differs according to the type of organ failure.[149] Therefore, patients with ACLF and >3 organ failures, particularly those with organ failures leading to high mortality (*i.e.*, respiratory failure) should be excluded from therapeutic trials, since their short-term mortality is exceedingly high.[150] In addition, considering the heterogeneity of this population, we suggest stratifying patients according to the severity of ACLF.

Given the rapid clinical course of this condition,[151] the time frame for including patients with ACLF in trials warrants specific comment. Ideally, therapeutic trials for ACLF should enter patients into studies soon after a diagnosis is made. We believe that a screening period of 24 hours from diagnosis, followed by randomization and start of treatment within the next 24 hours is reasonable and feasible. However, in a real-life scenario, patients with ACLF are relatively frequently referred from other hospitals to tertiary care centres a variable period after the diagnosis of ACLF. In this situation, if ACLF persists at the time of referral, we recommend that patients could still be included in therapeutic trials; however, patients should be stratified according to the time from the diagnosis of ACLF to the initiation of treatment.

Endpoints. Short-term survival (*i.e.* in-hospital and 28-day) is the most appropriate primary endpoint of any therapeutic trial on ACLF.

Secondary endpoints. As secondary endpoints, we suggest including changes in ACLF stage (worsening or improvement), according to the number of organ failures and/or changes in the CLIF-SOFA score. Although there is evidence supporting the

Table 10. Recommended characteristics of the target population and endpoints for the design of clinical trials evaluating interventions for the management of ACLF.

Target population	
Inclusion criteria	• Use the most updated international definition for ACLF, according to the recommendations of the main international scientific societies
Exclusion criteria	• Patients with ACLF with 4 or more organ failures. • Comorbidities or clinical conditions that modify only the long-term prognosis may not be relevant in the setting of ACLF and, thus, patients with these conditions should not be excluded
Endpoints	
Primary endpoint	• Short-term survival (in-hospital and 28-day)
Secondary endpoints	• Changes in ACLF stage (worsening or improvement) • Treatment-related adverse events

ACLF, acute-on-chronic liver failure.

prognostic importance of the evolution of ACLF after 3–7 days from diagnosis,[151] we consider that evidence is not strong enough to recommend a specific timeframe for the evaluation of improvement/worsening of ACLF in all therapeutic trials. Therefore, a suitable secondary endpoint should be "time to" worsening or improvement in ACLF stages or specific organ failures.

Since liver transplantation may be an effective therapeutic strategy in patients with ACLF, liver transplantation should be considered a competing event for death, and transplant-free survival should be evaluated as a secondary endpoint.

Prophylactic trials

Because of high mortality rates in patients with ACLF, the prevention of this condition in patients at risk is of major relevance. Unfortunately, since the predictive factors for ACLF development are still ill-defined, defining the population at risk for inclusion in prophylactic trials is still challenging.

Recently, two prospective observational studies collected data about clinical and laboratory predictors of ACLF, both in outpatients[25] and in hospitalized patients with cirrhosis and acute decompensation.[152] However, we agree that, to date, there is not enough evidence to propose specific criteria to define patients at risk of developing ACLF who should thus be included in trials aimed at evaluating prevention strategies. Therefore, further results from multicentric prospective trials are needed to appropriately address this issue.

Patient-reported outcomes

When investigating a new intervention potentially able to modify the natural history of cirrhosis or its complications, the evaluation of patient-reported outcomes (PROs), patient preferences and HRQOL should also be considered. The collection of HRQOL data is part of cost-effectiveness and cost-utility analysis, which are increasingly recognized as a useful guide for clinical decision-making and health policies. Thus, we recommend that, when designing interventional RCTs for patients with decompensated cirrhosis, the evaluation of HRQOL should be included, whenever possible, among secondary endpoints. HRQOL should be directly reported by patients themselves and not assessed by an external observer or interpreted by a proxy (*e.g.* clinician or caregivers) to avoid sources of bias.[153,154]

Target population

HRQOL should be evaluated in any subgroup of patients with decompensated cirrhosis. However, HRQOL assessment may be unreliable in the presence of OHE grade II or higher; in this situation, HRQOL evaluation should be delayed until improvement of the patient's cognitive status has been reached. Similarly, patients experiencing life-threatening complications of cirrhosis or other complications leading to hospital admission should be surveyed only after stabilisation of their clinical conditions and hospital discharge.[88]

Tools for HRQOL assessment

Several tools are available to help quantify HRQOL that are based on self-administered questionnaires to evaluate a wide range of aspects of life. Questionnaires can be classified as: "generic", applicable to any group of patients; "disease-specific", designed to explore patients affected by a specific disease; and "domain-specific" that focus on one specific area of interest.

At present, there is insufficient evidence to recommend the use of one tool over the others. However, we recommend the use of a reliable and validated generic measure (*e.g.* SF-36 or EQ-5 D), in combination with a disease-specific one (*e.g.* CLDQ or LDQOL).[155,156] It is important to select a questionnaire for which norms are available for the country where the study is developed. In addition, it is advisable to avoid questionnaires with long completion times, both because of feasibility in the clinical context and the risk of poor patient compliance. Similarly, there is consensus that the use of a single questionnaire (either a robust generic tool or a well-validated disease-specific one) is acceptable, albeit suboptimal when HRQOL assessment is not a primary endpoint.[11,88,136]

Functional and nutritional assessment

Along with classical clinical trial endpoints, a special mention should be reserved for functional and nutritional assessment tools. Malnutrition,

sarcopenia and physical frailty often characterize advanced phases of cirrhosis and contribute to the impairment of patients' HRQOL, as well as to increased risk of complications, decompensation and death.[157–159] Consequently, we recommend assessing sarcopenia and physical frailty at study inclusion and using them as secondary endpoints in clinical trials of decompensated cirrhosis, whenever possible. A variety of strategies and models have been proposed for identification of sarcopenia and frailty. There was agreement that we still cannot recommend one preferred method based on the available evidence. However, among different methods, the liver frailty index has emerged as an objective, fast and easy to perform method that correlates with frailty and predicts mortality in patients with cirrhosis.[160,161]

Other assessments

In trials evaluating new strategies for the management of patients with decompensated cirrhosis the evaluation of cost-effectiveness is also important (see supplementary material).

Abbreviations

ACLF, acute-on-chronic liver failure; AIH, autoimmune hepatitis; AKI, acute kidney injury; CKD, chronic kidney disease; CRP, C reactive protein; CHE, covert hepatic encephalopathy; ELPA, European Liver Patient Association; GI, gastrointestinal; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HE, hepatic encephalopathy; HRQOL, health-related quality of life; HRS-AKI, hepatorenal syndrome - acute kidney injury; ICU, intensive care unit; LVP, large-volume paracentesis; MELD, model for end-stage liver disease; MELD-Na, MELD-sodium; MDR, multidrug resistant bacteria; NASH, non-alcoholic steatohepatitis; NGAL, neutrophil gelatinase-associated lipocalin; OHE, overt hepatic encephalopathy; RCT, randomized controlled trial; RRT, renal replacement therapy; SBP, spontaneous bacterial peritonitis; SCr, serum creatinine; SOFA, sequential organ failure assessment score; TIPS, transjugular intrahepatic portosystemic shunt; UTI, urinary tract infection.

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Conflict of interest

ES, CA, RH, EP, SM, CF, RM have nothing to declare. The other authors declare the following: PG has participated on advisory boards for the following: Grifols, Gilead, Intercept, Mallinckrodt and Ferring. He has received Investigator promoted research grants from Mallinckrodt, Gilead and Grifols. All outside the submitted work. SM research group has received consultancy fees and/or research donations from Merz Pharmaceuticals GmbH, Norgine, Alfasigma and Umecrine Cognition. VV speaking fees from Intercept Pharmaceuticals; advisory board fees from Promethera Biosciences PC Grifols SA: advisory board, speaking bureau; Octapharma. SA: speaking bureau; Takeda SA: speaking bureau. JT: reports other from - Gore, Bayer, Alexion, MSD, Gilead, Intercept, Norgine, Grifols, Versantis, Martin Pharmaceuticals outside the submitted work. PSK is Principal Investigator of the Sequana Medical sponsored POSEIDON study in North America. He does not receive any personal remuneration. HW declares he is currently and employee of EVOTEC and has shares in Sanofi, both of which are unrelated to the work submitted. JGA reports grants from Gilead, lecture fees from Ferring, and consulting fees from Gilead, Pfizer, Intercept, Boehringer-Ingelheim, Lupin and Genfit outside the submitted work. UB Research funding from South African PSC Patient Foundation, Netherlands gastroenterology and hepatology (MDLS) Foundation, Investigator initiated research funding from Intercept, USA. AK Speaker and advisory board: Norgine, Siemens.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualization: PG; ES; EP Data review: ES; EP; DC; SP; OR; MS; FU; KW; GZ. Data discussion; consensus meeting: ES; EP; DC; SP; OR; MS; FU; KW; GZ, CA; UB, PC; RM; CF; JT; VV; MS; FT; SM; AK; MK; HW; JG; PK, PG.

Statistical considerations: MS; FT; RH. Writing – drafting of the manuscript: ES; EP; DC; SP; OR; MS; FU; KW; GZ. Supervision: CA; UB, PC; RM; CF; JT; VV; PG. Critical review of the manuscript: ES; EP; DC; SP; OR; MS; FU; KW; GZ, CA; UB, PC; RM; CF; JT; VV; MS; FT; SM; AK; RH; MK; HW; JG; PK, PG. Funding acquisition, project administration: PG.

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Supplementary data

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Author names in bold designate shared co-first authorship

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