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A living systematic review and comprehensive network meta-analysis of ALS clinical trials: study protocol

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0.0 Abstract

Introduction: Amyotrophic lateral sclerosis (ALS) is a fatal neurogenerative disease with no effective treatment to date. Despite numerous clinical trials, the majority of studies have been futile in their effort to significantly alter the course of the disease. These studies, however, may still provide valuable information for identifying subgroups of patients and generating new hypotheses for future research. Therefore, we aim to synthesize the available evidence from ALS clinical trials.

Methods and analysis: We will conduct a systematic review to identify all clinical trials that have assessed disease-modifying pharmaceutical therapies, cell therapies, or supplements in patients with ALS. Subsequently, individual patient data and aggregate data will be synthesized in meta-analytical models. The final model will be presented as an open-source web-application, with biannual updates of the underlying data, thereby providing a 'living' overview of the ALS clinical trial landscape.

Discussion: The model aims to serve as a tool for clinical trial design and information dissemination, and to generate new hypotheses for future research. The synthesis of evidence from available clinical trials may overcome limitations of individual studies. Network meta-analysis may refine the assessment of efficacy in particular subgroups of patients or evaluate intervention characteristics, such as mode of administration or targeted biological mechanisms, and rank order promising therapeutic areas of interest. The 'living' network will perpetually summarize the currently available data, offering investigators an actualized overview of the clinical trial landscape and up-to-date input for trial design.

Ethics and dissemination: No ethics approvals are required. Findings will be presented at relevant conferences and submitted at peer-reviewed journals. Data will be stored anonymously in secure repositories.

Keywords: *amyotrophic lateral sclerosis, protocol, systematic review, network meta-analysis, living review*

0.1 Strengths and limitations of this study

- This network meta-analysis combines both aggregate and individual patient data (IPD), increasing the resolution of the synthesized evidence for ALS treatments.
- Synthesizing these trials may provide valuable insights in subgroup efficacy, for the role of mode of administration, and areas of interest for new therapeutic leads.
- The living review will aid in dissemination of the findings and provide an overview of the clinical trial landscape.
- The main limitation of this study is the potential unavailability of IPD for certain trials. For these trials, IPD can be supplemented with aggregate data.

1.0 Introduction

Amyotrophic lateral sclerosis (ALS) is a rare and fatal neurogenerative disease which is characterized by the loss of motor neurons and progressive muscle weakness, followed by death within, on average, three to five years after symptom onset.(1-3) Although over 100 clinical trials have been conducted in the last 25 years,(4) treatment options remain limited, with no substantial improvement in the patient's life expectancy.(5) The futile clinical trial landscape is the result of an interplay of various elements, including, but not limited to, a weak a priori study rationale; underestimation of the pathophysiological and clinical heterogeneity; and a suboptimal or flawed study design.(4)

By combining the results and outcomes of previous clinical trials, it may be possible to improve the design and conduct of future studies.(6) This has been demonstrated by initiatives such as the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) or the Answer ALS database,(7, 8) which have been of significant value for characterizing the natural history of ALS. These datasets provide key input for sample size calculations, eligibility criteria and overall trial design considerations.(9) Current initiatives are, however, lacking data on the received experimental treatment and individual studies are not identifiable. This limits the value of the data, as key therapeutic questions, such as subgroup efficacy(10) or the impact of intervention characteristics such as mode of administration and patient burden,(11) cannot be addressed.

Hence, study-level evidence synthesis may improve the use of the available data. Moreover, it provides an opportunity to study between-trial variability,(12) and overcome limitations of

individual clinical trials. By combining all clinical trials into a network, i.e. a network meta-analysis (NMA), information can be jointly harvested across studies through direct and indirect study comparisons.(13) This approach yields increased statistical power to detect trends that may not be observed in single studies.(14) From the network, head-to-head intervention comparisons can be made to rank order interventions based on their treatment effects, and identify areas of therapeutic interest where more research is needed. This would be of particular value for large drug screening platforms such as HEALEY,(15) MND-SMART,(16) and EXPERTS ALS, as it may provide insight for investigating new therapeutic leads.(17)

In this study, therefore, we aim to systematically identify all completed randomized clinical trials (RCTs) in ALS and synthesize their evidence through a comprehensive NMA, thereby improving the utilization of existing clinical trial information and augmenting current large data initiatives. The final NMA model will be presented as an open-source web-application, with biannual updates of the underlying data, to provide a 'living' overview of the ALS clinical trial landscape and serve as a tool for trial design, information dissemination, and generating new hypotheses.(18)

1.1 Objectives

The primary objective of this study is to perform an NMA and synthesize the available data from randomized clinical trials, to enable the creation of efficacy rankings, to identify potentially responding subgroups, and to generate new hypotheses for future research. The subobjectives include: 1) conducting a systematic review of RCTs in ALS that evaluate disease modifying drugs, cell therapies, or supplements; 2) obtaining and combining aggregate and individual patient data (IPD) from each study; 3) developing a network meta-analytical model; and 4) disseminating the findings through an open-source web-application with biannual updates of the underlying data.

2.0 Methods and analysis

The protocol was designed based on principles outlined in The Cochrane Handbook for Systematic Reviews of Interventions, and the Centre for Reviews and Dissemination's Guidance for Undertaking Reviews in Health Care.(19, 20) Due to the nature of this study, no public or patient involved in planned.

2.1 Search strategy

The aim of the search is to identify phase II and III RCTs for ALS that assess the efficacy of disease-modifying therapies. In brief, we will search Embase and PubMed, employing a prespecified search string developed in conjunction with information experts from the University Medical Center Utrecht (UMCU). The search string includes terms for "ALS" and "trial" and sets a publication date filter from 1999 and onwards. The full search term is included in Supplement data table I. Two reviewers will deduplicate and independently cross-reference the search output and will screen the references of (systematic) reviews and included studies for additional eligible studies (snowballing).

2.2.1 Screening process

The eligibility of each study will be determined by applying the inclusion and exclusion criteria for title/abstract, with ASReview (section 2.3).(21) Subsequently, the remaining studies will undergo a second screening process by applying the inclusion and exclusion criteria for full-texts (section 2.4). All studies will be screened by two reviewers, after which the results will be compared and discussed until consensus is reached. If no consensus is reached, a third reviewer will be consulted. The number of excluded studies and the reasons for exclusion will be recorded in Figure 1.

<insert figure 1 here>

2.2.2 Types of studies

RCTs consisting of two or more comparative arms are eligible. The control group may be treated with a placebo, sham, another therapeutic intervention, or usual care. To ensure the inclusion of phase II and III RCTs, the total randomized sample size must contain at least 20 patients with ALS and the randomized treatment period must not be shorter than 12 weeks. The treatment period is defined as the time from blinded treatment initiation until the last follow-up or the commencement of an open-label extension period. Hence, phase I and IV studies are excluded alongside clinical trials with deviating designs such as a single-arm, crossover, or externally controlled design. Studies with an open-label extension are included only if they are

preceded by a randomized treatment period of at least 12 weeks. Multi-stage trials are eligible if at least one stage fulfills the inclusion criteria.

2.2.3 Types of interventions

Interventions can be classified as either disease-modifying (e.g., slowing of clinical progression rate) or symptomatic (e.g., drug therapy for sialorrhea, cramps, depression, or pain).(22) The primary interest of this review are disease-modifying interventions, and the following types of interventions will be considered: (1) disease-modifying pharmaceutical interventions (all modes of administration), (2) cell therapies, and (3) supplements if they were intended to be disease-modifying. Studies that evaluate symptomatic treatments will be excluded. Studies investigating devices, dietary interventions other than supplements (e.g., high-caloric intake), or physical activity programs (e.g., strength or endurance training) will also be excluded.

2.2.4 Types of outcomes

The outcomes of interest are measures of clinical disease progression and overall survival. Eligible outcomes include functional rating scales (e.g., the revised ALS functional rating scale [ALSFRS-R]), lung function (e.g., slow or forced vital capacity [VC], peak cough flow), and survival (either defined as death alone or as a composite, e.g. with respiratory insufficiency and/or time to reach a clinical disease stage).

2.2.5 Study population

Eligible patient populations are patients diagnosed with ALS according to the (revised) El Escorial, Awaji, or Gold Coast criteria.(23) Studies enrolling patients before 1996 will be excluded, as thereafter riluzole was introduced as a new standard of care, and the revised version of the ALSFRS, which more adequately measures respiratory involvement, was adopted.(24, 25)

2.3 ASReview for study selection based on title/abstract

ASReview is a machine-learning tool that increases screening efficiency by presenting the abstract of studies most similar to eligible ones.(21) The ASReview process starts with a manual preselection of eligible and ineligible studies. To achieve an informative preselection set, these studies are heterogeneous in terms of intervention and publication date. The preselected studies can be found in Supplemental data table II. Eligibility for the title/abstract screening and (systematic) review screening will be based on the exclusion criteria listed in Table 1. The selection process continues until a stopping criterion has been reached, which will be defined as a consecutive sequence of 100 ineligible studies.(21) A random sample of 5% of the unseen studies will be selected to examine whether any eligible studies have been missed. If so, the screening process will recommence until the stopping criterion has been reached.

Table 1: Selection criteria for title and abstract screening

Study type	**Criteria**
Eligible studies	1. Study is not a clinical trial for ALS 2. Study is not randomized 3. Intervention is not a pharmaceutical drug, cell therapy, or supplement 4. Study does not report clinical efficacy outcomes 5. Study is not the primary report of the trial (i.e., a post-hoc analysis) 6. The randomized period is shorter than 12 weeks 7. Randomized population consists of fewer than 20 patients 8. Study has a deviating design (fully open-label, cross-over, historically controlled) 9. Patient enrollment started before 1999 10. Study is a phase I or IV trial
Systematic reviews	1. Study is a review for ALS 2. Study summarizes clinical trial evidence of disease-modifying therapies

2.4 Full-text criteria

The studies found to be eligible in ASReview will undergo a full-text screening. The final set of inclusion and exclusion criteria, based on the eligibility described in section 2.2.2 to 2.2.5, is listed in Table 2. These criteria are slightly stricter than the title/abstract criteria, as they finalize the set of included studies.

Table 2: Full-text screening inclusion and exclusion criteria

Criterion type	Criteria
Inclusion criteria	1. Study reports a randomized clinical trial in either phase II or III 2. Study population consists of patients diagnosed with ALS according to the (revised) El Escorial, Awaji, or Gold Coast criteria 3. Intervention is a pharmaceutical drug, cell therapy, or supplement 4. Clinical efficacy outcomes are included as one of the endpoints
Exclusion criteria	1. Study is a phase I or IV trial 2. The randomized treatment period is shorter than 12 weeks 3. Total randomized population consists of fewer than 20 patients with ALS 4. Study design is ineligible (e.g., open-label, cross-over, externally-controlled) 5. Patient enrollment started before 1999 6. Intervention is intended for symptomatic treatment 7. Study is incomplete or inaccessible (e.g., no full-text available) 8. Study is not the primary report of the trial (e.g., a post-hoc analysis)

2.5 Data extraction

Aggregated data (AD) of key study characteristics and outcomes will be extracted from all included studies, while corresponding authors will be approached for IPD via e-mail. For the studies where IPD collection is not feasible for any reason, the analysis will proceed using only the available AD from the respective study. Supplemental data table III and IV contain essential IPD and AD variables that will be extracted from the studies per randomized treatment group. Supplemental data table V contains the code list for the AD variable extraction.

2.6 Data management

IPD will be collected in compliance with local regulations and under supervision of a database manager appointed at the UMCU. All aggregate and patient-level data will be stored securely at the servers of the UMCU. Access to patient-level data will be restricted to authorized staff; costs of the data storage will be covered by the UMCU.

2.7 Statistical analysis

The primary aim of the analysis is to synthesize the available individual patient and aggregate data from all included RCTs and evaluate the efficacy of each intervention. As IPD will likely not be available for every study, we will employ network meta-analytical techniques for synthesizing IPD and AD.

In brief, efficacy of the interventions will be evaluated as follows. First, we will estimate the overall efficacy of ALS treatments by conducting a random-effects pairwise meta-analysis for the ALSFRS-R, VC and survival outcome data, to determine whether any treatment provides benefits compared to placebo.(26) We will pool the AD from the different active treatment arms into one group and compare the pooled group to all pooled patients who received placebo.(27)

Secondly, we will employ a random-effects NMA model. The utilization of NMA offers several advantages, including the ability to 1) compare interventions that have not been performed in previous studies;(28) 2) obtain more precise estimates compared to pairwise meta-analysis through direct and indirect comparisons;(29) and 3) establish a ranked order or

hierarchy for each investigational intervention based on their efficacy.(30) The statistical model consists of a two-stage approach to combine the AD and IPD.(31, 32).

'Disconnected' networks – e.g. as a result of different modes of administration – will be 'reconnected' by matching on prognostic variables through propensity scores.(33) Missing data in any of the covariates will be addressed by multiple imputation.(34) Model assumptions, including transitivity, will be evaluated by a global assessment using the Q-statistic under the full design-by-treatment interaction random-effects model, by integrating inconsistency factors in the inconsistency detection process, and through the node-split method.(35-37) Network heterogeneity will be explored further through network meta-regression and subgroup analyses. We will conduct sensitivity analyses by restricting the model to include only studies where IPD are available, or studies that are at low risk of bias, or have total sample sizes ≥ 50 patients.

Finally, the network structure will be visually presented through a network plot, while the output of the NMA model will be presented through forest plots, league tables, and tables displaying ranking metrics such as P-scores.(38) A demonstrative network plot and table with ranking metrics is provided in Figure 2.

<insert figure 2 here>

2.8 Quality assessment

We will assess the quality of the included studies in two ways. Initially, the short version of the revised Cochrane risk-of-bias tool for randomized trials will serve as a framework for summarizing the risk of bias in five domains, namely: randomization process; deviations from intended interventions; missing outcome data; outcome assessment; and selective reporting. Each domain will be rated as 'low risk', 'some concerns', or 'high risk', and an overall score will be determined. Secondly, quality of the evidence in the individual studies will be assessed with the GRADE approach. This method evaluates the outcomes of each study and determines how closely the estimated effect approximates the true effect and is rated on a 4-level scale from 'very low' to 'high'. The outcomes of both assessments will be summarized and presented in a figure. Lastly, the Confidence in Network Meta-Analysis (CINeMA) framework will be used to display bias, coherence, and heterogeneity in the evidence found, and aid in the transparent reporting of the NMA.(39)

2.9 Living NMA model framework

Finally, the output of the NMA model will be presented as an interactive, open-source web-application using the R package *Shiny*.(40) A standardized operating procedure will be developed for routinely updating the NMA model, including biannual reviews of the literature to identify new studies, and a pipeline for IPD data requests, and to update the data analysis models accordingly. This will create a 'living NMA model' that could potentially serve as a perpetual overview of the clinical trial landscape of ALS and an interactive environment to support trial design.

3.0 Discussion

In this study, we will aim to synthesize the available evidence from ALS clinical trials through a comprehensive systematic review and NMA to ultimately create a living overview of the clinical trial landscape. This may provide valuable information which can be used to identify subgroups of patients who could benefit, and to generate new hypotheses for future research. By combining both direct and indirect evidence, it will not only become possible to compare ALS interventions, but also to create novel insights that were previously unattainable, and better inform future trial design. Hence, a NMA may expand the current body of evidence and potentially increase the likelihood of successful drug development for ALS.

The major strength of a NMA is the ability to the increase the available information by both pooling trial data, resulting in larger sample sizes, and by borrowing information through indirect treatment comparisons.(27) This increased precision may be of particular interest to potentially identify subgroups of responding patients in otherwise futile clinical trials. Especially in smaller studies, efficacy signals in a few patients may be lost when there is a large group of non-responders.(10) The value of such a meta-analytical approach has been shown previously for lithium carbonate.(41) A potential responding subgroup was identified for patients homozygous for the c-allele of the *UNC13A* gene, which is now being investigated in a confirmatory study.(42) A NMA is capable of conducting such subgroup analyses on a larger scale with increased precision, potentially generating a high number of novel therapeutic leads that could be confirmed in large drug screening platforms such as HEALEY,(15) MND-SMART,(16)and EXPERTS ALS.(17)

Another area of interest is the study of trial-related factors, such as the impact of inclusion criteria or protocol burden on study enrollment and retention rates, which affect study timelines, trial validity and the costs of drug development,(43) or to study the impact of the mode of administration. The significance of the latter was recently highlighted for intravenous therapies, where a potential procedural risk of prolonged intravenous administration may have had a negative impact on the patient's prognosis, potentially jeopardizing patient safety and confounding study results.(44-46) As these trial-related factors are applicable to all patients within a single study, regardless of randomized treatment allocation, they cannot be assessed within a single study; meta-analytical models are needed to investigate their impact.

One of the potential challenges of this study is the acquisition of IPD, especially from industry-sponsored studies due to intellectual property restrictions. This was the main reason for the proposed statistical framework as it is flexible and could utilize both IPD as well as AD from the published literature. Hence, the missing IPD can be supplemented with AD which may limit the impact on the main study objectives. Naturally, IPD will be required for subgroup analysis – especially for those subgroups that are not commonly reported – and to overcome 'disconnected' networks as a result of, for example, differential modes of administration. Other limitations of the network will be primarily driven by the limitations of the underlying study quality and available data.

In conclusion, creating a living systematic review and conducting a NMA for ALS clinical trials could be of significant value to the international ALS research community, as the synthesis of evidence from available clinical trials may overcome limitations of individual studies. These results may refine the assessment of efficacy in particular subgroups of patients, evaluate intervention characteristics, inform trial design, and aid in dissemination of the findings, offering investigators an actualized overview of the clinical trial landscape.

4.0 Ethics and dissemination

This study will meta-analyze previously collected, anonymized datasets. No ethics approvals are necessary for the initiation of this project. An overview of all included studies will be provided, as well as an overview of the search procedure. The AD dataset will be made available upon reasonable request with the corresponding author. The IPD datasets will not be made publicly available due to personal data protection considerations.

The findings obtained in this project will be presented at relevant ALS conferences (e.g., ENCALS and MNDA conferences) and submitted to peer-reviewed scientific journals. In addition, as previously stated, the NMA model will be presented as an open-access web-application to aid in dissemination.

5.0 Statements

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None

Author contributions

FvL, GS, SN & RvE drafted the protocol. FvL & RvE developed the search string and criteria. FvL & IB will be involved in screening and data collection. FvL, GS, DM, DW, JvU, LvdB, SN & RvE are involved with revision. FvL, GS, DM, SN & RvE will be involved in developing the statistical framework. FvL, GS, SN & RvE will be involved in data analysis and manuscript writing. RvE is the guarantor. All authors have read and approved the final protocol.

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Competing interests

The authors declare that they have no competing interests.

6.0 List of abbreviations

In order of appearance:

- ALS: Amyotrophic Lateral Sclerosis
- IPD: Individual Patient Data
- PRO-ACT: Pooled Resource Open-Access ALS Clinical Trials
- NMA: Network Meta-Analysis

- RCT: Randomized Clinical Trial
- UMCU: University Medical Centre Utrecht
- ALSFRS-R: ALS Functional Rating Scale Revised
- VC: Vital Capacity
- AD: Aggregated Data
- CINeMA: Confidence in Network Meta-Analysis

7.0 References

EndNote V20.6 (Clarivate Analytics, PA, USA) was used as reference manager.

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Figure 1: Flow diagram of study selection

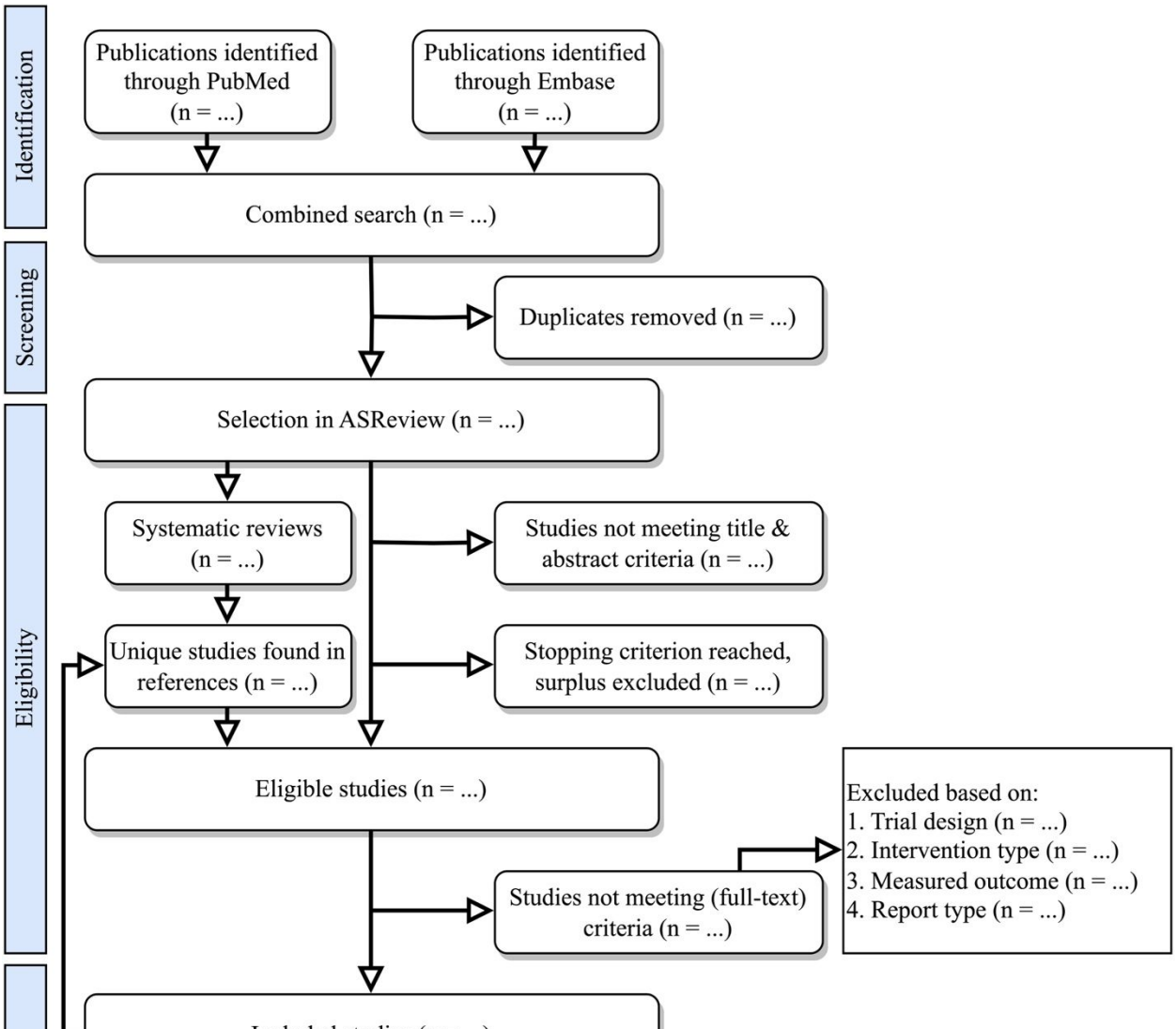
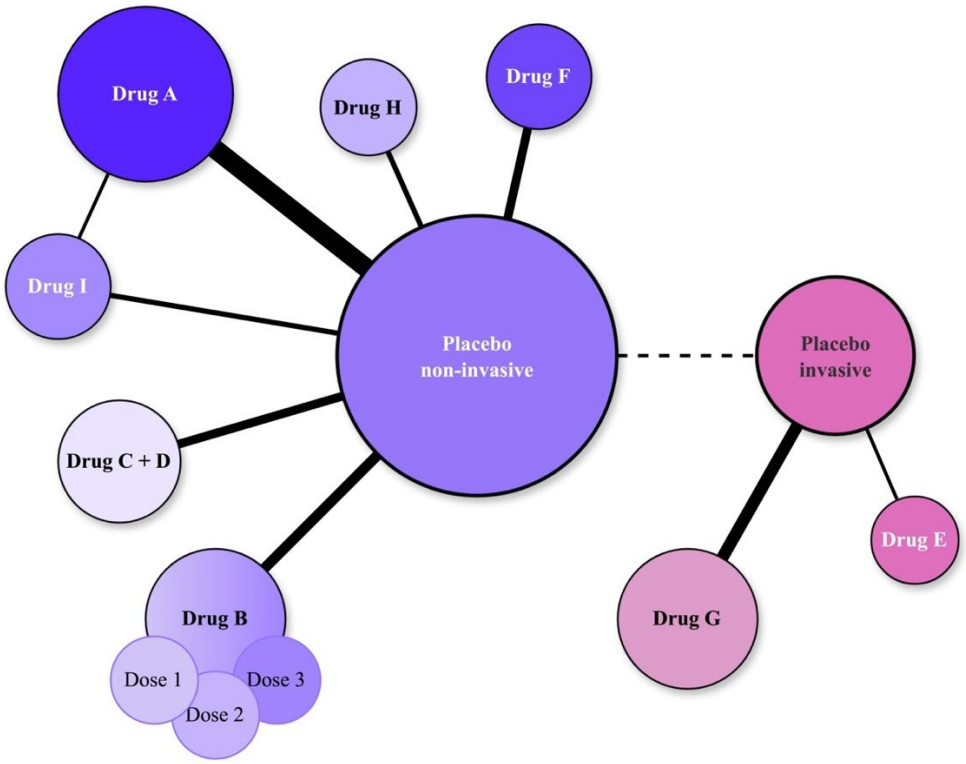


Figure 1 legend. Figure denotes the search process. After study completion, the number (n) of studies selected in each step will be indicated in each box.

Figure 2. Hypothetical network diagram and harm/benefits table



Rank	Intervention	Expected benefit
1	Drug A	1.72
2	Drug F	1.53
	…	…
9	Drug B – Dose 1	-0.97
10	Drug C + D	-1.81

Mode of administration	Expected harm
Non-invasive (purple)	0.00 (reference)
Invasive (lilac)	-0.41

Figure 2 legend. The figure above represents a hypothetical network. The network consists of intervention and placebo nodes (grouped per administration mode), and the solid lines connecting them indicate direct comparisons. Non-invasive nodes consist of oral and transdermal, while invasive nodes consist of intravenous, intrathecal, intramuscular, and subcutaneous modes of administration. The dashed lines reflect 'disconnected' networks that are reconnected through matching and propensity score methods. The table ranks the interventions based on their expected benefit, compared to placebo, as well as the expected harm of administration modes estimated through matching.

Supplemental data

Table I: Search strings for PubMed and Embase search

Database	PubMed	Embase
Search string	("Amyotrophic Lateral Sclerosis"[Mesh] OR "Motor Neuron Disease"[Mesh] OR "ALS"[TIAB] OR "amyotrophic lateral sclerosis"[TIAB] OR "Gehrig*"[TIAB] OR "Motor Neuron Disease*"[TIAB] OR "Charcot*"[TIAB] OR "MND"[TIAB] AND (1999/1/1:2023/10/31[pdat])) AND ("Clinical Trials as Topic"[Mesh] OR "trial*"[TIAB] OR "randomi*"[TIAB] AND (1999/1/1:2023/10/31[pdat]))	('amyotrophic lateral sclerosis'/exp OR 'motor neuron disease'/exp OR 'als':ti,ab,kw OR 'amytrophic lateral sclerosis':ti,ab,kw OR 'gehrig*':ti,ab,kw OR 'motor neuron disease*':ti,ab,kw OR 'charcot*':ti,ab,kw) AND ('clinical trial'/exp OR 'trial*':ti,ab,kw OR 'randomi*':ti,ab,kw) AND [1999-2023]/py AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

Table II: Preselected studies used for ASReview

Eligible studies	Ineligible studies
1. "Trial of Sodium Phenylbutyrate-Taurursodiol for Amyotrophic Lateral Sclerosis" (2020, NEJM) 2. "Trial of celecoxib in amyotrophic lateral sclerosis" (2006, Neurology) 3. "Dexpramipexole versus placebo for patients with amyotrophic lateral sclerosis (EMPOWER): a randomised, double-blind, phase 3 trial" (2013, The Lancet Neurology)	1. "Genetic variation in APOE, GRN, and TP53 are phenotype modifiers in frontotemporal dementia" (2020, Neurobiology of Aging) 2. "MTBVAC vaccine mediates immune response through the upregulation of T-regulatory cells in an ALS mouse model" (2021, Cell Reports Medicine)

4. "Efficacy and safety of CNM-Au8 in amyotrophic lateral sclerosis (RESCUE-ALS study): a phase 2, randomised, double-blind, placebo-controlled trial and open label extension" (2023, Elsevier) 5. "Efficacy of minocycline in patients with amyotrophic lateral sclerosis: a phase III randomized trial" (2007, The Lancet Neurology) **6.** "A randomized, placebo-controlled trial of topiramate in amyotrophic lateral sclerosis" (2003, Neurology)	

Table III: IPD variables

Individual patient data variables

• Study information
  ○ Study ID
  ○ Country
• Patient data
  ○ Patient ID
  ○ Age (years)
  ○ Sex (male/female)
  ○ Height (cm)
  ○ Weight (kg)
  ○ Site of onset (bulbar/spinal)
  ○ Symptom duration (months)
  ○ Diagnostic delay (months)
• Intervention data
  ○ Treatment group
  ○ Mode of administration
  ○ Follow-up duration (months)
• Longitudinal

- ALSFRS-R total
- ALSFRS-R items (1-12)
- ALSFRS-R date
- Predicted VC (%)
- VC (liter)
- VC date

- Time-to-event data
  - Death or composite survival endpoint (days)
  - Censor if not deceased (days)
  - Dropout (days)

7

Table IV: AD variables

Aggregate-level data variables	**Variable name**
General information • First author • Year • Title • DOI • Country • Sponsor	**General information** • AUTHOR • YEAR • TITLE • DOI • COUNTRY • SPONSOR
Population data (for each treatment group) • Group size • Age (mean yrs at enrollment) • Sex (% male) • Weight (mean kg) • BMI • Site of onset (% bulbar) • Symptom duration (mean months) • Diagnostic delay (mean months) • Riluzole use at enrollment • ALSFRS-R total score (at baseline) • VC (%predicted) at baseline • ΔFRS	**Population data** • N • AGE • SEX • WEIGHT • BMI • ONSET • DISDUR • DXDELAY • RILUSE • TOTAL • VC • SLOPE *Add [_CON] for control group* *Add [_TRT] for treatment group* *Add [_TRT2] for second treatment etc* *e.g.: N_CON, N_TRT*
Intervention data • Name intervention (+ dosage)	**Intervention data** • NAME_INT

• Type of intervention (pharm, cell, suppl) • Mode of administration • Randomization ratio • Trial study design • Lead-in duration (months) • Treatment duration (mean months) • Total duration (months)	• TYPE_INT • ADMIN • RATIO • DESIGN • DUR_LEAD • DUR_TRT • DUR_TOT

Outcome data (for each treatment group)
• Analysis used for outcome
• ALSFRS-R at end FU
• ALSFRS-R slope
• ALSFRS-R mean standard error
• ALSFRS-R error slope
• ALSFRS-R mean p-value
• ALSFRS-R p-value slope
• 95% Confidence interval ALSFRS-R
• Adjustment variables in ALSFRS-R analysis
• N of ALSFRS-R in analysis
• VC at end FU
• VC slope
• VC mean standard error
• VC error slope
• VC mean p-value
• VC p-value slope
• 95% Confidence interval VC
• Adjustment variables in FVC analysis
• N of VC in analysis
• **Survival:**
  ○ Hazard ratio mean
  ○ Hazard ratio standard error
  ○ Hazard ratio 95% confidence interval
	Outcome data (end of follow-up)
	• ANALYSIS
	• FRS-R_MEAN
	• FRS-R_SLOPE
	• FRS-R_MEAN_SE
	• FRS-R_SLOPE_SE
	• FRS-R_MEAN_P
	• FRS-R_SLOPE_P
	• FRS-R_CI
	• ADJUST
	• N_FU
	• VC_MEAN
	• VC_SLOPE
	• VC_MEAN_SE
	• VC_SLOPE_SE
	• VC_MEAN_P
	• VC_SLOPE_P
	• VC_CI
	• VC_ADJUST
	• VC_N_FU
	• **Survival:**
	  ○ SURV_HR
	  ○ SURV_HR_SE
	  ○ SURV_HR_CI

○ Hazard ratio p-value • **Drop-outs:** ○ Death ○ Adverse event ○ Termination of participation ○ Disease progression ○ Other • AEs reported • SAEs reported	○ SURV_HR_P • **Dropout:** ○ DROP_DEATH ○ DROP_AE ○ DROP_TERM ○ DROP_PROG ○ DROP_OTHER • AE • SAE *Add [_CON] for control group* *Add [_TRT] for treatment group* *Add [_TRT2] for second treatment etc* *e.g.: N_CON, N_TRT*
Study descriptives • Primary outcome (ALSFRS-R, VC, survival) • Protocol published/accessible? (y/n) • IPD published/accessible? (y/n) • Kaplan-Meier survival curve present? (y/n) • ALSFRS-R analysis method mentioned? (y/n) • Survival analysis method mentioned? (y/n) • Sample size calculation mentioned (y/n) • Placebo arm? (y/n) • **Outcome reported?** ○ ALSFRS-R (y/n) ○ VC (y/n) ○ Survival (y/n) ○ Electrophysiology (y/n) ○ Muscle strength (ISOMETRIC/HHD/MRC) (y/n) ○ Neurofilament Light Chain (y/n)	**Dummies** • OUTCOME • PROT_ACC • IPD_ACC • KAPMEI • FRS-R_METH • SURV_METH • SAMP_CALC • PLACEBO • **Reported:** ○ FRS-R_REP ○ VC_REP ○ SURV_REP ○ ELECT_REP ○ MUSC_REP ○ NFL_REP

Table V: variable code list

Name	Definition	Levels
TITLE	Title of article	Nominal
DOI	DOI number	Nominal
AUTHOR	Name of first author	Nominal
COUNTRY	Country	Nominal
SPONSOR	Source of funding	0 = academic, 1 = industry, 2 = mixed
PUB_DATE	Publication date	Date
N (for all treatment groups)	Number of participants in treatment group at enrollment	Continuous
AGE (for all treatment groups)	Mean age at enrollment	Continuous (years)
SEX (for all treatment groups)	% of participants that are male	% Male
WEIGHT (for all treatment groups)	Mean weight of participants	Continuous (kg)
BMI (for all treatment groups)	Mean BMI of participants	Continuous (kg/m^2)
ONSET (for all treatment groups)	% of participants that have bulbar onset	% Bulbar onset
DISDUR (for all treatment groups)	Mean duration of symptoms at enrollment	Continuous (months)
DXDELAY (for all treatment groups)	Mean time from onset to diagnosis	Continuous (months)

RILUSE (for all treatment groups)	% of participants that use riluzole at enrollment	Percentage users
TOTAL (for all treatment groups)	ALSFRS-R total score at baseline	Ordinal
VC (for all treatment groups)	VC (%predicted) at baseline	% Of predicted capacity
SLOPE	Monthyl decline of ALSFRS-R at baseline	Continuous
NAME_INT (for all treatment groups)	Name of the treatment	Nominal
TYPE_INT (for all treatment groups)	Treatment type	0 = pharmaceutical, 1 = cell therapy, 2 = supplement
GROUP_INT (for all treatment groups)	Subgrouping	<<undefined>>
ADMIN (for all treatment groups)	Mode of administration	0 = oral, 1 = IV, 2 = intrathecal, 3 = subcutaneous, 4 = intramuscular, 5 = transdermally
RATIO	Randomization ratio of intervention:control	Continuous (ratio)
DESIGN	Type of study design in trial	Nominal
DUR_LEAD	Lead-in duration, time when enrolled but not yet treated	Continuous (months)
DUR_TRT	Treatment duration	Continuous (months)
DUR_TOT	Total duration of study	Continuous (months)

ANALYSIS	Type of analysis used to determine primary outcome	Nominal
FRS-R_MEAN (for all treatment groups)	ALSFRS-R total score at end of follow-up	Continuous
FRS-R_SLOPE (for all treatment groups)	ALSFRS-R monthly change ((ALSFRS_MEAN - TOTAL) / DUR_TRT)	Continuous
FRS-R_MEAN_SE (for all treatment groups)	ALSFRS-R mean standard error at end of follow-up	Continuous
FRS-R_SLOPE_SE (for all treatment groups)	ALSFRS-R monthly change in standard error	Continuous
FRS-R_MEAN_P (for all treatment groups)	ALSFRS-R mean p-value at end of follow-up	Continuous
FRS-R_SLOPE_P (for all treatment groups)	ALSFRS-R monthly change in p-value	Continuous
FRS-R_CI (for all treatment groups)	ALSFRS-R 95% confidence interval at end of follow-up	[lower bound, upper bound]
ADJUST (for all treatment groups)	Variables that were used for stratifying or adjusting ALSFRS-R	Nominal
N_FU (for all treatment groups)	Number of patients with ALSFRS-R scores used in analysis	Continuous
VC_MEAN (for all treatment groups)	VC % of predicted capacity at end of follow-up	% Of predicted capacity

VC_SLOPE (for all treatment groups)	VC % of predicted capacity monthly change ((VC_MEAN - VC)/DUR_TRT)	% Of predicted capacity
VC_MEAN_SE (for all treatment groups)	VC mean standard error at end of follow-up	Continuous
VC_SLOPE_SE (for all treatment groups)	VC monthly change in standard error	Continuous
VC_MEAN_P (for all treatment groups)	VC mean p-value at end of follow-up	Continuous
VC_MEAN_SE (for all treatment groups)	VC monthly change in p-value	Continuous
VC_CI (for all treatment groups)	VC 95% confidence interval at end of follow-up	[lower bound, upper bound]
ADJUST_VC (for all treatment groups)	Variables that were used for stratifying or adjusting VC	Nominal
N_FU_VC (for all treatment groups)	Number of patients with VC scores used in analysis	Continuous
SURV_HR	Hazard ratio mean	Continuous
SURV_HR_SE	Hazard ratio standard error	Continuous
SURV_HR_CI	Hazard ratio 95% confidence interval	[lower bound, upper bound]
SURV_HR_P	Hazard ratio p-value	Continuous
DROP_DEATH (for all treatment groups)	Number of drop-outs due to death	Continuous
DROP_AE (for all treatment groups)	Number of drop-outs due to adverse events	Continuous

DROP_TERM (for all treatment groups)	Number of drop-outs due to terminating participation	Continuous
DROP_PROG (for all treatment groups)	Number of drop-outs due to disease progression	Continuous
DROP_OTHER (for all treatment groups)	Number of drop-outs due to other reasons	Continuous
AE (for all treatment groups)	Number of adverse events in group at end of follow-up	Continuous
SAE (for all treatment groups)	Number of serious adverse events in group at end of follow-up	Continuous
OUTCOME	Primary outcome (e.g., ALSFRS-R, survival, safety)	Nominal
PLACEBO	Is a placebo arm present?	0 = no, 1 = yes
PROT_ACC	Is the study protocol accessible?	0 = no, 1 = yes
IPD_ACC	Is IPD accessible?	0 = no, 1 = yes
KAPMEI	Are Kaplan-Meier survival curves used?	0 = no, 1 = yes
FRS-R_METH	Method of ALSFRS-R analysis mentioned?	0 = no, 1 = yes
SURV_METH	Method of survival analysis mentioned?	0 = no, 1 = yes
SAMP_CALC	Method of sample size calculation mentioned?	0 = no, 1 = yes
FRS-R_REP	Is ALSFRS-R reported as outcome?	0 = no, 1 = yes
VC_REP	Is VC reported as outcome?	0 = no, 1 = yes
SURV_REP	Is survival reported as outcome?	0 = no, 1 = yes

ELECT_REP	Is electrophysiology reported as outcome?	0 = no, 1 = yes
MUSC_REP	Is muscle strength reported as outcome? (ISOMETRIC/HHD/MRC)	0 = no, 1 = yes
NFL_REP	Is neurofilament light chain reported as outcome?	0 = no, 1 = yes

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐	☒	
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	3-24
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	328-333
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	334-337
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	334-337
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	334-337
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	66-101
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	103-111, 139-173
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	139-195
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	119-125
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	119-127
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	205-29
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	129-137
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	197-203
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	Supplemental data
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	216-221
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	244-256
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	211-242
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	211-242
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	211-242
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	244-256
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	244-256

BMJ Open

A living systematic review and comprehensive network meta-analysis of ALS clinical trials: study protocol

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Manuscript ID	bmjopen-2024-087970.R1
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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Neurology
Keywords:	Systematic Review, Network Meta-Analysis, Neuromuscular disease < NEUROLOGY

A living systematic review and comprehensive network meta-analysis of ALS clinical trials: study protocol

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Word count: 3454

0.0 Abstract

Introduction: Amyotrophic lateral sclerosis (ALS) is a fatal neurogenerative disease with no effective treatment to date. Despite numerous clinical trials, the majority of studies have been futile in their effort to significantly alter the course of the disease. However, these studies may still provide valuable information for identifying patient subgroups and generating new hypotheses for future research. Additionally, synthesizing evidence from these studies may help overcome limitations of individual studies. Network meta-analysis may refine the assessment of efficacy in specific patient subgroups, evaluate intervention characteristics such as mode of administration or biological mechanisms of action, and rank order promising therapeutic areas of interest Therefore, we aim to synthesize the available evidence from ALS clinical trials.

Methods and analysis: We will conduct a systematic review to identify all clinical trials that assessed disease-modifying pharmaceutical therapies, cell therapies, or supplements in patients with ALS. Outcomes of interest are clinical disease progression outcomes and survival. We will conduct this search in the period Q4 2024 in three databases: PubMed, Embase, and clinicaltrials.gov, for studies from 1999 to 2023. Individual patient data and aggregate data will be collected and subsequentially synthesized in meta-analytical models. The final model will be presented as an open-source web-application, with biannual updates of the underlying data, thereby providing a 'living' overview of the ALS clinical trial landscape.

Ethics and dissemination: No ethics approvals are required. Findings will be presented at relevant conferences and submitted at peer-reviewed journals. Data will be stored anonymously in secure repositories.

Keywords: *amyotrophic lateral sclerosis, protocol, systematic review, network meta-analysis, living review*

0.1 Strengths and limitations of this study

- This network meta-analysis (NMA) and living review will centrally synthetize all randomized clinical trials in ALS investigating disease-modifying therapies
- Retrieved studies will be screened with a validated machine-learning tool (ASReview) and through predefined eligibility criteria.
- • Specific efforts will be made to disentangle the effects of study-level characteristics, including mode of administration and mechanism of action, and quantify heterogeneity in treatment responses.
- The main challenges for this study will be the unavailability of individual patient data (IPD) and large between-study differences in trial design, which will be partially addressed through hybrid use of patient-level and aggregate data.

1.0 Introduction

Amyotrophic lateral sclerosis (ALS) is a rare and fatal neurogenerative disease which is characterized by the loss of motor neurons and progressive muscle weakness, followed by death within, on average, three to five years after symptom onset.(1-3) Although over 100 clinical trials have been conducted in the last 25 years,(4) treatment options remain limited, with no substantial improvement in the patient's life expectancy.(5) The futile clinical trial landscape is the result of an interplay of various elements, including, but not limited to, a weak a priori study rationale; underestimation of the pathophysiological and clinical heterogeneity; and a suboptimal or flawed study design.(4)

By combining the results and outcomes of previous clinical trials, it may be possible to improve the design and conduct of future studies.(6) This has been demonstrated by initiatives such as the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) or the Answer ALS database,(7, 8) which have been of significant value for characterizing the natural history of ALS. These datasets provide key input for sample size calculations, eligibility criteria and overall trial design considerations.(9) Current initiatives are, however, lacking data on the received experimental treatment and individual studies are not identifiable. This limits the value of the data, as key therapeutic questions, such as subgroup efficacy(10) or the impact of intervention characteristics such as mode of administration and patient burden,(11) cannot be addressed.

Hence, study-level evidence synthesis may improve the use of the available data. Moreover, it provides an opportunity to study between-trial variability,(12) and overcome limitations of individual clinical trials. By combining all clinical trials into a network, i.e. a NMA, information can be jointly harvested across studies through direct and indirect study comparisons.(13) This approach yields increased statistical power to detect trends that may not be observed in single studies.(14)

From the network, head-to-head intervention comparisons can be made to rank order interventions based on their treatment effects and to identify areas of therapeutic interest where more research is needed. This would be of particular value for large drug screening platforms such as HEALEY,(15) MND-SMART,(16) and EXPERTS ALS, as it may provide insight for investigating new therapeutic leads.(17)

The increased precision may be of particular interest to potentially identify subgroups of responding patients in otherwise futile clinical trials. Especially in smaller studies, efficacy signals in a small subset of patients may be lost when there is a large group of non-responders.(10) The value of such a meta-analytical approach has been shown previously for lithium carbonate.(18) A potentially responding subgroup was identified for patients homozygous for the c-allele of the *UNC13A* gene, which is under investigation in a confirmatory study.(19)

Another area of interest is trial-related factors, such as mode of administration or mechanism of action. The significance of the former was recently highlighted for intravenous therapies, where a potential procedural risk of prolonged intravenous administration may have had a negative impact on the patient's prognosis, potentially jeopardizing patient safety and confounding study results.(20-22). A meta-analytical approach on the latter may reveal that groups of treatments sharing a common biological mechanism are more efficacious on certain outcomes or for specific subgroups. As these trial-related factors are applicable to all patients within a single study, regardless of randomized treatment allocation, they cannot be assessed within a single study; meta-analytical models are needed to investigate their impact.

In this study, therefore, we aim to systematically identify all completed randomized clinical trials (RCTs) in ALS and synthesize their evidence through a comprehensive NMA, thereby improving the utilization of existing clinical trial information and augmenting current large data initiatives. The final NMA model will be presented as an open-source web-application, with biannual updates of the underlying data, to provide a 'living' overview of the ALS clinical

trial landscape and serve as a tool for trial design, information dissemination, and generating new hypotheses.(23)

1.1 Objectives

The primary objective of this study is to perform an NMA and synthesize the available data from randomized clinical trials, to enable the creation of efficacy rankings, to identify potentially responding subgroups, and to generate new hypotheses for future research.

Subobjectives include: 1) conducting a systematic review of RCTs in ALS that evaluate disease modifying drugs, cell therapies, or supplements; 2) obtaining and combining aggregate and individual patient data (IPD) from each study; 3) developing a network meta-analytical model; and 4) disseminating the findings through an open-source web-application with biannual updates of the underlying data.

2.0 Methods and analysis

The protocol was designed based on principles outlined in The Cochrane Handbook for Systematic Reviews of Interventions, and the Centre for Reviews and Dissemination's Guidance for Undertaking Reviews in Health Care.(24, 25) Due to the nature of this study, no public or patient involved in planned.

2.1 Search strategy

The aim of the search is to identify phase II and III RCTs for ALS that assess the efficacy of disease-modifying therapies. In brief, we will search PubMed, Embase, and trial registries (clinicaltrials.gov, EU Clinical Trials Register, and ANZCTR), employing a prespecified search string developed in conjunction with information experts from the University Medical Center Utrecht (UMCU). The search string for PubMed and Embase includes terms for "ALS" and "trial" and sets a publication date filter from 1999 and to present, in clinicaltrials.gov we will search for trials conducted within the same timeframe. The databases will be searched in the period Q4 2024. The full search term is included in Supplement data Table I. Two reviewers will deduplicate and independently cross-reference the search output. As a last step, the

references of included studies and any systematic reviews found in the search will be screened for additional eligible studies not found the database search (snowballing).

2.2.1 Screening process

The eligibility of each study will be determined by applying the inclusion and exclusion criteria for title/abstract, with ASReview (section 2.3).(26) Subsequently, the remaining studies will undergo a second screening process by applying the inclusion and exclusion criteria for full-texts (section 2.4). All studies will be screened by two reviewers, after which the results will be compared and discussed until consensus is reached. If no consensus is reached, a third reviewer will be consulted. The number of excluded studies and the reasons for exclusion will be recorded in Figure 1.

<insert figure 1 here>

2.2.2 Types of studies

RCTs consisting of two or more comparative arms are eligible. The control group may be treated with a placebo, sham, another therapeutic intervention, or usual care. To ensure the inclusion of phase II and III RCTs, the total randomized sample size must contain at least 20 patients with ALS and the randomized treatment period must not be shorter than 12 weeks. The treatment period is defined as the time from blinded treatment initiation until the last follow-up or the commencement of an open-label extension period. We chose to exclude phase I studies, as the sample sizes are too small and follow-up duration is too short to allow investigation of efficacy. Larger phase Ib/IIa may be eligible if they fulfill the inclusion criteria. Moreover, phase IV trials are excluded, as new drugs are added-on to standard of care, rending it not feasible to randomize a comparative trial of standard of care vs. a new drug. Clinical trials with deviating designs such as a single-arm, crossover, or externally controlled design are excluded, alongside studies with an open-label extension unless they are preceded by a randomized treatment period of at least 12 weeks. Multi-stage trials are eligible if at least one stage fulfills the inclusion criteria.

2.2.3 Types of interventions

Interventions can be classified as either disease-modifying (e.g., slowing of clinical progression rate) or symptomatic (e.g., drug therapy for sialorrhea, depression, or pain).(27) The primary interest of this review are disease-modifying interventions, and the following types of interventions will be considered: (1) pharmaceutical interventions, (2) cell therapies, and (3) supplements (if intended to be disease-modifying). Studies that evaluate symptomatic treatments will be excluded. Studies investigating devices, dietary interventions other than supplements (e.g., high-caloric intake), or physical activity programs will also be excluded.

2.2.4 Types of outcomes

The outcomes of interest are measures of clinical disease progression and overall survival. Eligible outcomes include functional rating scales (e.g., the revised ALS functional rating scale [ALSFRS-R]), lung function (e.g., slow or forced vital capacity [VC]), and survival (either defined as death alone or as a composite, e.g. with respiratory insufficiency [non-invasive ventilation ≥16h/day] and/or tracheostomy).

2.2.5 Study population

Eligible patient populations are patients diagnosed with ALS according to the (revised) El Escorial, Awaji, or Gold Coast criteria.(28) Studies enrolling patients before 1999 will be excluded, as thereafter riluzole was introduced as a new standard of care, and the revised version of the ALSFRS, which more adequately measures respiratory involvement, was adopted.(29, 30)

2.3 ASReview for study selection based on title/abstract

ASReview is a machine-learning tool that increases screening efficiency by presenting the title and abstract of studies most similar to eligible ones.(26) The ASReview process starts with a manual preselection of eligible and ineligible studies. To achieve an informative preselection set, these studies are heterogeneous in terms of intervention and publication date. The preselected studies can be found in Supplemental data Table II. Eligibility for the title/abstract screening and (systematic) review screening will be based on the selection criteria listed in Table 1. The selection process continues until a stopping criterion has been reached, which will

be defined as 100 consecutive ineligible studies.(26) Five percent of the unseen studies will be randomly sampled to examine whether any eligible studies have been missed. If so, the screening process will recommence until the stopping criterion has been reached.

Table 1: Selection criteria for title/abstract screening

Study type	**Criteria**
Studies eligible for full-text screening	Exclusion criteria: 1. Study is not a clinical trial for ALS 2. Study is not randomized 3. Intervention is not a pharmaceutical drug, cell therapy, or supplement 4. Study does not report clinical efficacy outcomes 5. Study is not the primary report of the trial (i.e., a post-hoc analysis) 6. The randomized period is shorter than 12 weeks 7. Randomized population consists of fewer than 20 patients 8. Study has a deviating design (fully open-label, cross-over, historically controlled) 9. Patient enrollment started before 1999 10. Study is a phase I or IV trial
Systematic reviews	Inclusion criteria: 1. Study is a systematic review for ALS 2. Study summarizes clinical trial evidence of disease-modifying therapies

2.4 Full-text criteria

The studies found to be eligible in ASReview will undergo a full-text screening. The final set of selection criteria, based on the eligibility described in section 2.2.2 to 2.2.5, is listed in Table 2. These criteria are slightly stricter than the title/abstract criteria, as they finalize the set of included studies.

Table 2: Full-text screening inclusion and exclusion criteria

Criterion type	Criteria
Inclusion criteria	1. Study reports a randomized clinical trial in either phase II or III 2. Study population consists of patients diagnosed with ALS according to the (revised) El Escorial, Awaji, or Gold Coast criteria 3. Intervention is a pharmaceutical drug, cell therapy, or supplement 4. Clinical efficacy outcomes are included as one of the endpoints
Exclusion criteria	1. Study is a phase I or IV trial 2. The randomized treatment period is shorter than 12 weeks 3. Total randomized population consists of fewer than 20 patients with ALS 4. Study design is ineligible (e.g., open-label, cross-over, externally-controlled) 5. Patient enrollment started before 1999 6. Intervention is intended for symptomatic treatment 7. Study is incomplete or inaccessible (e.g., no full-text available) 8. Study is not the primary report of the trial (e.g., a post-hoc analysis)

2.5 Data extraction

Aggregated data (AD) of key study characteristics and outcomes will be extracted from all included studies, while corresponding authors will be approached for IPD via e-mail. For the

studies where IPD collection is not feasible, the analysis will proceed using only the available AD from the respective study. We strive to send out data request in autumn 2024. We will assume the author is uninterested if no reply has been received after 90 days, unless other reasons for inaccessibility arise. We will extract AD in Q4 2024, after the database search and study inclusion has been completed.

AD of interest includes general study information, baseline data (e.g., age, treatment group size, ALSFSR-R at baseline), intervention data (e.g., name, mode of administration, treatment duration), and outcome data (e.g., hazard ratio's, ALSFRS-R change from baseline, p-values). Supplemental data Table III and IV contain the complete list of essential IPD and AD variables that will be extracted from the studies. Supplemental data Table V contains the code list for the AD variable extraction.

2.6 Data management

IPD will be collected in compliance with local regulations and under supervision of a database manager appointed at the UMCU. All aggregate and patient-level data will be stored securely at the servers of the UMCU. Access to patient-level data will be restricted to authorized staff; costs of the data storage will be covered by the UMCU.

2.7 Statistical analysis

The primary aim of the analysis is to synthesize the available individual patient and aggregate data from all included RCTs and evaluate the efficacy of each intervention. As IPD will likely not be available for every study, we will employ network meta-analytical techniques for synthesizing IPD and AD.

In brief, efficacy of the interventions will be evaluated as follows. First, we will estimate the overall efficacy of ALS treatments by conducting a random-effects pairwise meta-analysis for the ALSFRS-R, VC and survival outcome data, to determine whether any treatment provides benefits compared to placebo.(31) We will pool the AD from the different active treatment arms into one group and compare the pooled group to all pooled patients who received placebo.(32)

Secondly, we will employ a random-effects NMA model. The utilization of NMA offers several advantages, including the ability to 1) compare interventions that have not been performed in previous studies;(33) 2) obtain more precise estimates compared to pairwise meta-analysis through direct and indirect comparisons;(34) and 3) establish a ranked order or hierarchy for each investigational intervention based on their efficacy.(35) The statistical model consists of a two-stage approach to combine the AD and IPD.(36, 37). As our objective is exploratory and hypothesis-generating, a standard 95% confidence interval will be employed to display treatment effect estimates. Missing data in any of the covariates will be addressed by multiple imputation.(38)

We will conduct sensitivity analyses by restricting the model to include only studies where IPD are available, studies within the same class of mechanism of action (with classes delineated by Mead et al.)(39), studies that are at low risk of bias, or have total sample sizes ≥ 50 patients. To further investigate the impact of different classes of mechanisms of action, we will perform IPD network meta-regression. This will allow us to assess the differential effects associated with each class category and enable us to simultaneously account for and analyze the variability across different classifications, providing a comprehensive understanding of the effects of the class of mechanism of action on the outcomes of interest.(40)

Finally, the network structure will be visually presented through a network plot, while the output of the NMA model will be presented through forest plots, league tables, and tables displaying ranking metrics such as P-scores.(41) A demonstrative network plot and table with ranking metrics is provided in Figure 2.

<insert figure 2 here>

2.8 Addressing heterogeneity

Heterogeneity in an essential principle when synthesizing data from different sources, as it may bias results when improperly accounted for. The random-effects NMA model was chosen to address between-trial variability and heterogeneity in study populations, outcomes and results. We will employ covariate adjustment and matching through propensity scores based on key prognostic characteristics (as defined by Westeneng et al. (42)) to address differences in patient characteristics. Additionally, we will conduct subgroup analyses (among e.g., bulbar patients,

fast-progressors) to determine which factors might modify the treatment effect, identify sources of outcome variability, or whether outcome variation may be caused by potentially random confounding factors.

Moreover, matching also allows us to 'reconnect' networks. Networks may be 'disconnected' as a result of differences in a study-level variable, such as mode of administration.(43) This connection allows us to explore the effect of mode of administration by comparing the pooled placebo groups of, e.g., invasive vs. non-invasive modes. Furthermore, outcomes may be measured differently (e.g., change from baseline, mean difference, % reduction). To ensure comparability, the ALSFRS-R and VC will be recalculated as monthly decline during the randomized period. A monthly rate of decline is chosen as it is time-independent and allows pooling of results from studies with varying lengths of follow-up. Survival will be amalgamated amongst studies that share the same event definition and are expressed as hazard ratio.

Heterogeneity in the model will be explored by visually inspecting forest plots and through the global assessment of the Q-statistic. Moreover, it will be quantified with the metrics τ^2 and I^2 estimated with the Restricted Maximum Likelihood method. I^2 denotes the percentage of variability due to heterogeneity rather than chance, while a large value of I^2 coupled with a relatively large estimate of τ^2 signifies the presence of heterogeneity. If substantial heterogeneity is detected, it will be further explored through network meta-regression and subgroup analyses. These methods help identify potential sources of heterogeneity by examining the influence of study-level and patient-level characteristics.

A key assumption of NMA is that of transitivity, which refers to the ability to infer through indirect evidence. A violation of transitivity threatens the validity of the NMA findings. To statistically evaluate transitivity, consistency will be used as a proxy. The presence of a notable difference between direct and indirect evidence signifies the presence of inconsistency, which may mask the presence of heterogeneity. Network consistency will be tested both globally and locally. Global methods test whether the network is inconsistent as a whole, while local methods identify inconsistent network comparisons. Global assessment of inconsistency includes the integration of inconsistency factors in the inconsistency detection process and the use of between-designs Q-statistic under the full design-by-treatment interaction random-effects model, while local assessment involves the use of node-split methods.(44-46)

2.9 Quality assessment

We will assess the quality of the included studies in two ways. Initially, the short version of the revised Cochrane risk-of-bias tool for randomized trials will serve as a framework for summarizing the risk of bias in five domains, namely: randomization process; deviations from intended interventions; missing outcome data; outcome assessment; and selective reporting. Each domain will be rated as 'low risk', 'some concerns', or 'high risk', and an overall score will be determined. Secondly, quality of the evidence in the individual studies will be assessed with the GRADE approach. This method evaluates the outcomes of each study and determines how closely the estimated effect approximates the true effect and is rated on a 4-level scale from 'very low' to 'high'. The outcomes of both assessments will be summarized and presented in a figure. Lastly, the Confidence in Network Meta-Analysis (CINeMA) framework will be used to display bias, coherence, and heterogeneity in the evidence found, and aid in the transparent reporting of the NMA.(47)

2.10 Living NMA model framework

Ultimately, the output of the NMA model will be presented as an interactive, open-source web-application using the R package *Shiny*.(48) A standardized operating procedure will be developed for routinely updating the NMA model, including biannual reviews of the literature to identify new studies, and a pipeline for IPD data requests, and to update the data analysis models accordingly. This will create a 'living NMA model' that could potentially serve as a perpetual overview of the clinical trial landscape of ALS and an interactive environment to support trial design.

2.11 Expected challenges and considerations

One of the potential challenges of this study is the acquisition of IPD, especially from industry-sponsored studies due to intellectual property restrictions. This was the main reason for the proposed statistical framework as it is flexible and could utilize both IPD as well as AD from the published literature. Hence, the missing IPD can be supplemented with AD which may limit the impact on the main study objectives. Naturally, IPD will be required for subgroup analysis – especially for those subgroups that are not commonly reported – and to overcome 'disconnected' networks as a result of, for example, differential modes of administration.

Other limitations of the network will be primarily driven by the limitations of the underlying study quality and available data. These will be evaluated with the tools outlined in Quality assessment (section 2.8).

2.12 Patient and Public involvement

This study protocol has been initiated without prior patient involvement. However, the rationale for undertaking it is deeply rooted in patients' urgent need for better disease-modifying treatment for this relentless and rapidly progressing disease. Topline results of this study will be disseminated to patients via communications from the Dutch ALS Foundation.

3.0 Ethics and dissemination

This study will meta-analyze previously collected, anonymized datasets. No ethics approvals are necessary for the initiation of this project. An overview of all included studies will be provided, as well as an overview of the search procedure. The AD dataset will be made available upon reasonable request with the corresponding author. The IPD datasets will not be made publicly available due to personal data protection considerations.

The findings obtained in this project will be presented at relevant ALS conferences (e.g., ENCALS and MNDA conferences) and submitted to peer-reviewed scientific journals. In addition, as previously stated, the NMA model will be presented as an open-access web-application to aid in dissemination.

4.0 Statements

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None

Author contributions

FvL, GS, SN & RvE drafted the protocol. FvL & RvE developed the search string and criteria. FvL & IB will be involved in screening and data collection. FvL, GS, DM, DW, JvU, LvdB, SN & RvE are involved with revisions. FvL, GS, DM, SN & RvE will be involved in developing the statistical framework. FvL, GS, SN & RvE will be involved in data analysis

and manuscript writing. RvE is the guarantor. All authors have read and approved the final protocol.

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Competing interests

The authors declare that they have no competing interests.

5.0 List of abbreviations

In order of appearance:

- ALS: Amyotrophic Lateral Sclerosis
- NMA: Network Meta-Analysis
- IPD: Individual Patient Data
- PRO-ACT: Pooled Resource Open-Access ALS Clinical Trials
- RCT: Randomized Clinical Trial
- UMCU: University Medical Centre Utrecht
- ALSFRS-R: ALS Functional Rating Scale Revised
- VC: Vital Capacity
- AD: Aggregated Data
- CINeMA: Confidence in Network Meta-Analysis

5.1 Figure 1: Flow diagram of study selection

Figure 1 legend. Figure 1 denotes the search process. After study completion, the number (n) of studies selected at each step will be indicated in each box. The dotted line represents the reference screening in the included studies for those studies not found in the database search.

5.2 Figure 2. Hypothetical network diagram and harm/benefits table

Figure 2 legend. The figure above represents a hypothetical network. The network consists of intervention and placebo nodes (grouped per administration mode), and the solid lines connecting them indicate direct comparisons. Non-invasive nodes consist of oral and transdermal, while invasive nodes consist of intravenous, intrathecal, intramuscular, and subcutaneous modes of administration. The dashed lines reflect 'disconnected' networks that are reconnected through matching and propensity score methods. The table ranks the interventions based on their expected benefit, compared to placebo, as well as the expected harm of administration modes estimated through matching.

6.0 References

EndNote V20.6 (Clarivate Analytics, PA, USA) was used as reference manager.

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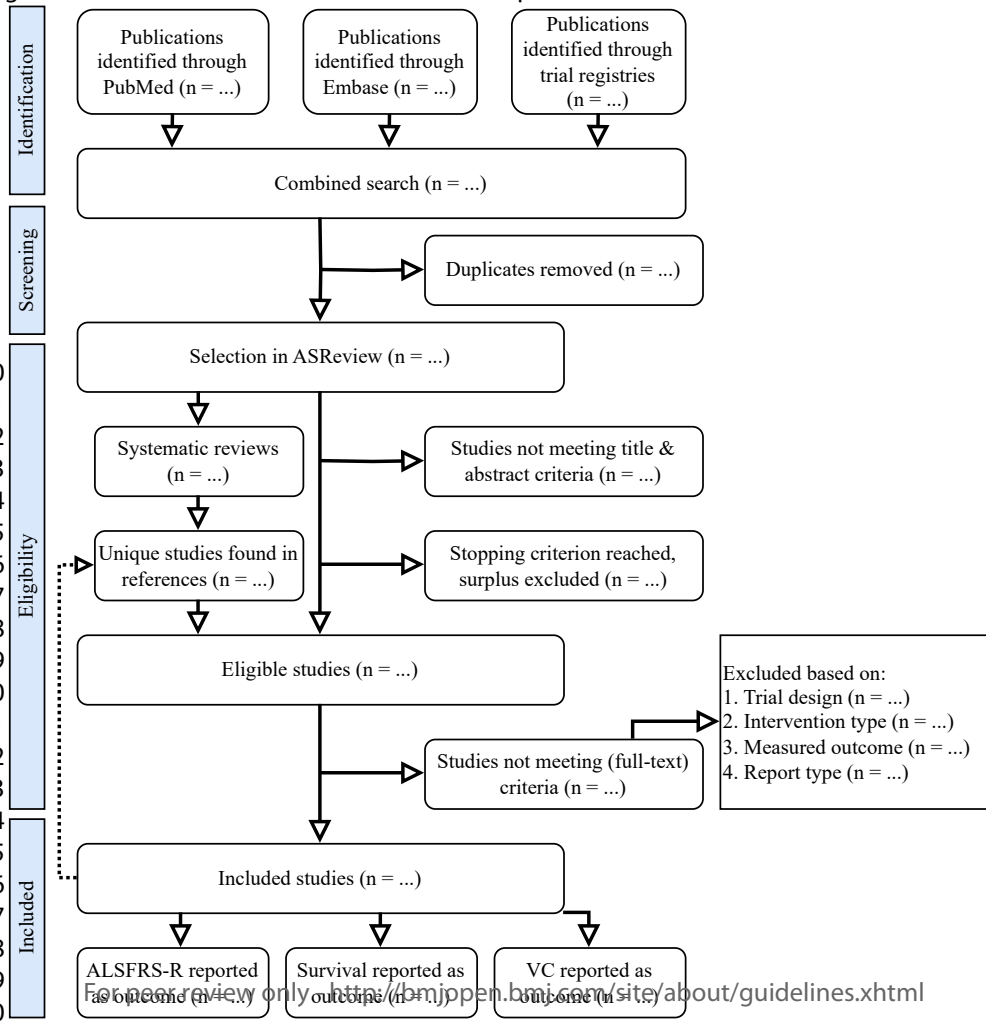

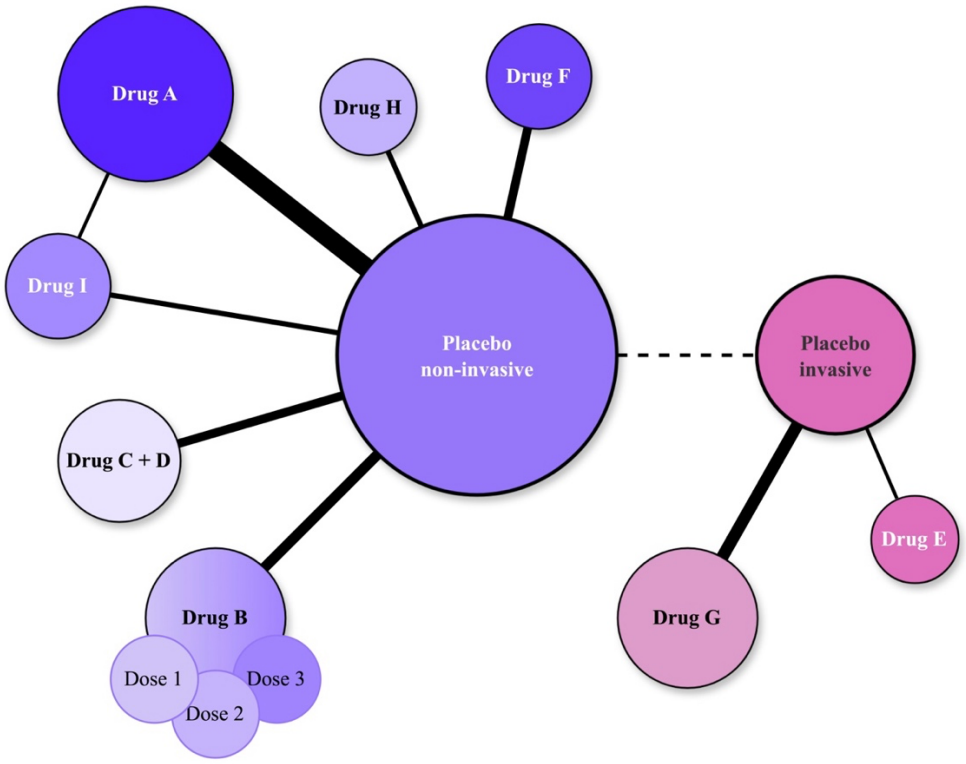

Rank	Intervention	Expected benefit
1	Drug A	1.72
2	Drug F	1.53
	…	…
9	Drug B – Dose 1	-0.97
10	Drug C + D	-1.81

Mode of administration	Expected harm
Non-invasive (purple)	0.00 (reference)
Invasive (lilac)	-0.41

Supplemental data

Table I: Search strings for PubMed, Embase, and trial registries search

Database	PubMed	Embase	Trial registries
Search string	("Amyotrophic Lateral Sclerosis"[Mesh] OR "Motor Neuron Disease"[Mesh] OR "ALS"[TIAB] OR "amyotrophic lateral sclerosis"[TIAB] OR "Gehrig*"[TIAB] OR "Motor Neuron Disease*"[TIAB] OR "Charcot*"[TIAB] OR "MND"[TIAB] AND (1999/1/1:2023/01/01[pdat])) AND ("Clinical Trials as Topic"[Mesh] OR "trial*"[TIAB] OR "randomi*"[TIAB] AND (1999/1/1:2024/01/01[pdat]))	('amyotrophic lateral sclerosis'/exp OR 'motor neuron disease'/exp OR 'als':ti,ab,kw OR 'amytrophic lateral sclerosis':ti,ab,kw OR 'gehrig*':ti,ab,kw OR 'motor neuron disease*':ti,ab,kw OR 'charcot*':ti,ab,kw) AND ('clinical trial'/exp OR 'trial*':ti,ab,kw OR 'randomi*':ti,ab,kw) AND [1999-2023]/py AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	ALS \(Amyotrophic Lateral Sclerosis\) | Completed, Terminated studies | Interventional studies | Study start from 01/01/1999 to 01/01/2024

Table II: Preselected studies used for ASReview

Eligible studies	Ineligible studies
1. "Trial of Sodium Phenylbutyrate-Taurursodiol for Amyotrophic Lateral Sclerosis" (2020, NEJM) 2. "Trial of celecoxib in amyotrophic lateral sclerosis" (2006, Neurology)	1. "Genetic variation in APOE, GRN, and TP53 are phenotype modifiers in frontotemporal dementia" (2020, Neurobiology of Aging) 2. "MTBVAC vaccine mediates immune response through the

3. "Dexpramipexole versus placebo for patients with amyotrophic lateral sclerosis (EMPOWER): a randomised, double-blind, phase 3 trial" (2013, The Lancet Neurology) 4. "Efficacy and safety of CNM-Au8 in amyotrophic lateral sclerosis (RESCUE-ALS study): a phase 2, randomised, double-blind, placebo-controlled trial and open label extension" (2023, Elsevier) 5. "Efficacy of minocycline in patients with amyotrophic lateral sclerosis: a phase III randomized trial" (2007, The Lancet Neurology) **6.** "A randomized, placebo-controlled trial of topiramate in amyotrophic lateral sclerosis" (2003, Neurology)	upregulation of T-regulatory cells in an ALS mouse model" (2021, Cell Reports Medicine)

Table III: IPD variables

Individual patient data variables

• Study information
  ○ Study ID
  ○ Country
• Patient data
  ○ Patient ID
  ○ Age (years)
  ○ Sex (male/female)
  ○ Height (cm)
  ○ Weight (kg)
  ○ Site of onset (bulbar/spinal)
  ○ Symptom duration (months)
  ○ Diagnostic delay (months)

- Intervention data
  - Treatment group
  - Mode of administration
  - Follow-up duration (months)
- Longitudinal
  - ALSFRS-R total
  - ALSFRS-R items (1-12)
  - ALSFRS-R date
  - Predicted VC (%)
  - VC (liter)
  - VC date
- Time-to-event data
  - Death or composite survival endpoint (days)
  - Censor if not deceased (days)
  - Dropout (days)

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Table IV: AD variables

Aggregate-level data variables	**Variable name**
General information • First author • Year • PMID • Title • DOI • Country • Sponsor	**General information** • AUTHOR • YEAR • PMID • TITLE • DOI • COUNTRY • SPONSOR
Baseline data (for each treatment group) • Group size • Age (mean yrs at enrollment) • Standard deviation age • Sex (% male) • Weight (mean kg) • Standard deviation weight • BMI • Standard deviation BMI • Site of onset (% bulbar) • Symptom duration (mean months) • Standard deviation symptom duration • Diagnostic delay (mean months) • Standard deviation diagnostic delay • Diagnostic duration (mean months) • Standard deviation diagnostic duration • Riluzole use at enrollment • ALSFRS-R total score (at baseline) • Standard deviation total score • VC (%predicted) at baseline	**Baseline data** • N • AGE • AGE_SD • SEX • WEIGHT • WEIGHT_SD • BMI • BMI_SD • ONSET • DISDUR • DISDUR_SD • DXDELAY • DXDELAY_SD • DXDUR • DXDUR_SD • RILUSE • TOTAL • TOTAL_SD • VC

• Standard deviation %VC • ΔFRS • Standard deviation ΔFRS	• VC_SD • SLOPE • SLOPE_SD *Add [_CON] for control group* *Add [_TRT] for treatment group* *Add [_TRT2] for second treatment etc* *e.g.: N_CON, N_TRT*
Intervention data • Name intervention (+ dosage) • Type of intervention (pharm, cell, suppl) • Mode of administration • Mechanism of action class • Randomization ratio • Trial study design • Lead-in duration (months) • Treatment duration (mean months) • Total duration (months)	**Intervention data** • NAME_INT • TYPE_INT • ADMIN • CLASS • RATIO • DESIGN • DUR_LEAD • DUR_TRT • DUR_TOT
Outcome data (for each treatment group) • Analysis used for outcome • Mean ALSFRS-R score (at end of FU) • St. error mean ALSFRS-R • Mean difference ALSFRS-R • St. error mean difference ALSFRS-R • 95% CI mean difference • Comparison arm mean difference • Mean ALSFRS-R (monthly) slope • St. error mean ALSFRS-R slope • Mean difference ALSFRS-R slope • Mean difference slope p-value	**Outcome data (end of follow-up)** • ANALYSIS • FRSR_MEAN • FRSR_MEAN_SE • FRSR_MEAN_DIFF • FRSR_MEAN_DIFF_P • FRSR_MEAN_DIFF_CI • FRSR_MEAN_DIFF_COMP • FRSR_SLOPE • FRSR_SLOPE_SE • FRSR_SLOPE_DIFF • FRSR_SLOPE_DIFF_P

• 95% CI mean difference slope
• Comparison arm mean difference slope
• ALSFRS-R change from baseline (CFB)
• ALSFRS-R CFB p-value
• ALSFRS-R CFB 95% CI
• Comparison arm ALSFRS-R CFB
• ALSFRS-R CFB timeframe (months)
• Adjusted variables in ALSFRS-R analysis
• N of ALSFRS-R in analysis
• Mean VC (at end FU)
• St. error mean VC
• Mean difference VC
• St. error mean difference VC
• 95% CI mean difference VC
• Comparison arm mean difference VC
• Mean VC (monthly) slope
• St. error mean VC slope
• Mean difference VC slope
• Mean difference VC slope p-value
• 95% CI mean difference slope
• Comparison arm mean difference slope
• Adjustment variables in FVC analysis
• N of VC in analysis
• **Survival:**
  ○ Mean hazard ratio
  ○ St. error hazard ratio
  ○ 95% CI hazard ratio
  ○ Hazard ratio p-value
  ○ Comparison arm hazard ratio
• **Drop-outs:**
  ○ Death
  ○ Adverse event
	• FRSR_SLOPE_DIFF_CI
	• FRSR_SLOPE_DIFF_COMP
	• FRSR_CFB
	• FRSR_CFB_P
	• FRSR_CFB_CI
	• FRSR_CFB_COMP
	• FRSR_CFB_TIME
	• ADJUST
	• N_FU
	• VC_MEAN
	• VC_MEAN_SE
	• VC_MEAN_DIFF
	• VC_MEAN_DIFF_P
	• VC_MEAN_DIFF_CI
	• VC_MEAN_DIFF_COMP
	• VC_SLOPE
	• VC_SLOPE_SE
	• VC_SLOPE_DIFF
	• VC_SLOPE_DIFF_P
	• VC_SLOPE_DIFF_CI
	• VC_SLOPE_DIFF_COMP
	• VC_ADJUST
	• VC_N_FU
	• **Survival:**
	  ○ SURV_HR
	  ○ SURV_HR_SE
	  ○ SURV_HR_CI
	  ○ SURV_HR_P
	  ○ SURV_COMP
	• **Dropout:**
	  ○ DROP_DEATH
	  ○ DROP_AE

○ Termination of participation ○ Disease progression ○ Other reasons • AEs reported • SAEs reported	○ DROP_TERM ○ DROP_PROG ○ DROP_OTHER • AE • SAE *Add [_CON] for control group* *Add [_TRT] for treatment group* *Add [_TRT2] for second treatment etc* *e.g.: N_CON, N_TRT*
Study descriptives • Primary outcome (ALSFRS-R, VC, survival) • Protocol published/accessible? (y/n) • IPD published/accessible? (y/n) • Kaplan-Meier survival curve present? (y/n) • ALSFRS-R analysis method mentioned? (y/n) • Survival analysis method mentioned? (y/n) • Definition of survival event • Sample size calculation mentioned (y/n) • Placebo arm? (y/n) • **Outcome reported?** ○ ALSFRS-R (y/n) ○ VC (y/n) ○ Survival (y/n) ○ Electrophysiology (y/n) ○ Muscle strength (ISOMETRIC/HHD/MRC) (y/n) ○ Neurofilament Light Chain (y/n)	**Dummies** • OUTCOME • PROT_ACC • IPD_ACC • KAPMEI • FRS-R_METH • SURV_METH • SURV_DEF • SAMP_CALC • PLACEBO • **Reported:** ○ FRS-R_REP ○ VC_REP ○ SURV_REP ○ ELECT_REP ○ MUSC_REP ○ NFL_REP

Table V: variable code list

Name	Definition	Levels
AUTHOR	Name of first author	Nominal
YEAR	Year of publication	Continuous
PMID	PubMed ID of main publication	Nominal
TITLE	Title of article	Nominal
DOI	DOI number	Nominal
COUNTRY	Country	Nominal
SPONSOR	Source of funding	0 = academic, 1 = industry, 2 = mixed
PUB_DATE	Publication date	Date
N (for all treatment groups)	Number of participants in treatment group at enrollment	Continuous
AGE (for all treatment groups)	Mean age at enrollment	Continuous (years)
AGE_SD	Standard deviation age	Continuous
SEX (for all treatment groups)	% of participants that are male	% Male
WEIGHT (for all treatment groups)	Mean weight of participants	Continuous (kg)
WEIGHT_SD	Standard deviation weight	Continuous
BMI (for all treatment groups)	Mean BMI of participants	Continuous (kg/m^2)
BMI_SD	Standard deviation BMI	Continuous
ONSET (for all treatment groups)	% of participants that have bulbar onset	% Bulbar onset

DISDUR (for all treatment groups)	Mean duration of symptoms at enrollment	Continuous (months)
DISDUR_SD	Standard deviation disease duration	Continuous
DXDELAY (for all treatment groups)	Mean time from onset to diagnosis	Continuous (months)
DXDELAY_SD	Standard deviation diagnostic delay	Continuous
DXDUR	Mean time from diagnosis to enrollment	Continuous (months)
DXDUR_SD	Standard deviation diagnostic duration	Continuous
RILUSE (for all treatment groups)	% of participants that use riluzole at enrollment	Percentage users
TOTAL (for all treatment groups)	ALSFRS-R total score at baseline	Continuous
TOTAL_SD	Standard deviation total score	Continuous
VC (for all treatment groups)	VC (%predicted) at baseline	% Of predicted capacity
VC_SD	Standard deviation VC	Continuous
SLOPE	Monthly decline of ALSFRS-R at baseline	Continuous
SLOPE_SD	Standard deviation monthly decline	Continuous
NAME_INT (for all treatment groups)	Name of the treatment	Nominal

TYPE_INT (for all treatment groups)	Treatment type	0 = pharmaceutical, 1 = cell therapy, 2 = supplement
GROUP_INT (for all treatment groups)	Subgrouping	<<undefined>>
ADMIN (for all treatment groups)	Mode of administration	0 = oral, 1 = IV, 2 = intrathecal, 3 = subcutaneous, 4 = intramuscular, 5 = transdermal
CLASS (for all treatment groups)	Mechanism of action class	0 = miscellaneous, 1 = antioxidants, 2 = cell therapy, 3 = genetic therapy, 4 = mitochondrial dysfunction, 5 = neuroinflammation, 6 = proteostasis
RATIO	Randomization ratio of intervention:control	Continuous (ratio)
DESIGN	Type of study design in trial	Nominal
DUR_LEAD	Lead-in duration, time when enrolled but not yet treated	Continuous (months)
DUR_TRT	Treatment duration	Continuous (months)
DUR_TOT	Total duration of study	Continuous (months)
ANALYSIS	Type of analysis used to determine primary outcome	Nominal
FRSR_MEAN (for all treatment groups)	ALSFRS-R total score at end of follow-up	Continuous

FRSR_MEAN_SE (for all treatment groups)	Standard error mean ALSFRS-R total score	Continuous
FRSR_MEAN_DIFF (for all treatment groups)	Mean difference ALSFRS-R total score	Continuous
FRSR_MEAN_DIFF_P (for all treatment groups)	Mean difference ALSFRS-R total score p-value	Continuous
FRSR_MEAN_DIFF_CI (for all treatment groups)	Mean difference ALSFRS-R total score 95% CI	[lower bound, upper bound]
FRSR_MEAN_DIFF_COMP (for all treatment groups)	Mean difference ALSFRS-R total score comparison arm	Nominal
FRSR_SLOPE (for all treatment groups)	Mean ALSFRS-R monthly decline	Continuous
FRSR_SLOPE_SE (for all treatment groups)	Standard error mean ALSFRS-R monthly decline	Continuous
FRSR_SLOPE_DIFF (for all treatment groups)	Mean difference ALSFRS-R monthly decline	Continuous
FRSR_SLOPE_DIFF_P (for all treatment groups)	Mean difference ALSFRS-R monthly decline p-value	Continuous
FRSR_SLOPE_DIFF_CI (for all treatment groups)	Mean difference ALSFRS-R monthly decline 95% CI	[lower bound, upper bound]
FRSR_SLOPE_DIFF_COMP (for all treatment groups)	Mean difference ALSFRS-R monthly decline comparison arm	Nominal
FRSR_CFB (for all treatment groups)	Mean ALSFRS-R change from baseline	Continuous
FRSR_CFB_P (for all treatment groups)	Mean ALSFRS-R change from baseline p-value	Continuous

FRSR_CFB_CI (for all treatment groups)	Mean ALSFRS-R change from baseline 95% CI	[lower bound, upper bound]
FRSR_CFB_COMP (for all treatment groups)	Mean ALSFRS-R change from baseline comparison arm	Nominal
FRSR_CFB_TIME (for all treatment groups)	Mean ALSFRS-R change from baseline timepoint	Continuous (months)
ADJUST (for all treatment groups)	Variables that were used for stratifying or adjusting ALSFRS-R	Nominal
N_FU (for all treatment groups)	Number of patients with ALSFRS-R scores used in analysis	Continuous
VC_MEAN (for all treatment groups)	VC % of predicted capacity at end of follow-up	% Of predicted capacity
VC_MEAN_SE (for all treatment groups)	Standard error mean VC	Continuous
VC_MEAN_DIFF (for all treatment groups)	Mean difference VC	Continuous
VC_MEAN_DIFF_P (for all treatment groups)	Mean difference VC p-value	Continuous
VC_MEAN_DIFF_CI (for all treatment groups)	Mean difference VC 95% CI	[lower bound, upper bound]
VC_MEAN_DIFF_COMP (for all treatment groups)	Mean difference VC comparison arm	Nominal
VC_SLOPE (for all treatment groups)	Mean VC monthly decline	% Of predicted capacity

VC_SLOPE_SE (for all treatment groups)	Standard error mean VC monthly decline	Continuous
VC_SLOPE_DIFF (for all treatment groups)	Mean difference VC monthly decline	% Of predicted capacity
VC_SLOPE_DIFF_P (for all treatment groups)	Mean difference VC monthly decline p-value	Continuous
VC_SLOPE_DIFF_CI (for all treatment groups)	Mean difference VC monthly decline 95% CI	[lower bound, upper bound]
VC_SLOPE_DIFF_COMP (for all treatment groups)	Mean difference VC monthly decline comparison arm	Nominal
ADJUST_VC (for all treatment groups)	Variables that were used for stratifying or adjusting VC	Nominal
N_FU_VC (for all treatment groups)	Number of patients with VC scores used in analysis	Continuous
SURV_HR	Hazard ratio mean	Continuous
SURV_HR_SE	Hazard ratio standard error	Continuous
SURV_HR_CI	Hazard ratio 95% confidence interval	[lower bound, upper bound]
SURV_HR_P	Hazard ratio p-value	Continuous
SURV_COMP	Hazard ratio comparison arm	Nominal
DROP_DEATH (for all treatment groups)	Number of drop-outs due to death	Continuous
DROP_AE (for all treatment groups)	Number of drop-outs due to adverse events	Continuous
DROP_TERM (for all treatment groups)	Number of drop-outs due to terminating participation	Continuous

DROP_PROG (for all treatment groups)	Number of drop-outs due to disease progression	Continuous
DROP_OTHER (for all treatment groups)	Number of drop-outs due to other reasons	Continuous
AE (for all treatment groups)	Number of adverse events in group at end of follow-up	Continuous
SAE (for all treatment groups)	Number of serious adverse events in group at end of follow-up	Continuous
OUTCOME	Primary outcome (e.g., ALSFRS-R, survival, safety)	Nominal
PLACEBO	Is a placebo arm present?	0 = no, 1 = yes
PROT_ACC	Is the study protocol accessible?	0 = no, 1 = yes
IPD_ACC	Is IPD accessible?	0 = no, 1 = yes
KAPMEI	Are Kaplan-Meier survival curves used?	0 = no, 1 = yes
FRSR_METH	Method of ALSFRS-R analysis mentioned?	0 = no, 1 = yes
SURV_METH	Method of survival analysis mentioned?	0 = no, 1 = yes
SURV_DEF	Definition of an event in survival analysis (death/tracheostomy/etc.)	Nominal
SAMP_CALC	Method of sample size calculation mentioned?	0 = no, 1 = yes

FRSR_REP	Is ALSFRS-R reported as outcome?	0 = no, 1 = yes
VC_REP	Is VC reported as outcome?	0 = no, 1 = yes
SURV_REP	Is survival reported as outcome?	0 = no, 1 = yes
ELECT_REP	Is electrophysiology reported as outcome?	0 = no, 1 = yes
MUSC_REP	Is muscle strength reported as outcome? (ISOMETRIC/HHD/MRC)	0 = no, 1 = yes
NFL_REP	Is neurofilament light chain reported as outcome?	0 = no, 1 = yes

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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐	☒	
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	3-24
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	478-483
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	592-594
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	592-594
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	592-594
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	86-143

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	144-167
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	207-297
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	176-194
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	176-194
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	316-319
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	176-194
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	301-313
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	Supplemental data
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	244-248
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	424-435
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	322-359
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	322-359, 404-411

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	348-355, 390-393
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	424-435
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	424-435