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[Intervention Protocol]

Liver support systems for adults with acute-on-chronic liver failure

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the benefits and harms of liver support systems for adults with acute-on-chronic liver failure.

BACKGROUND

Description of the condition

Acute-on-chronic liver failure specifies a distinct, abrupt, life-threatening worsening of a clinical syndrome that develops in people with acute decompensation of cirrhosis or chronic liver disease (Moreau 2013; Zaccherini 2020). The term acute-on-chronic liver failure emerged from studies showing the development of a syndrome associated with a high risk of short-term death (i.e. death < 28 days after hospital admission) in people with acutely decompensated cirrhosis (Arroyo 2020). Currently, four scientific organisations, i.e. the European Association for the Study of the Liver - Chronic Liver Failure, North American Consortium for the Study of End-stage Liver Disease, Chinese Group on the Study of Severe Hepatitis B, and Asian Pacific Association for the Study of the Liver, proposed the definitions and diagnostic criteria of acute-on-chronic liver failure (Appendix 1). These proposals are based on seven items: (i) the category of the article(s) defining acute-on-chronic liver failure, (ii) patients considered in the definition, (iii) precipitating disorders, (iv) major organ systems considered for the definition, (v) basis of the definition, (vi) definition and stratification of acute-on-chronic liver failure, and (vii) short-term mortality rate of acute-on-chronic liver failure according to stratification (Zaccherini 2020). The wide variation in the definitions of acute-on-chronic liver failure across different continents is probably due to non-agreement on whether acute-on-chronic liver failure is a distinct syndrome or a terminal stage in all people with cirrhosis (Ginès 2021). However, and by consensus, acute liver failure is defined as an acute hepatic insult manifesting as jaundice (serum bilirubin ≥ 5 mg/dL (85 micromol/L) and coagulopathy (international normalised ratio (INR) ≥ 1.5 or prothrombin activity < 40%)) complicated within four weeks by clinical ascites or encephalopathy, or both, in a person with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, and associated with high 28-day mortality (Sarin 2019).

The global prevalence of acute-on-chronic liver failure among patients admitted with decompensated cirrhosis is 35% (95% confidence interval (CI) 33% to 38%). It is based on a systematic review and meta-analysis with 30 cohort studies and 43,206 people with acute-on-chronic liver failure and 140,835 without acute-on-chronic liver failure (Mezzano 2022).

Bacterial infection, gastrointestinal bleeding, acute alcoholism, drug-induced, and viral hepatitis are precipitating factors of acute-on-chronic liver failure (Arroyo 2016; Devarbhavi 2019; Gustot 2019; Hernaez 2019; Kumar 2020; Li 2020; Masnou 2022; Shi 2015; Sundaram 2021; Wu 2018; Xiu 2019). Studies report that existing acute-on-chronic liver failure cases without evident precipitating events, are probably related to intestinal translocation of bacterial products (Casulleras 2020; Kim 2021). These cases are called gut dysbiosis and have a significant predictive value for mortality (Chen 2015; Zhang 2018). Consensus exists that bacterial infection-triggered acute-on-chronic liver failure is associated with increased mortality (Fernández 2018; Fisher 2021; Masnou 2022; Mücke 2018; Rodina 2021; Sundaram 2021; Wong 2021). A hyperinflammatory state may be the foundation to explain the high risk of mortality in acute-on-chronic liver failure people with infection (Casulleras 2020; Chen 2019; Clària 2016). Hospitalised people with COVID-19 infection and cirrhosis have a high mortality risk (Satapathy 2021).

People with acute-on-chronic liver failure have a poor prognosis (Ginès 2021). The short-term mortality varies according to the degree of severity. The mortality at 28 days varies 23%, 31%, and 74% for grade 1, grade 2, and grade 3, respectively (Zaccherini 2020). A systematic review and meta-analysis about the global burden of acute-on-chronic liver failure conducted with a studies search between 3 January 2013 to 7 March 2020 reported that, over the world, the 90-day mortality was high (58%, 95% CI 51% to 64%), and the highest mortality was in South America, 73% (Mezzano 2022). The European Foundation for the Study of Chronic Liver Failure score, platelet to white blood cell ratio, and albumin-bilirubin score can better predict 28-day mortality in people with acute-on-chronic liver failure (Liu 2020). In contrast, the Model for End-Stage Liver Disease score has worse predictability (Liu 2020). The European Foundation for the Study of Chronic Liver Failure score is considered the best prognostic model among these models (Liu 2020). Platelet to white blood cell ratio may be a simple and valuable tool to predict 28-day mortality in acute-on-chronic liver failure people (Liu 2020). There is no consensus about what is the best score to predict mortality in people with acute-on-chronic liver failure (Balcar 2021; Dhiman 2014; Silva 2015; Zhang 2015).

The organ support and treatment of a precipitating event are basic therapy to treat people with acute-on-chronic liver failure (Kumar 2020). Acute-on-chronic liver failure is a life-threatening condition and can, in most cases, be overcome only by orthotropic liver transplantation (Karvellas 2021; Putignano 2017; Shah 2021). However, transplantation is expensive, and the donor organ is a significant limitation. Therefore, it has led to extracorporeal liver support devices as a therapeutic option (Baquerizo 2015; Karvellas 2021; Larsen 2019; Shah 2021). The essence of extracorporeal liver systems is to support patients. In contrast, liver donors are procured for transplantation, or the patient's liver is regenerated to regain organ function (Baquerizo 2015).

Description of the intervention

There are three types of liver support devices (Baquerizo 2015; Brumer 2020; Pless 2010; Stange 2020; van de Kerkhove 2004; Xie 2021).

1. Artificial liver support, also known as non-biological or cell-free techniques.

- Haemodialysis.
- Plasma exchange.
- Immobilised enzyme haemoperfusion.
- Advanced organ support.
- Single-pass albumin dialysis.
- Charcoal.
- Resin haemoperfusion.
- Molecular adsorbent recirculating system (MARS).
- Prometheus (fractionated plasma separation and adsorption system, FPSA).
- Li-non-bioartificial liver (Li-NABL) (Xie 2021).

All the above types of liver support devices use blood purification technology through membranes, adsorbents, and other biological materials (Xie 2021). Detoxification is the focus of these support systems (Zhang 2021b). The artificial support systems for liver failure are associated with several either serious or non-

serious adverse events, e.g. bleeding, hypotension, infections, and haemolysis (Xu 2021).

2. Biological extracorporeal liver perfusion devices incorporating whole extracorporeal animal or human livers.

- Li-bioartificial system.
- Bioartificial liver support system.
- Amsterdam Medical Center bioartificial liver (Zhang 2021a).

These support systems or devices can partially or totally perform liver functions such as detoxifying metabolites, protein synthesis, and producing substances necessary for digestion. The cell source and bioreactors are the crucial elements of this type of support device. The bioreactor is the critical device in the bioartificial liver. It provides a suitable environment for the hepatocytes to survive and perform liver cells' functions as close as possible to their performance in vivo (Zhang 2021a).

The source of hepatocytes varies in these support devices. In the Li-bioartificial system, the sources are diverse: primary human liver cells, primary porcine hepatocytes, tumour-derived liver cell lines, immortalised hepatocytes, and stem cells. In contrast, the bioartificial liver support system uses porcine hepatocytes (Zhang 2021a). The Amsterdam Medical Center bioartificial liver operates with fresh porcine hepatocytes (Zhang 2021a). To describe the characteristics of the bioreactors employed in these three support systems is beyond the scope of this Cochrane Review.

3. Bioartificial hybrid liver support.

This system combines the properties of the artificial and the biological liver support systems. Therefore, it takes over the liver function in terms of detoxification, synthesis, and biological transformation functions (Zhang 2021b). This combination supplies the nearest approach to an ideal artificial liver for hepatic-failure patients (Zhang 2021b). There are four types of these devices.

- HepatAssist system.
- Modular extracorporeal liver support (MELS).
- Amsterdam Medical Center bioartificial liver (AMC-BAL).
- Li-hybrid artificial liver support system (Li-HAL) (Zhang 2021b).

How the intervention might work

Overall, the extracorporeal liver support systems have three aims: to provide detoxification and synthetic function during liver failure, to remove or reduce the production of proinflammatory cytokines to correct the systemic inflammatory response of liver failure, and to provide temporary liver function until either functional recovery occurs or an organ is available for transplantation (Baquerizo 2015; Nyberg 2012). However, the artificial systems only clear toxins without providing synthetic support (Baquerizo 2015; Nyberg 2012). In contrast, the bioartificial systems combine detoxification with synthesis and regulative functions, i.e. the synthetic and biochemical production capabilities designed to restore metabolic stability (Villarreal 2019). The hybrid system combines the clearance capabilities of non-biological systems with the synthesis capabilities of the bioartificial systems (Zhang 2021b).

Bao and colleagues have authored a narrative review on the working mechanisms of various support systems, for treating people with liver failure (Bao 2021).

Why it is important to do this review

This review is important for several reasons. There is uncertainty about the evidence on artificial support systems, bioartificial support systems, and bioartificial hybrid liver support for people with acute-on-chronic liver failure. Two reviews had registered protocols in PROSPERO, an international database of prospectively registered systematic reviews in health and social care (Alshamsi 2020; Ocskay 2021). The primary focus of these reviews differed. Alshamsi and colleagues included people with either acute or acute-on-chronic liver failure (Alshamsi 2020). The other review included people with acute-on-chronic liver failure (Ocskay 2021). Two studies on people with acute-on-chronic liver failure were conducted without a protocol registration (Bañares 2019; Shen 2016). One narrative review in people with acute-on-chronic liver failure analysed biochemical outcomes, i.e. bilirubin, creatinine, urea, and gamma-glutamyl transferase (Tandon 2021). The included population in six studies was people with either acute or acute-on-chronic liver failure (Alshamsi 2020; He 2015; Khuroo 2004; Stutchfield 2011; Tandon 2021; Zheng 2013). The extracorporeal liver support systems varied among the studies; bioartificial support systems (He 2019), molecular adsorbent recirculating systems (Bañares 2019; He 2015; Khuroo 2004), single-pass albumin dialysis support systems (Tandon 2021), and any support system (Alshamsi 2020; Ocskay 2021; Stutchfield 2011; Zheng 2013). Only three of the studies assessed the risk of bias in the included trials, using Cochrane's methodology (Alshamsi 2020; Ocskay 2021; Stutchfield 2011). Since the publication of our Cochrane Hepato-Biliary Group systematic review on artificial and bioartificial support systems for people with liver failure (Liu 2004), a number of relevant randomised clinical trials have been published and need a critical appraisal. The updated consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL) suggest the following (Sarin 2019).

- Plasma exchange appears to be a promising and effective bridging therapy in people with acute-on-chronic liver failure to liver transplant or spontaneous regeneration. However, the quality of the evidence was assessed as low or very low (Sarin 2019). This means that further research is very likely to impact our confidence in the estimate of effect and may change the estimated effect.
- Plasma exchange can be safely undertaken in specialised liver units in people with acute-on-chronic liver failure. The quality of the evidence for this recommendation was moderate (Sarin 2019). This means, that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimated effect.
- Plasmapheresis may be considered a specific therapy for people with Wilson's disease and people with a severe flare of autoimmune liver disease (deemed unsuitable for steroids). The quality of the evidence for this recommendation was moderate (Sarin 2019). This means, that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimated effect.
- Combination of plasma exchange with therapies to potentiate liver regeneration should be evaluated in people with acute-on-chronic liver failure. Further research is very likely to impact

our confidence in the estimate of effect and may change the estimated effect. Any estimate of effect is uncertain (Sarin 2019).

The clinical benefits and harms of any bioartificial hybrid liver support system are unknown. Accordingly, we have split our Cochrane Review (Liu 2004) into two reviews: one, on acute liver failure (Martí-Carvajal 2022) and another on acute-on-chronic liver failure. Moreover, we will employ updated Cochrane methodology.

Hopefully, this systematic review will provide more robust conclusions as to the use of support systems in people with acute-on-chronic liver failure and facilitate better decision-making in clinical and epidemiological practice.

OBJECTIVES

To assess the benefits and harms of liver support systems for adults with acute-on-chronic liver failure.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials with a parallel-group design irrespective of publication status and format of publication (i.e. trials reported as full text, published as abstract only, and unpublished data) (McKenzie 2022a). We will not apply any limitation by language, country, year of publication, or outcomes assessed.

We do not expect to find cross-over or cluster-randomised trials because their study designs are not proper for the subject of our review. Though quasi-randomised studies can be assessed for bias using the RoB 2 tool (Sterne 2019), we will not include quasi-randomised studies in our review for benefits assessment as the allocation method is not truly random, nor will those studies be assessed for risk of bias. However, we will make a table to show adverse events as they are reported and describe them in the discussion section.

Types of participants

Adults (≥ 18-year-old) of any sex, diagnosed with acute-on-chronic liver failure, regardless of aetiology.

We will accept trial authors' definition of acute-on-chronic liver failure. Acute-on-chronic liver failure is defined as an acute hepatic insult manifesting as jaundice (serum bilirubin ≥ 5 mg/dL (85 micromol/L) and coagulopathy (INR ≥ 1.5 or prothrombin activity < 40%), complicated within four weeks by clinical ascites or encephalopathy, or both, in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, and associated with high 28-day mortality (Sarin 2019).

If a trial includes a subset of at least 10 participants fulfilling the inclusion criteria of our review, but relevant data in regard to these participants are lacking, then we will aim to obtain the data from study authors. If we cannot obtain the required data, we will exclude the trials, providing the reason(s) for exclusion. If the subset of participants with missing data is less than 10 participants, we will not contact trial authors, and we will exclude the trial, as small trials tend to overestimate treatment effects (Gluud 2008; Kjaergard 2001).

Types of interventions

We plan to compare the below experimental interventions versus the below conventional supportive therapy.

- Experimental interventions.
  - Artificial liver support system.
  - Bioartificial liver support system.
  - Bioartificial liver support: hybrid techniques.
- Control interventions.
  - Conventional supportive treatment.

We will accept supplementary interventions if both the experimental and control groups received the same supplementary interventions. We will investigate if the intervention effect is modified by the addition of the supplementary intervention through subgroup analyses (Deeks 2022). We will also report and discuss our findings.

Types of outcome measures

We plan to assess the following outcomes.

Primary outcomes

- Overall survival.
- Proportion of people with serious adverse events. Serious adverse events defined as any untoward medical occurrence that resulted in death, congenital anomaly or birth defect, was life-threatening, led to persistent or significant disability, hospitalisation, prolonged hospitalisation, or is a medically important event or reaction (ICH-GCP 2016). If the trialists do not use the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) definition, we will include the data if the trialists use the term 'serious adverse event'. Otherwise, we will follow the definition to select the serious adverse events from those reported as adverse events.

Secondary outcomes

- Quality of life. We will accept any validated scale used by trialists, such as Short Form (SF)-36 (Ware 1992) or chronic liver disease questionnaire (Younossi 1999). As we cannot say which of the two tools is the most used one, we will either combine their scores if they measure the same underlying concept or select the quality of life tool used in the trials, with the highest number of participants providing data for an outcome. If trials have used other validated tools to measure the quality of life, we will also consider combining their data. Due to the absence of specific scales for measuring the quality of life in patients with acute liver failure, we will accept the ones used by the trials, and we will find further guidance in Chapter 18 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Johnston 2022). We will consider the absence of specific scales as a limitation of the evidence in the discussion section of the review.
- Proportion of people with hepatic encephalopathy.
- Proportion of people with multi-organ failure.
- Proportion of people with adverse events considered non-serious (ICH-GCP 2016).

The most clinically relevant time point to assess overall survival in people with acute liver failure is considered to be by day 28 (Putignano 2018; Roberts 2004). Therefore, the primary time point for our main analysis of overall survival will be by day 28. We will

perform our secondary analyses on overall survival at 90 days and the longest follow-up. As to the remaining outcomes, the primary time point for our main analysis will be at the longest follow-up.

We will not consider any economic analysis in this Cochrane Review. However, we will mention related information to the economy in the discussion section.

Search methods for identification of studies

To minimise bias in our search results, we will follow the guidance in Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2022) and in PRISMA-S (Rethlefsen 2021) to plan and describe the search processes.

Electronic searches

We will search the Cochrane Hepato-Biliary Group (CHBG) Controlled Trials Register (searched internally by the CHBG Information Specialist via the Cochrane Register of Studies Web), the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE Ovid, Embase Ovid, LILACS (Latin American and Caribbean Health Science Information database) (Bireme), Science Citation Index Expanded (Web of Science), and Conference Proceedings Citation Index-Science (Web of Science). The latter two will be searched simultaneously through the Web of Science.

Appendix 2 contains the preliminary search strategies with the expected date range of the searches. We will provide the actual date of the electronic searches at the review stage.

We will impose no restriction on language of publication or publication status.

Searching other resources

We will search the US Food and Drug Administration (FDA; www.fda.gov), European Medicines Agency (EMA; www.ema.europa.eu/ema/), World Health Organization International Clinical Trial Registry Platform (www.who.int/ictrp), US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov/), ISRCTN registry (www.isrctn.com/), as well as relevant manufacturers' websites for trial information, i.e. State Key Laboratory for Diagnosis & Treatment of Infectious Diseases (www.zju.edu.cn/english/2018/0520/c19974a812273/page.htm) whose chief is Dr Lanjuan Li, and who created the Li's non-bioartificial liver system. We will also contact relevant individuals and organisations for information about unpublished or ongoing studies.

We will search relevant grey literature sources such as reports, dissertations, theses, and conference abstracts, e.g. in the System for Information on Grey Literature in Europe 'OpenGrey' (www.opengrey.eu/) or in Google Scholar.

We will use the PubMed/MEDLINE 'similar articles search' tool on all included studies. We will manually check citations and reference lists of the included studies, and any relevant systematic reviews identified.

We will also search for and examine any relevant retraction statements and errata in the Retraction Watch Database (Retraction Watch Database 2022) for information as errata can reveal important limitations or even fatal flaws in included studies (Lefebvre 2022).

We will contact authors of included trials for missing data and for information on additional published or unpublished trials.

We will provide the actual dates of searching other resources at the review stage. We will use relevant to our review items from the PRISMA-S checklist to ensure that we have reported and documented our searches as advised (PRISMA-S Checklist; Rethlefsen 2021).

Data collection and analysis

We will follow the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a).

Selection of studies

We will use Covidence (Covidence 2021) to manage our search results. We will pilot a data extraction form on several trials.

Three review authors (Arturo Martí-Carvajal (AMC), Diana Monge Martín (DMM), Ezequiel Mauro (EM)) will independently and in duplicate screen titles and abstracts for inclusion of all the potential studies identified from the search. We will code the studies as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there are any disagreements, another author will be asked to arbitrate (Christian Gluud (CG) or Lise Lotte Gluud (LLG)). We will retrieve the full-text study publication, and three review authors (AMC, Cristina Elena Martí-Amarista (CEMA), EM) will independently screen the full text and identify the trials for inclusion, and also identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult the same arbitrators (CG or LLG). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA-S flow diagram and 'Characteristics of excluded studies' table (Page 2021a; Page 2021b; Rethlefsen 2021).

We will check whether any of the identified trials have been retracted (Retraction Watch Database 2022). We will list the trials which were retracted in the excluded studies section.

For screening of non-English language publications, we will, in the first instance, use Google Translate (translate.google.com) to assist eligibility assessment. If needed, we will seek translators through the CHBG to assist with assessing eligibility of studies and, if eligible, assist with data extraction by native speakers.

If during the selection of trials, we identify observational studies (i.e. quasi-randomised studies, cohort studies, or patient reports) that report adverse events associated with the artificial liver support system, bioartificial liver support system, or bioartificial liver support: hybrid techniques, we will review these studies for report on adverse events. We will not specifically search for observational studies for inclusion in this review, which is a limitation of our review. We will acknowledge the limitations of this approach in the discussion section.

We will not analyse the extracted data on harms from non-randomised clinical studies together with the data on harms from

the randomised clinical trials included in the review; neither we will assess the bias risk in these studies. However, we will refer to the extracted narrative data on harm with a link to a table in an appendix. We are aware that the decision not to search for all observational studies might bias our review towards assessment of benefits and might overlook certain harms such as late or rare harms. If we demonstrate benefits from the use of artificial liver support system, bioartificial liver support system, or bioartificial liver support: hybrid techniques in adults with acute liver failure, then a systematic review of harms of artificial liver support system, bioartificial liver support system, or bioartificial liver support: hybrid techniques in adults with acute liver failure in observational studies will be recommended (Storebø 2018).

Data extraction and management

We will use an electronic data collection form for study characteristics and outcome data which would be piloted on at least six studies in the review. Three review authors (AMC, DMM, Susana Nicola (SN)) will extract study characteristics from included studies. EM, CEMA, and Gabriella Comunián-Carrasco (GCC) will check all this information. In case of disagreements, we will ask any of the two authors (CG or LLG) to arbitrate. If further clarifications are needed to extract data correctly, we will contact trial authors.

We will extract the following study characteristics.

- Methods: study design, the total duration of the study, follow-up period, details of any 'run in' period, number of study centres and location, type of trial (superiority, equivalence, or non-inferiority trial), and date of the study.
- Participants: diagnosis, number (N) randomised, N lost to follow-up/withdrawn, N analysed, mean age, age range, sex, hepatic encephalopathy stage, international normalised ratio (INR), creatinine, bilirubin, lactate, factor V, ammonia, alanine transaminase, aspartate aminotransferase, and phosphates serum levels, acute kidney injury, acute liver failure aetiology, number of days of the interval between the onset of jaundice and hepatic encephalopathy, type of support system (artificial, bioartificial, or hybrid), number of procedure used, inclusion criteria, and exclusion criteria.
- Interventions: intervention, comparison, supplementary interventions, excluded medications, and adverse events. Appendix 3 presents details of the intervention description (Hoffmann 2014; Hoffmann 2017).
- Outcomes: primary and secondary outcomes specified and collected, and time points reported. Any other outcomes measured. If the trial protocol is available, we will use it for later comparison during risk of bias assessment.
- Notes: identifier trial number register (De Angelis 2004, trial conduction dates, a priori sample estimation, financial disclosures, notable conflicts of interest of trial authors, eventual other disclosures, ethics committee approval), and funding/support.
- Journal title in which the trial report is published.
- Information needed to assess bias (e.g. any deviations from intended interventions, were data imputed for key outcomes, stopping a trial early for benefit).
- Information needed to assess GRADE (e.g. baseline risk in the control group for key outcomes). We will transfer all data from the electronic form in RevMan Web (RevMan Web 2022), using 'copy' and 'paste', if possible, and authors will be asked to recheck the entered data in RevMan Web against the data in the electronic form.

We will also prepare a table showing the study characteristics of the included trials as well as information on study type, participant type, intervention type, and end of follow-up and ranges. We will group this information following our planned comparisons and for each study comparison, we will list the studies which have data available for numerical meta-analysis; the studies which have data that need to be converted for meta-analysis; and the studies that are suitable for a narrative synthesis. If we need to convert study data to a format appropriate for meta-analysis, we will follow the methods described in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022b).

In the 'Characteristics of included studies' and in the 'Results' section, we will present a summary of the PICOT (participants, interventions, comparisons, time) for each of the planned comparisons (McKenzie 2022b).

We will conduct a numerical meta-analysis only if we judge that the treatments, participants, and the underlying clinical question are similar enough for meta-analysing the result. If for any reason, a meta-analysis is not possible to perform, we will identify the best approach among those presented in the section in the *Cochrane Handbook for Systematic Reviews of Interventions* on 'Synthesis using other methods' (McKenzie 2022c).

Based on the *Cochrane Handbook for Systematic Reviews of Interventions*, we will collect details about adverse events (Li 2022). See Appendix 4.

Assessment of risk of bias in included studies

Two review authors (AMC, DMM) will independently and in duplicate assess the risk of bias for each study, using version 2 of the Cochrane risk of bias tool (RoB2), outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Boutron 2022; Higgins 2022c; Sterne 2019). We will resolve any disagreements by discussion or by involving another author (CG). We will assess the risk of bias for all our review outcomes. We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

As we are interested in quantifying the effect of assignment to the interventions at baseline, regardless of whether the interventions are received as intended, we will use the intention-to-treat (ITT) principle.

We will use the following domains to assess the risk of bias in the individually randomised trials (Higgins 2019; Higgins 2022c; Higgins 2022d).

- Bias arising from the randomisation process (Figure 1).
- Bias due to deviations from intended interventions (effect of assignment to intervention) (Figure 2).
- Bias due to missing outcome data (Figure 3).
- Bias in measurement of the outcome (Figure 4).
- Bias in the selection of the reported result (Figure 5).

Figure 1. Algorithm for suggested judgement of risk of bias arising from the randomisation process (Higgins 2019).

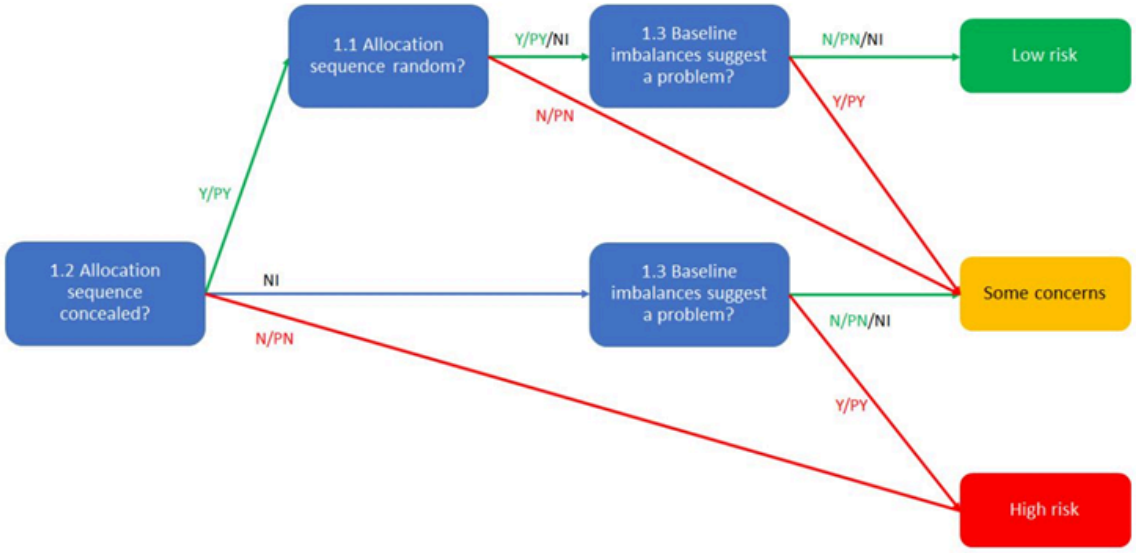


Figure 2. Algorithm for suggested judgement of risk of bias due to deviations from the intended interventions (effect of assignment to intervention) (Higgins 2019).

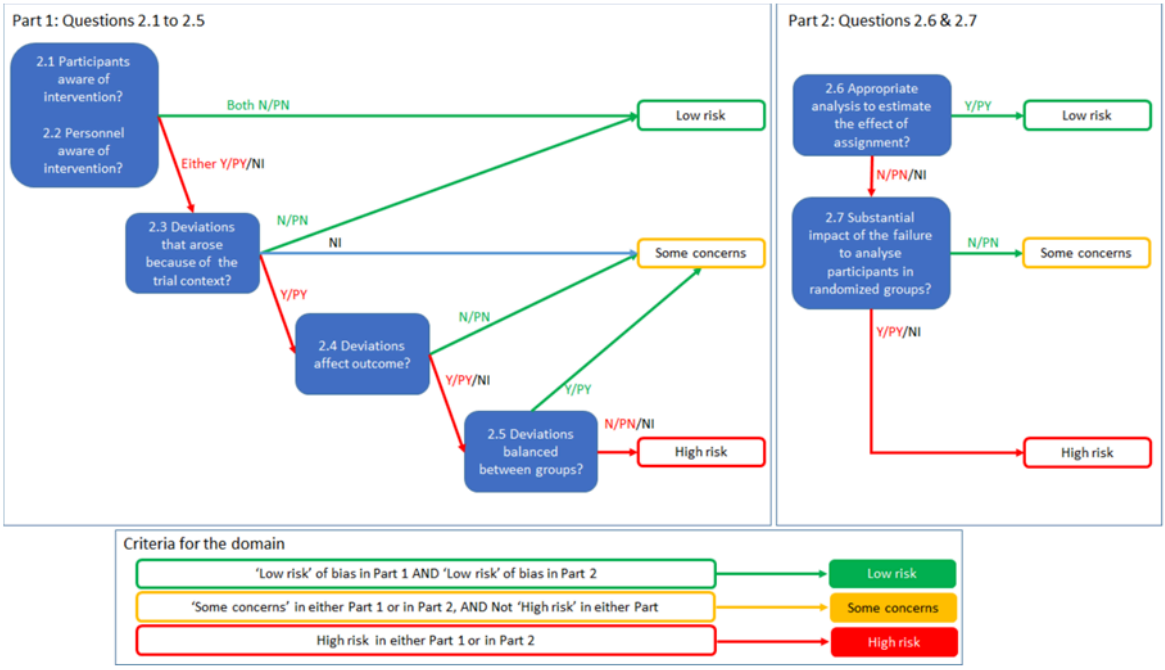


Figure 3. Algorithm for suggested judgement of risk of bias due to missing outcome data (Higgins 2019).

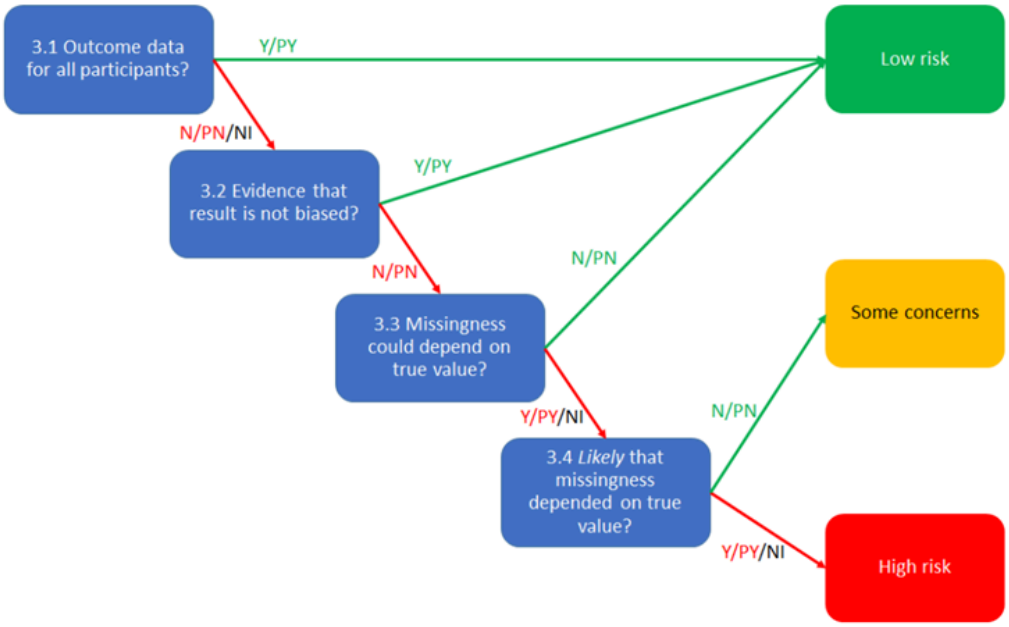


Figure 4. Algorithm for suggested judgement of risk of bias in measurement of the outcome (Higgins 2019).

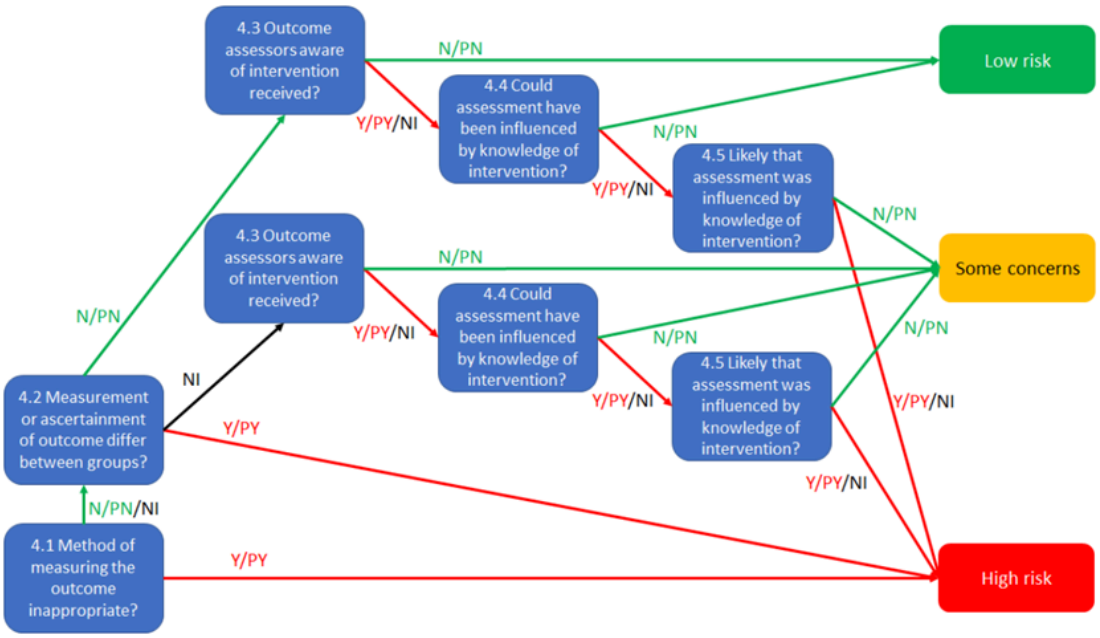
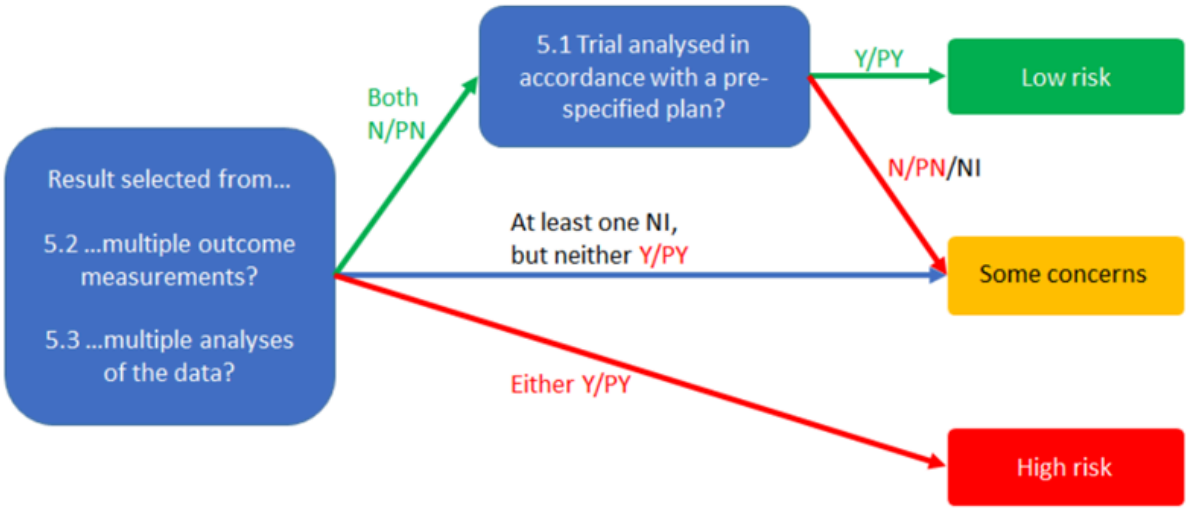


Figure 5. Algorithm for suggested judgement of risk of bias in selection of the reported result (Higgins 2019).



We will use the signalling questions in the RoB2 tool to rate each domain as 'low risk of bias', 'some concerns', or 'high risk of bias' (Higgins 2022c; Sterne 2019). The response options for the signalling questions will be.

- Probably yes.
- Probably no.
- No.
- No information.

We will use the most recent RoB 2 Excel tool (Higgins 2019; Sterne 2019). An algorithm, in Excel, maps the responses to the signalling questions per outcome and proposes a risk of bias judgement for each domain.

When we judge a result to be at a particular level of risk of bias for an individual domain, it implies that the overall result has a risk of bias that is at least this severe. Therefore, a judgement of 'high' risk of bias within any domain will have a similar implication for the result as a whole, irrespective of which domain is being assessed. 'Some concerns' in multiple domains may lead the review authors to decide on an overall judgement of 'high' risk of bias for that outcome or group of outcomes (Higgins 2022c).

The overall risk of bias for the result is the least favourable assessment across the domains of bias (Figure 6).

Figure 6. The overall risk of bias (Table prepared by authors based on Higgins 2019.).

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Overall Risk
Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Low risk	Some concerns	Some concerns	Low risk	Some concerns	High risk
Low risk	Low risk	Low risk	High risk	Low risk	High risk

- Low risk of bias will denote that the study will be judged to be at low risk of bias for all domains for this result.
- Some concerns will denote that the study will be judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.

- High risk of bias will denote that study will be judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

We will use the Microsoft Excel tool available on www.riskofbias.info, and we will make it available online (we will provide details at the review stage).

Our risk of bias assessment will inform GRADE and the summary of findings tables. We will present all six outcomes in our summary of findings table (Schünemann 2022a), i.e. overall survival, serious adverse events, quality of life, hepatic encephalopathy (number of people without improvement), multi-organ failure, and non-serious adverse events. For each outcome, we will provide information on the measures, timing, and range for measuring the outcome.

We will not limit our primary analysis to trials at overall low risk of bias, but we will perform subgroup analyses comparing trials at low risk of bias to trials at some concern and to trials at high risk of bias to illustrate the effect of risk of bias on the compared interventions. We will also use sensitivity analyses presenting data only from trials at low risk of bias.

Measures of treatment effect

For time-to-event data, such as overall survival, we will estimate the hazard ratio (HR) with 95% confidence intervals (CIs).

We will analyse dichotomous data, such as adverse events (serious and non-serious adverse events), with the risk ratio (RR) and 95% CIs. Furthermore, we will estimate the risk difference in absolute terms. We will follow the GRADE recommendations (Guyatt 2013). If they are reported as incidence rate (count data), we will report the count data (events) with rate ratio and 95% CI.

For continuous data, such as quality of life, we will estimate mean differences (MD) with 95% CIs. If different scales are used for measuring the quality of life, we plan to use the standardised mean difference (SMD) with 95% CIs. We will also estimate the ratio of means (RoM) with 95% CIs from the mean difference (Friedrich 2011). Due to practitioners' understanding and preference for dichotomous presentations of continuous outcomes, which they perceive to be the more useful (Johnston 2016), we will estimate odds ratios (ORs) with 95% CIs and the number needed to treat (NNT) for an additional beneficial outcome from the SMD with Furukawa's method (Furukawa 1999; Furukawa 2011).

As recommended in Section 6.5.1.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022b), if necessary, we will multiply the mean values from one set of studies by -1 to ensure that all the scales point to the same direction.

If it is necessary, we will estimate the mean and standard deviation from medians and interquartile ranges (Shi 2020).

If statistical information is missing in a trial report (such as standard deviations), we will try to extract the missing values from P values and 95% CIs.

We will calculate the number needed to benefit for an additional beneficial outcome which is a measure of assessment of clinical usefulness of the consequences of treatment (Laupacis 1988). We will estimate the number needed to benefit with GraphPad software (GraphPad 2022).

If data are not reported in a trial in a format that we can use, we will attempt to convert the data to the required format, following guidance in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022b).

Unit of analysis issues

The unit analysis of this Cochrane Review will be the participant.

Where a single trial reports multiple trial intervention groups, we will include only the relevant groups for our comparison, and we will compare in separate each of the relevant experimental group with each half of the control group if used within the same comparison to avoid double-counting. For our outcome on adverse events, we will record whether the trial measures adverse events in relation to the frequency of a participant with an adverse event (e.g. three participants reported an adverse event), or to multiple adverse events in the same participant (e.g. one participant had three episodes of e.g. pneumonia). We will also record occasions where multiple events in a participant have been incorrectly treated as independent without taking into account the interdependence of the events. Where the number of events appears to be equal to the number of participants, we will treat the events as the unit of analysis as described in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022b).

Due to the nature of the clinical condition and the intervention's characteristics, neither cross-over nor cluster-randomised trials are expected.

Dealing with missing data

We will assess the percentage of dropouts for each included trial, and for each intervention group, and we will evaluate whether an ITT analysis had been performed or could have been performed from the available published information. We will try to contact the study authors to resolve any questions arising from this issue if this is possible.

In order to undertake an ITT analysis, we will seek data from the trial authors about the number of participants in treatment groups, irrespective of their compliance and whether they were later thought to be ineligible, otherwise excluded from treatment, or lost to follow-up. If ITT analysis is not always possible, then we will use the trial data as available to us.

We will include participants with incomplete or missing data in sensitivity analyses by imputing them according to the following scenarios (Hollis 1999).

- 'Best-worst' case scenario analyses: participants with missing outcome data are considered successes in the experimental group and failures in the control group. The denominator will include all the participants in the trial.
- 'Worst-best' case scenario analyses: participants with missing outcome data are considered failures in the experimental group and successes in the control group. The denominator will include all the participants in the trial.

We will use Stata software to assess the impact of missing data (Stata 2021).

Assessment of heterogeneity

Based on the study characteristics, including study design, population, and details on the interventions, we will describe the clinical diversity and methodological variability of the evidence in our review.

We will use a P value of less than 0.10 to indicate statistical heterogeneity, as described in Chapter 10.10.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022), and we will quantify heterogeneity using the I^2 statistic if the P value is less than 0.10.

Using the I^2 statistic (Higgins 2003), we will measure the heterogeneity among the trials in each analysis, and we will interpret it as in Deeks 2022:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity. If we identify substantial or considerable heterogeneity, we will report it and explore possible causes by the prespecified subgroup analyses (see further down).

When there are few studies, there is uncertainty around the I^2 statistic and Tau measurements, and therefore, we will not use the simple thresholds to interpret statistical heterogeneity (Deeks 2022).

If there are 10 or more randomised clinical trials reporting the outcome and I^2 is considerable, we plan to conduct meta-regression analyses. We hypothesise that the following covariates could explain the potential statistical heterogeneity: sex, age, aetiologies, type of support system, and the risk of bias. We will use Stata statistical software to conduct the meta-regression (Stata 2021).

Assessment of reporting biases

If there are 10 or more randomised clinical trials per outcome, we will use the contour enhanced funnel plot to differentiate asymmetry that is due to publication bias from that due to other factors (Peters 2008). We will assess the likelihood of publication bias with Harbord's and Peter's tests (Sterne 2011). We will use Stata statistical software to produce conventional and contour funnel plots (Stata 2021).

We are aware that funnel plot asymmetry may arise because of small-study effects and not just non-reporting bias.

We will assess reporting biases that arise from missing outcome results in the identified trial publications, on the following core outcomes: overall survival, hepatic encephalopathy, multi-organ failure, and adverse events. To ascertain the missing data, we will compare outcome information and data results across the identified trial publications, in addition to contacting trial authors, checking trial registers, trial protocol, or whatever else we can find to verify that data were indeed missing. If we find non-reporting of any study outcome results of relevance to our review, then we will try to explore the potential reasons, and if the non-reporting of a result is associated with an undesirable finding for the trial authors, then we will use the RoB2 domain – bias in the selection of the reported result – to judge the risk of bias of the specific outcome.

Data synthesis

We will perform meta-analyses with 95% CI using random-effects model as our primary analysis in order to explore the average intervention effect. We will use the fixed-effect model as sensitivity analysis (Deeks 2022).

Synthesis using other methods

We will determine the 95% prediction interval, which takes into account the whole distribution of the effects (Kontopantelis 2010; Riley 2011). Prediction intervals in meta-analysis show the expected range of true effects in similar studies (Borenstein 2017; IntHout 2016). We will use Stata software to estimate the 95% prediction interval (Stata 2021).

We will conduct a meta-analysis with RevMan Web (RevMan Web 2022).

Trial Sequential Analysis

We will apply Trial Sequential Analysis (TSA) to control random errors in our meta-analysis (Brok 2008; Brok 2009; Thorlund 2009; Thorlund 2010; Thorlund 2017; TSA 2017; Wetterslev 2008; Wetterslev 2009; Wetterslev 2017). We will calculate the required information size (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) which should also consider the diversity observed in the meta-analysis (Wetterslev 2008; Wetterslev 2009; Wetterslev 2017).

We will calculate the required information size for dichotomous outcomes based on the event proportion in the control group of the included trials; assumption of an a priori RR of 10%; a risk of type I error of 3.30% for our two primary outcomes, and a risk of type I error of 2% for our four secondary outcomes (Jakobsen 2014); a risk of type II error of 10% (power 90%); and the observed diversity of the meta-analysis (Wetterslev 2017). We plan also to conduct a TSA using the RR in trials at low risk of bias, but if we find no such trials, this analysis will have to wait until such trials are identified. For the continuous outcome, quality of life, we will estimate the required information size based on the standard deviation observed in the control group of the meta-analysis and a minimal relevant difference of 50% of this standard deviation, and the observed diversity in the trials in the meta-analysis. For HR, we will conduct robustness analyses by changing them into RR as described above, or we will use software that can handle HRs (Miladinovic 2013a; Miladinovic 2013b).

We will add the trials according to year of publication. Based on the required information size, we will construct trial sequential monitoring boundaries (Thorlund 2017; Wetterslev 2008). These boundaries determine the statistical inference that one may draw regarding the cumulative meta-analysis that has not reached the required information size. If the trial sequential monitoring boundary is crossed before the required information size is reached, firm evidence may be established, and further trials may be superfluous. In contrast, if the boundary is not surpassed, it is most likely necessary to continue conducting trials to detect or reject a certain intervention effect. This can be determined by assessing whether the cumulative Z-curve crosses the trial sequential monitoring boundary for futility (Wetterslev 2008). We

will conduct TSA using software from the Copenhagen Trial Unit (Thorlund 2017; TSA 2017).

We will report and compare the results with TSA as sensitivity analysis to imprecision assessed by GRADE. In TSA, we downgrade imprecision by two levels if the accrued number of participants is below 50% of the diversity-adjusted required information size (DARIS), and one level if it is between 50% and 100% of DARIS. Furthermore, we do not downgrade if the cumulative Z-curve crosses the monitoring boundaries for benefit, harm, or futility, or if DARIS is reached.

We will conduct TSA for all outcomes.

Fragility index

We will calculate the fragility index (FI) when the RR is significant ($P \leq 0.05$). FI is a measure used to identify the number of events required to change statistically significant results to non-significant results (Walsh 2014). We will apply the FI only to randomised clinical trials that allocate in a 1:1 ratio, and to binary data (e.g. all-cause mortality). We will estimate the FI with the Fragility Index Calculator.

Bayes factors

We will estimate the threshold for clinical relevance through the use of Bayes factors (Dienes 2014; Dienes 2018; Goodman 1999; Goodman 2005). The Bayes factor is a likelihood ratio that indicates the relative strength of evidence for two theories (Dienes 2014; Dienes 2018; Goodman 1999; Goodman 2005). The Bayes factor is a comparison of how well two hypotheses (the null hypothesis - H0 - and the alternative hypothesis - H1) predict the data (Goodman 1999). The Bayes factor provides a continuous measure of evidence for H1 over H0. When the Bayes factor is 1, the evidence is insensitive, the data are equally well predicted by both models and the evidence does not favour either model over the other (1 means the data are as well predicted by H1 as H0, so it should not be interpreted as favouring H0; rather the evidence does not point either way). As the Bayes factor increases above 1 (towards infinity), the evidence favours H1 over H0. As the Bayes factor decreases below 1 (towards 0), the evidence favours H0 over H1 (Dienes 2014; Dienes 2018). We will estimate the Bayes factor for all outcomes.

Subgroup analysis and investigation of heterogeneity

Based on information in the background of our review, we plan to conduct the following subgroup analyses (see below).

- Participants stratified by aetiology (Putignano 2018).
- Trials stratified by the type of liver support system as we are not sure if different types may cause differences in effect.

We will conduct the specified subgroup analyses for all outcomes.

Sensitivity analysis

In the addition to the sensitivity analyses described in 'Dealing with missing data', we plan to carry out the following sensitivity analyses.

- Excluding trials at some concern or at high risk of bias.
- Fixed-effect model meta-analysis, for all outcomes.
- Trials without missing data, for all outcomes.
- Assessment of imprecision with TSA (see Data synthesis), for all listed in the summary of findings table outcomes.
- Trials at low risk of bias compared to trials at some concern plus trials at high risk of bias as described earlier (Higgins 2022c). The rationale for this is the risk of overestimation of beneficial intervention effects and underestimation of harmful intervention effects in randomised clinical trials at risk of bias (Kjaergard 2001; Moher 1998; Savović 2012a; Savović 2012b; Savović 2018; Schulz 1995; Wood 2008).
- Trials without for-profit funding compared to trials funded for profit. We assume that 'for-profit bias' would increase benefits and decrease harms associated with the review interventions (Lundh 2017).

We will judge whether there is a difference between the primary analysis and sensitivity analysis by comparing changes in P values.

Summary of findings and assessment of the certainty of the evidence

We plan to create three summary of findings tables, one for each of our review comparisons, and present the outcome results for the following outcomes: overall survival, serious adverse events, quality of life, hepatic encephalopathy (number of people without improvement), multi-organ failure, and non-serious adverse events. For each outcome, we will provide the primary time point of measuring the outcome (i.e. follow-up time, with mean/median and range).

Two review authors (AMC, Chavdar S Pavlov (CSP)) working independently, will make judgements about the certainty of the evidence. We will resolve disagreements by discussion, or we will involve a third author (LLG). We will justify, document, and incorporate all judgements into reporting of results for each outcome.

We will use the five GRADE factors (risk of bias, heterogeneity (consistency of effect), imprecision (calculating also the optimal information size), indirectness, and publication bias) to assess the certainty of a body of evidence as it relates to the trials which contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004; Guyatt 2011).

We will use the methods and recommendations described in Section 8.5 and 8.7, and Chapters 13, 14, and 15 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022c; Page 2022; Schünemann 2022a; Schünemann 2022b) and the GRADE Handbook (Schünemann 2013) using GRADEpro software (GRADEpro GDT). Each intervention compared with conventional supportive treatment alone will get a separate summary of findings table.

- Artificial liver support system compared with conventional supportive treatment.
- Bioartificial liver support system compared with conventional supportive treatment.
- Bioartificial liver support: hybrid techniques compared with conventional supportive treatment.

The levels of evidence are defined as 'high', 'moderate', 'low', or 'very low'. These grades are defined as follows.

- High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

We will communicate the findings of interventions following the GRADE Working Group's recommendations (Santesso 2020).

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

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APPENDICES

Appendix 1. Definitions and characteristics of acute-on-chronic liver failure (ACLF)

Characteristics	European Association for the Study of the Liver - Chronic Liver Failure (EASL-CLIF) Consortium	North American Consortium for the Study of End-stage Liver Disease (NACSELD)	Chinese Group on the Study of Severe Hepatitis B (COSSH)	Asian Pacific Association for the Study of the Liver (APASL) ACLF Research Consortium (AARC)
Category of article(s) defining ACLF	Original article reporting the results of the CANONIC study, which is a prospective, observational study performed in 1343 patients with cirrhosis non-electively admitted to 29 liver units in 12 European countries	Original article reporting results of an analysis of 507 patients with cirrhosis whose data were prospectively collected in the NACSELD database, which includes non-electively hospitalised patients in 18 liver units across the USA and Canada	Original article reporting the results of the COSSH study, which is a prospective, observational study performed in 1322 patients with cirrhosis or severe liver injury due to chronic hepatitis B, non-electively hospitalised in 13 liver centres in China	Consensus document involving international experts from the APASL, published in 2009 and updated in 2014 and 2019, in the context of AARC; the last 2 updates used internally reviewed data from 1402 patients, and 3300 patients, respectively
Patients considered in the definition	Patients with acutely decompensated cirrhosis, with or without prior episode(s) of decompensation	Patients with acutely decompensated cirrhosis, with or without prior episode(s) of decompensation	Patients with acute decompensation of HBV-related chronic liver disease, with or without cirrhosis	Patients with compensated cirrhosis (diagnosed or undiagnosed) or non-cirrhotic chronic liver disease, who had a 1st episode of acute liver deterioration due to an acute insult directed to the liver

(Continued)

Precipitating disorders	Intrahepatic (alcoholic hepatitis), extrahepatic (infection, gastrointestinal haemorrhage), or both	Extrahepatic (infection)	Intrahepatic (HBV reactivation), extrahepatic (bacterial infection) or both	Intrahepatic
Major organ systems considered for the definition	There are 6: liver, kidney, brain, coagulation, circulation, and respiration	There are 4: kidney, brain, circulation, and respiration. Liver and coagulation are not considered	There are 6: liver, kidney, brain, coagulation, circulation, and respiration	Liver dysfunction is central to the definition; hepatic encephalopathy may be present, as a consequence
Basis of the definition	The definition of ACLF is based on the existence of the failure of 1 of the 6 major organ systems. The failure of each organ system is assessed using the CLIF-C Organ Failure scale	The definition of ACLF is based on the existence of 2 organ system failures or more (maximum 4)	The definition of ACLF is based on the failure of 1 of the 6 major organ systems. The failure of each organ system is assessed using the CLIF-C Organ Failure scale	The definition of ACLF is based on the presence of liver dysfunction Extrahepatic organ failures may subsequently develop but are not included in the definition
Definition and stratification of ACLF	ACLF is divided into 3 grades of increasing severity: 1. ACLF grade 1 (3 subgroups): a. patients with single kidney failure b. patients with single liver, coagulation, circulatory or lung failure that is associated with creatinine levels ranging from 1.5 mg/dL to 1.9 mg/dL or hepatic encephalopathy grade 1 or grade 2, or both c. patients with single brain failure with creatinine levels ranging from 1.5 mg/dL to 1.9 mg/dL 2. ACLF grade 2: patients with 2 organ failures 3. ACLF grade 3: patients with 3 organ failures or more had ACLF grade 3	Patients are stratified according to the number of organ failures 2, 3, or all 4 organ failures, respectively	ACLF is divided into 3 grades of increasing severity. 1. ACLF grade 1 (4 subgroups): a. patients with single kidney failure b. patients with single liver failure and either an INR of 1.5 or more, creatinine levels ranging from 1.5 mg/dL to 1.9 mg/dL, hepatic encephalopathy grade I or II, or any combination of these alterations c. patients with single type of organ failure of the coagulation, circulatory or respiratory systems and either creatinine levels ranging from 1.5 mg/dL to 1.9 mg/dL, hepatic encephalopathy grade I or II, or both d. patients with cerebral failure alone plus creatinine levels ranging from 1.5 mg/dL to 1.9 mg/dL 2. ACLF grade 2: patients with 2 organ failures 3. ACLF grade 3: patients with 3 organ failures or more	Acute hepatic insult manifesting as jaundice (total bilirubin levels of 5 mg/dL or more) and coagulopathy (INR of 1.5 or more, or prothrombin activity of less than 40%) complicated within 4 weeks by clinical ascites, encephalopathy, or both The severity of ACLF is assessed using the AARC score. The grading system, defines: Grade 1 by scores of 5 to 7, Grade 2 by scores 8 to 10, and Grade 3 for 11 to 15
Short-term mortality rate of ACLF according to stratification	By 28 days: grade 1: 20% grade 2: 30% grade 3: 80%	By 30 days: 2 organ failures: 49% 3 organ failures: 64%	By 28 days: grade 1: 23% grade 2: 61% grade 3: 93%	By 28 days: grade 1: 13% grade 2: 45% grade 3: 86%

(Continued)

	4 organ failures: 77%

Source: modified from Zaccherini 2020.

INR: international normalised ratio.

Appendix 2. Search strategies

Database	Time span	Search strategy
Cochrane Hepato-Biliary Group Controlled Trials Register (via the Cochrane Register of Studies Web)	Date of search will be given at review stage	((((artificial or bioartificial or bio-artificial or nonbioartificial or non-bioartificial or biological next extracorporeal or recirculating or (plasma and (separati* or exchang*)) or adsorb* or absorb* or "advanced organ") and (support* or assist* or device* or system or systems or liver*)) or ((single-pass or "single pass") and albumin and dialys*) or MARS or ADVOS or SPAD or Hepa-wash or "Hepa wash" or Hepawash) or (liver and (support* or assist* or device* or system or systems)) or (hemodialys* or haemodialys* or hemofiltrati* or haemofiltrati* or hemoperfusion* or haemoperfusion* or hemodiabsorption* or haemodiabsorption* or hemodynamic* or haemodynamic* or charcoal or Prometheus or FPSA or Li-NABL or HepatAssist or MELS or AMC-BAL or Li-HAL)) and (((acute-on-chronic or (acute adj2 on adj2 chronic)) and (liver or hepatic) and failure*) or ACLF)
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	Latest issue	#1 MeSH descriptor: [Liver, Artificial] explode all trees #2 MeSH descriptor: [Renal Dialysis] explode all trees #3 MeSH descriptor: [Hemofiltration] explode all trees #4 MeSH descriptor: [Hemoperfusion] explode all trees #5 MeSH descriptor: [Hemodynamics] explode all trees #6 (((artificial or bioartificial or bio-artificial or nonbioartificial or non-bioartificial or (biological next extracorporeal) or recirculating or (plasma and (separati* or exchang*)) or adsorb* or absorb* or "advanced organ") and (support* or assist* or device* or system or systems or liver*)) or ((single-pass or "single pass") and albumin and dialys*) or MARS or ADVOS or SPAD or Hepa-wash or "Hepa wash" or Hepawash) #7 liver and (support* or assist* or device* or system or systems) #8 (hemodialys* or haemodialys* or hemofiltrati* or haemofiltrati* or hemoperfusion* or haemoperfusion* or hemodiabsorption* or haemodiabsorption* or hemodynamic* or haemodynamic* or charcoal or Prometheus or FPSA or Li-NABL or HepatAssist or MELS or AMC-BAL or Li-HAL) #9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 #10 MeSH descriptor: [Acute-On-Chronic Liver Failure] explode all trees #11 (((acute-on-chronic or (acute adj2 on adj2 chronic)) and (liver or hepatic) and failure*) or ACLF) #12 #10 or #11 #13 #9 and #12

(Continued)

MEDLINE Ovid	1946 to date of search	1. exp Liver, Artificial/ 2. exp Renal Dialysis/ 3. exp Hemofiltration/ 4. exp Hemoperfusion/ 5. exp Hemodynamics/ 6. (((artificial or bioartificial or bio-artificial or nonbioartificial or non-bioartificial or biological next extracorporeal or recirculating or (plasma and (separati* or exchang*)) or adsorb* or absorb* or advanced organ) and (support* or assist* or device* or system or systems or liver*)) or ((single-pass or single pass) and albumin and dialys*) or MARS or ADVOS or SPAD or Hepa-wash or Hepa wash or Hepawash).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 7. (liver and (support* or assist* or device* or system or systems)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 8. (hemodialys* or haemodialys* or hemofiltrati* or haemofiltrati* or hemoperfusion* or haemoperfusion* or hemodiabsorption* or haemodiabsorption* or hemodynamic* or haemodynamic* or charcoal or Prometheus or FPSA or Li-NABL or HepatAssist or MELS or AMC-BAL or Li-HAL).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 9. or/1-8 10. exp Acute-On-Chronic Liver Failure/ 11. (((acute-on-chronic or (acute adj2 on adj2 chronic)) and (liver or hepatic) and failure*) or ACLF).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 12. 10 or 11 13. 9 and 12 14. (randomized controlled trial or controlled clinical trial or retracted publication or retraction of publication).pt. 15. clinical trials as topic.sh. 16. (random* or placebo*).ab. or trial.ti. 17. 14 or 15 or 16 18. exp animals/ not humans.sh. 19. 17 not 18

(Continued)

		20. 13 and 19
Embase Ovid	1974 to date of search	1. exp artificial liver/ 2. exp hemodialysis/ 3. exp hemofiltration/ 4. exp hemoperfusion/ 5. exp hemodynamics/ 6. (((artificial or bioartificial or bio-artificial or nonbioartificial or non-bioartificial or biological next extracorporeal or recirculating or (plasma and (separati* or exchang*)) or adsorb* or absorb* or advanced organ) and (support* or assist* or device* or system or systems or liver*)) or ((single-pass or single pass) and albumin and dialys*) or MARS or ADVOS or SPAD or Hepa-wash or Hepa wash or Hepawash).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] 7. (liver and (support* or assist* or device* or system or systems)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] 8. (hemodialys* or haemodialys* or hemofiltrati* or haemofiltrati* or hemoperfusion* or haemoperfusion* or hemodiabsorption* or haemodiabsorption* or hemodynamic* or haemodynamic* or charcoal or Prometheus or FPSA or Li-NABL or HepatAssist or MELS or AMC-BAL or Li-HAL).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] 9. or/1-8 10. exp acute on chronic liver failure/ 11. (((acute-on-chronic or (acute adj2 on adj2 chronic)) and (liver or hepatic) and failure*) or ACLF).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] 12. 10 or 11 13. 9 and 12 14. Randomized controlled trial/ or Controlled clinical study/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/ or retracted article/ 15. (random$ or placebo or parallel group$1 or crossover or cross over or assigned or allocated or volunteer or volunteers).ti,ab. 16. (compare or compared or comparison or trial).ti. 17. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 18. (open adj label).ti,ab. 19. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

(Continued)

		20. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. 21. (controlled adj7 (study or design or trial)).ti,ab. 22. (erratum or tombstone).pt. or yes.ne. 23. or/14-22 24. (random$ adj sampl$ adj7 ('cross section$' or questionnaire$ or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) 25. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) 26. (((case adj control$) and random$) not randomi?ed controlled).ti,ab. 27. (Systematic review not (trial or study)).ti. 28. (nonrandom$ not random$).ti,ab. 29. 'Random field$'.ti,ab. 30. (random cluster adj3 sampl$).ti,ab. 31. (review.ab. and review.pt.) not trial.ti. 32. 'we searched'.ab. and (review.ti. or review.pt.) 33. 'update review'.ab. 34. (databases adj4 searched).ab. 35. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ 36. Animal experiment/ not (human experiment/ or human/) 37. or/24-36 38. 23 not 37 39. 13 and 38
LILACS (Bireme)	1982 to date of search	(((artificial or bioartificial or bio-artificial or nonbioartificial or non-bioartificial or biological extracorporeal or recirculating or (plasma and (separati$ or exchang$)) or adsorb$) and (support$ or assist$ or device$ or system or systems or liver$)) or (liver and (support$ or assist$ or device$ or system or systems)) or (hemodialys$ or haemodialys$ or hemofiltrati$ or haemofiltrati$ or hemoperfusion$ or haemoperfusion$ or hemodiabsorption$ or haemodiabsorption$ or hemodynamic$ or haemodynamic$ or charcoal or Prometheus or FPSA or Li-NABL or HepatAssist or MELS or AMC-BAL or Li-HAL)) [Words] and (((acute-on-chronic or acute on chronic) and (liver or hepatic) and failure$) or ACLF) [Words]
Science Citation Index Expanded (Web of Science)	1900 to date of search	#8 #6 AND #7 #7 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*) #6 #4 AND #5

(Continued)

		#5 TS=(((acute-on-chronic or (acute near/2 on near/2 chronic)) and (liver or hepatic) and failure*) or ACLF) #4 #1 or #2 or #3 #3 TS=(hemodialys* or haemodialys* or hemofiltrati* or haemofiltrati* or hemoperfusion* or haemoperfusion* or hemodiabsorption* or haemodiabsorption* or hemodynamic* or haemodynamic* or charcoal or Prometheus or FPSA or Li-NABL or HepatAssist or MELS or AMC-BAL or Li-HAL) #2 TS=(liver and (support* or assist* or device* or system or systems)) #1 TS=(((artificial or bioartificial or bio-artificial or nonbioartificial or non-bioartificial or biological next extracorporeal or recirculating or (plasma and (separati* or exchang*)) or adsorb* or absorb* or advanced organ) and (support* or assist* or device* or system or systems or liver*)) or ((single-pass or single pass) and albumin and dialys*) or MARS or ADVOS or SPAD or Hepa-wash or Hepa wash or Hepawash)
Conference Proceedings Citation Index – Science (Web of Science)	1990 to date of search	#8 #6 AND #7 #7 TI=(random* or blind* or placebo* or meta-analys* or trial*) OR TS=(random* or blind* or placebo* or meta-analys*) #6 #4 AND #5 #5 TS=(((acute-on-chronic or (acute near/2 on near/2 chronic)) and (liver or hepatic) and failure*) or ACLF) #4 #1 or #2 or #3 #3 TS=(hemodialys* or haemodialys* or hemofiltrati* or haemofiltrati* or hemoperfusion* or haemoperfusion* or hemodiabsorption* or haemodiabsorption* or hemodynamic* or haemodynamic* or charcoal or Prometheus or FPSA or Li-NABL or HepatAssist or MELS or AMC-BAL or Li-HAL) #2 TS=(liver and (support* or assist* or device* or system or systems)) #1 TS=(((artificial or bioartificial or bio-artificial or nonbioartificial or non-bioartificial or biological next extracorporeal or recirculating or (plasma and (separati* or exchang*)) or adsorb* or absorb* or advanced organ) and (support* or assist* or device* or system or systems or liver*)) or ((single-pass or single pass) and albumin and dialys*) or MARS or ADVOS or SPAD or Hepa-wash or Hepa wash or Hepawash)

Appendix 3. Intervention description

1. Brief name: provide the name or a phrase that describes the intervention.
2. Why: describe any rationale, theory, or goal of the elements essential to the intervention.
3. What (materials): describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in the training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).
4. What (procedures): describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.
5. Who provided: for each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background, and any specific training given.
6. How: describe the modes of delivery (such as face to face or by some other mechanism, such as Internet or telephone) of the intervention and whether it was provided individually or in a group.
7. Where: describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.

8. When and how much: describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity, or dose.
9. Tailoring: if the intervention was planned to be personalised, titrated, or adapted, then describe what, why, when, and how.
10. Modifications: if the intervention was modified during the course of the study, describe the changes (what, why, when, and how).
11. How well (planned): if intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.
12. How well (actual): if intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.

Source: Hoffmann 2014.

Appendix 4. Strategy to recollect adverse events information

- Name of the adverse events (e.g. dizziness).
- Reported intensity of the adverse event (e.g. mild, moderate, severe).
- Whether the trial investigators categorised the adverse event as 'serious'.
- Whether the trial investigators identified the adverse event as being related to the intervention.
- Time point (most commonly measured as a count over the duration of the study).
- Any reported methods for how adverse events were selected for inclusion in the publication (e.g. 'We reported all adverse events that occurred in at least 5% of participants').

Source: Li 2022.

CONTRIBUTIONS OF AUTHORS

- Arturo Martí-Carvajal: drafted the protocol and addressed comments from authors.
- Christian Gluud: commented and revised the protocol.
- Lise Lotte Gluud: commented and revised parts of the protocol.
- Jian Ping Liu: commented and revised parts of the protocol.
- Chavdar S Pavlov: commented and revised parts of the protocol.
- Diana Monge Martín: commented and revised parts of the protocol.
- Susana Nicola: commented and revised parts of the protocol.
- Ezequiel Mauro: commented and revised parts of the protocol.
- Gabriella Comunián-Carrasco: commented and revised parts of the protocol.
- Cristina Elena Martí-Amarista: commented and revised parts of the protocol.

All authors have read and approved the current protocol version.

DECLARATIONS OF INTEREST

- Arturo Martí-Carvajal declared no competing interests directly related to the submitted protocol.
- Christian Gluud declared no competing interests directly related to the submitted protocol.
- Lise Lotte Gluud declared the following conflict of interests: Novo Nordisk (ad board, funding for research), Gilead (funding for research), Vingmed (funding for research), Alexion (funding for research), Pfizer (expert testimony).
- Jian Ping Liu declared no competing interests directly related to the submitted protocol.
- Chavdar S Pavlov declared no competing interests directly related to the submitted protocol.
- Diana Monge Martín declared no competing interests directly related to the submitted protocol.
- Susana Nicola declared no competing interests directly related to the submitted protocol.
- Ezequiel Mauro declared no competing interests directly related to the submitted protocol.
- Gabriella Comunián-Carrasco declared no competing interests directly related to the submitted protocol.
- Cristina Elena Martí-Amarista declared no competing interests directly related to the submitted protocol.

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