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Nutritional therapy in amyotrophic lateral sclerosis: Protocol for a systematic review and meta-analysis

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1 ABSTRACT

2 **Introduction:** Amyotrophic Lateral Sclerosis (ALS) is a complex neurodegenerative disease
3 characterized by the degeneration of motor neurons. Nutritional interventions in ALS are essential
4 and must be based on scientific evidence to provide quality of health care, improve the quality of
5 life, and increase survival time. Therefore, this protocol of systematic reviews and meta-analyses
6 aims to present a synthesis of evidence-based recommendations to support adequate nutrition
7 therapy for patients with ALS.

8 **Methods and analysis:** The search will be performed using the following databases: PubMed,
9 Excerpta Medica Database (Embase), Scopus, SciELO, Web of Science, LILACS, Cochrane
10 Central Register of Controlled Trials (CENTRAL), ScienceDirect, ProQuest, and Google Scholar.
11 We will include clinical practice guidelines, treatment protocols, systematic reviews, and clinical
12 trials according to the three research questions to be answered related to nutrition therapy and
13 interventions in ALS patients. This protocol will be developed in accordance with the Preferred
14 Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P). To evaluate
15 the methodological quality of the studies, AGREE II, Cochrane Risk of Bias (RoB 2.0), and
16 ROBINS-I tools will be used. In addition, The Grading of Recommendations Assessment,
17 Development and Evaluation (short GRADE) will be used to assess the quality of evidence and
18 the strength of the recommendations. The findings will be summarized and presented descriptively
19 according to the Cochrane Collaboration Handbook and the standard statistical meta-analysis
20 techniques.

21 **Ethics and dissemination:** Ethical approval and human consent are not required because this is a
22 protocol for systematic review and only secondary data will be used. Findings will be published
23 in a peer-reviewed journal and presented at conferences. In case of any changes in this protocol,

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3 24 amendments will be updated in PROSPERO and the modifications will be explained in the final
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5 25 report of this review.
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8 26 **PROSPERO registration number:** CRD42021233088.
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12 28 **Keywords:** amyotrophic lateral sclerosis, nutrition therapy, quality of health care
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14 29

17 30 **Strengths and limitations of this study:**

- 19 31 • In this study a synthesis of evidence-based recommendations to support adequate nutrition
20 32 therapy in ALS will be provided.
- 21 33 • This protocol encompasses two systematic reviews and adheres to the Preferred Reporting
22 34 Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement
23 35 guidelines.
- 24 36 • No restrictions of time and language will be applied in our search.
- 25 37 • The methodological quality of the studies will be performed using the AGREE II statement.
- 26 38 • For the methodological quality and risk of bias of clinical trials will be accomplished using
27 39 the Cochrane Risk of Bias (RoB 2.0) and ROBINS-I tools for randomized and non-
28 40 randomized studies, respectively.
- 29 41 • Meta-analysis may not be possible for certain outcomes due to a limited number of eligible
30 42 studies.
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44 44 **INTRODUCTION**

45 45 ALS is a multisystemic neurodegenerative disease characterized by progressive cell death of
46 46 upper and lower motor neurons.[1, 2] Worldwide ALS prevalence varies from 1.57 cases per
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3 47 100,000 to 9.62 per 100,000. Its incidence varies from 0.42 per 100,000 to 2.76 per 100,000
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5 48 people/year. Both ALS prevalence and incidence are higher in developed regions.[3] Clinical
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7 49 signs of the disease have a low incidence before age 50 years, with a peak around age 85 years
8
9 50 followed by a marked decrease in incidence. However, the onset of this disease is rarely possible
10
11 51 in early adulthood.[4] The severity of the disease points to a short median survival of 3 to 4 years
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13 52 after the initial diagnosis.[5-8]

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17 53 Malnutrition is a frequent condition in patients with ALS, with prevalence ranging from 16 to
18
19 54 53%.[9] The Body Mass Index (BMI) is an important anthropometric parameter for diagnosing
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21 55 malnutrition among these patients. BMI reduction is related to faster disease progression and
22
23 56 increased risk of mortality.[10] Marin et al.[11] demonstrated that 5% of body weight loss
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25 57 increases the risk of death by 30% in patients with ALS. Thus, nutritional care is essential for
26
27 58 maintaining adequate nutritional status, which positively affects these patients' functional
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29 59 capacity, quality of life, and survival time.[12-14]

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33 60 Several risk factors such as dysphagia, anorexia, gastrointestinal disorders, cognitive
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35 61 impairment, apathy, psychological disorders, and inadequate energy and nutrient intake
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37 62 contribute to malnutrition in patients with ALS. In addition, hypermetabolism may be present
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39 63 and can increase the risk of malnutrition or aggravate this condition, especially in the absence of
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41 64 nutritional care.[15, 16] Therefore, evidence-based nutritional interventions for ALS are of the
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43 65 utmost importance and must consider the different stages of the disease.[17]

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47 66 Clinical Practice Guidelines (CPGs) have been developed to provide scientific evidence to
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49 67 support clinical decision-making of health professionals and establish standards of care for many
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51 68 conditions.[18, 19] CPGs focused on all aspects of nutritional therapy for ALS are still lacking.
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53 69 Existent guidelines on this matter only address some nutritional aspects, most of them related to

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3 70 gastrostomy and dysphagia. Many other aspects of nutritional therapy have not been covered,
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5 71 such as energy and nutrient requirements, modified consistency diet, micronutrients and
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8 72 bioactive compounds supplementation, and nutrition advice for comorbidities in ALS patients.
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10 73 Considering this gap and aiming to provide broader guidance on nutrition therapy for ALS
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12 74 patients, it is essential to gather and synthesize recommendations on this subject, based on
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15 75 available scientific evidence of clinical protocols and guidelines. Also, based on the effectiveness
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17 76 of nutritional interventions verified through clinical trials. We believe that a synthesis of
18
19 77 recommendations on nutrition therapy in ALS will help and guide the nutrition care process and
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21 78 benefit the patients.[20, 21]
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24 79 Given the information above, this protocol will seek to answer the following questions: **RQ1**
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26 80 - What are the evidence-based nutritional recommendations to maintain or restore the nutritional
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28 81 status of patients with ALS? **RQ2** - What is the effect of a diet rich in energy and protein in
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30 82 people with ALS? **RQ3** - What are the effects of supplementing isolated micronutrients or
31
32 83 bioactive compounds in people with ALS?
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35 84 Therefore, this protocol aims to build an outline of upcoming systematic reviews and meta-
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37 85 analyses to present a synthesis of evidence-based recommendations to support adequate nutrition
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39 86 therapy and improve the nutritional status of patients with ALS.
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43 44 88 **METHODS AND ANALYSIS**

45 46 89 **Protocol Registration**

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49 90 This protocol was registered on the International Prospective Register of Systematic Reviews
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51 91 (PROSPERO) database on April 12, 2021 (CRD42021233088). This protocol is in line with
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53 92 international ethical parameters and because it is a study with secondary data, there is no need to
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3 93 seek approval from a research ethics committee. Also, it was developed in accordance with the
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5 94 Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P)
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8 95 statement guidelines.[22] The PRISMA-P checklist used to prepare this protocol has been
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10 96 provided as an online supplemental file. To report the systematic review, the PRISMA statement
11
12 97 with a 27-item checklist and descriptive flow diagram will be used.[23] This present protocol
13
14 98 encompasses two systematic reviews and meta-analyses. The first one will be a review of
15
16 99 protocols/guidelines aimed to answer the RQ1. The second one will be a review of clinical trials
17
18 100 aimed to answer RQ2 and RQ3. The information regarding methods and analysis are described
19
20
21 101 according to the research questions.
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26 103 **Selection Criteria**

28 104 For RQ1, we will include CPGs, treatment protocols, and systematic reviews. For RQ2 and RQ3,
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30 105 we will only include clinical trials with control groups.
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35 107 **Participants**

38 108 For all RQ's we will include studies comprised of adults (aged 18 and over) and seniors of both
39
40 109 sexes with a clinical diagnosis of ALS as defined, probable, or possible.
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45 111 **Types of interventions**

47 112 For RQ1, we will include studies involving nutrition therapy recommendations to maintain or
48
49 113 restore the nutritional status of patients with ALS. For RQ2, we will include studies
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51 114 implementing a diet rich in energy and/or protein as an intervention. For RQ3, we will include
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54 115 studies supplementing single micronutrients or bioactive compounds as an intervention.
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117 Outcomes measures

118 For RQ1, only the summary of the recommendations will be performed, with no outcomes to be
119 measured. For the RQ2, the outcome will be the change of body mass index, percentage of
120 weight loss, progression rate of total revised ALS Functional Rating Scale (ALSFRS-R), and
121 mortality rate. For the RQ3, the outcome will be the antioxidant effect, ALSFRS-R progression
122 rate, and mortality rate.

123

124 Exclusion Criteria

125 For all RQ's we will exclude studies with other neurodegenerative diseases or without nutritional
126 recommendations. No restrictions of time and language will be applied in our search.

127

128 Search strategy

129 A comprehensive electronic search will be performed in the following databases: PubMed,
130 Excerpta Medica Database (Embase), Scopus, SciELO, Web of Science, LILACS, Cochrane
131 Central Register of Controlled Trials (CENTRAL), ScienceDirect, ProQuest, and Google
132 Scholar. The search strategy will include the following descriptors (MeSH): “Amyotrophic
133 Lateral Sclerosis”, “Motor Neuron Disease”, “Nutrition”, “Nutritional Assessment”, “Nutrition
134 Therapy”, “Diet”, “Dietary Supplements”, “Deglutition Disorders”, “Guideline”, and “Clinical
135 Protocols”. In addition, the EMTREE terms “Diet Therapy”, “Dysphagia”, and “Practice
136 Guideline” will be included for the Embase database. A draft of our search strategy has been
137 provided as an online supplemental file.

138

139 **Searches of other resources**

140 To ensure the comprehensiveness of this research, we will supplement searches by hand-
141 searching in the reference lists of retrieved studies or relevant reviews. To identify unpublished
142 studies and assess publication bias, we will also examine *ClinicalTrials.gov* and
143 *ensaiosclinicos.gov.br* for registered clinical trials using interventions such as high-energy and/or
144 high-protein diet and supplementation of micronutrients or bioactive compounds in people with
145 ALS.

146

147 **Study selection**

148 For all identified studies, at least 2 authors (MDCV and LLL) will independently select and
149 review titles and abstracts using the Rayyan QCRI® tool. Papers that meet the inclusion criteria
150 will be ordered for a full review. Any disagreement will be resolved by discussion with a third
151 reviewer (SHLV). A manual search will be performed if any relevant studies are found using the
152 defined search strategies. All investigators will then review the full text of all eligible studies.
153 The information on the phases of the selection process will be described through PRISMA flow
154 diagram.[23]

155

156 **Data extraction**

157 The data extraction will be done in a standardized way, using Microsoft Excel by 2 independent
158 authors (MDCV and LLL). Discrepancies between the data extraction will be resolved by
159 consensus. The study characteristics will be collated according to the research questions. For
160 RQ1, the following data will be extracted: general information about the guideline (title,
161 responsible organization, year of publication, and funding); nutritional recommendations

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2
3 162 addressed; and the stratification of the level of evidence used. For RQ2 and RQ3, the following
4
5 163 data will be extracted: general information (title, authors, journal, year, country); study
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7 164 characteristics (study design, study duration); sample characteristics (sample size, mean age,
8
9 165 ALS subtype, ALSFRS-R); intervention (type of intervention, duration, diet characteristics,
10
11 166 energy and/or protein amount); outcomes (changes in body mass index, percentage of weight
12
13 167 loss, progression rate of functional status, mortality rate); and statistical results. If study reports
14
15 168 are incomplete or missing data, corresponding authors will be contacted. If we do not receive
16
17 169 clarification, the requested data will be excluded from our analysis and will be commented in the
18
19 170 Discussion section.
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25 26 172 **Evaluation of methodological quality**

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28 173 Two independent authors (SHLV and MDCV) will evaluate the methodological quality of the
29
30 174 studies using the AGREE II statement. This instrument assesses six domains: 1. Scope and
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32 175 purpose, 2. Stakeholder involvement, 3. Rigour of development, 4. Clarity of presentation, 5.
33
34 176 Applicability, and 6. Editorial independence.[24] To assess the methodological quality and risk
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36 177 of bias of clinical trials, the Cochrane Risk of Bias (RoB 2.0) and ROBINS-I tools will be used
37
38 178 for randomized and non-randomized studies, respectively.[25, 26]
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43 44 45 180 **Data synthesis**

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47 181 For the first systematic review (RQ1), the findings and main recommendations will be
48
49 182 narratively summarized. For the second systematic review (RQ2 and RQ3), meta-analysis will
50
51 183 be performed, if possible. If meta-analysis is not possible, we will conduct a systematic review
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53 184 with narrative analysis tabling the results.
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186 **Assessment of heterogeneity**

187 To assess the heterogeneity, we plan to calculate the standard chi-square statistic, which is a
188 quantitative measure of inconsistency between the studies. Next, the I^2 index will be calculated
189 to quantify heterogeneity. The I^2 statistic describes the percentage of variation across studies due
190 to heterogeneity rather than chance. No heterogeneity is observed when I^2 is 0%, and the
191 variability can be explained by chance alone. A value of $I^2 >50\%$ indicates high heterogeneity.

192

193 **Meta-analysis**

194 If there is the possibility of meta-analysis, standard statistical techniques will be used. If I^2 value
195 is $<50\%$ and p-value is >0.05 , the fixed effect model will be chosen. If I^2 is $<50\%$ or p-value is
196 <0.05 , the random effect model will be used to combine the tests to calculate relative risk (RR)
197 and 95% CI using the DerSimonian-Laird method. If substantial heterogeneity occurs, we will
198 perform subgroup analysis and meta-regression to explore the source of heterogeneity.

199 Publication bias will be assessed using a funnel plot and its asymmetry will be verified by linear
200 regression.

201

202 **Subgroup analysis**

203 For the RQ1 the analysis of subgroups is not applicable. If sufficient data are available for the
204 RQ2 and RQ3, the subgroup analysis will consider disease onset (bulbar or spinal), age of onset,
205 disease duration, and disease stages (early, middle, late, and end).

206

207 **Assessment of quality of evidence (GRADE)**

208 Two independent authors (MDCV and LLL) will assess the quality of the evidence and the
209 strength of the recommendations provided by the selected studies. For this purpose, we will use
210 the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)[27] for
211 decision-making in health, which classifies the quality of evidence into four levels (high,
212 moderate, low, and very low) and the strength of the evidence into two levels (strong or weak).

213

214 **Patient and public involvement**

215 No patients or the public will be directly engaged in this research, as it is conducted using
216 secondary data.

217

218 **DISCUSSION**

219 This study aims to gather and synthesize recommendations for nutritional intervention and
220 treatment based on available scientific evidence from clinical protocols and guidelines. Also, the
221 effectiveness of interventions will be verified through clinical trials.

222 Weight loss, low BMI, and malnutrition are frequent in ALS patients. According to the
223 guideline conducted by Burgos et al.,[28] the BMI reduction in ALS patients is associated with
224 shortened survival and high risk of mortality.

225 A systematic review states that there is no cure or effective treatment for ALS to date.

226 Multidisciplinary care is the basis for its treatment, including nutritional support as well as
227 respiratory and symptom management during the disease. Furthermore, the review highlights
228 that dietary intervention can help to improve nutrition status. For example, gastrostomy is
229 indicated if oral intake is insufficient or is no longer safe.[29]

230 Dorst et al. found that high-energy supplementation effectively stabilizes the body weight of
231 patients with ALS and no side effects were detected. The authors also observed a positive impact
232 on the survival of the patients. Thus, the use of high-energy supplementation was suggested.[30]
233 In a cohort study, Traynor et al.[31] demonstrated that ALS patients who received
234 multidisciplinary care had a better prognosis than patients who received general care through a
235 neurology clinic.

236 Scientific entities specialized in ALS recognize nutrition as integral part of care during the
237 course of the disease and address some nutritional recommendations.[32, 33] Nutrition therapy
238 seeks to prevent malnutrition, maintain adequate nutritional status, promote hemodynamic
239 stability, reduce the rate of disease progression, and positively impact the quality of life and
240 survival of ALS patients.[34] Thus, identifying consistent recommendations for nutrition
241 intervention in ALS is of the utmost importance and will contribute to more assertive patient
242 care.[35-38] Nevertheless, systematic reviews and guidelines about ALS nutritional therapy are
243 scarce and some of them present gaps because they do not discuss specific aspects regarding
244 nutritional treatment and management that should be implemented in this type of patient.

245 For example, the recommendations by Garcia et al.[39] describe the nutritional aspects of
246 ALS and nutritional management with recommendations for high energy intake and those related
247 to enteral and parenteral nutrition. However, it does not address percentages of macronutrients
248 distribution, micronutrients requirements, or adjuvant nutritional supplements.

249 In a review paper about nutrition management in ALS, Greenwood et al.[37] prioritize the
250 quantitative recommendation of protein but do not determine recommendations for lipids,
251 carbohydrates, fibers, micronutrients, bioactive compounds, and nutritional supplements. The
252 pieces of information we gathered show how these two systematic reviews proposed by our

253 group are needed and can be helpful in assisting the nutrition care of ALS patients with robust
254 recommendations based on scientific evidence.

255 In this sense, the development of updated systematic reviews with meta-analyses and
256 synthesized recommendations on nutrition therapy of patients with ALS can reduce the
257 nutritional risk and positively influence their quality of life and survival time. Furthermore, it
258 will support the first Brazilian guideline of nutrition therapy in ALS, which will guide the
259 clinical nutrition practice with greater safety and efficiency. Thus, we believe this protocol is
260 relevant and it will benefit the scientific community, health care professionals, caregivers, and
261 especially patients with ALS. In addition, the systematic reviews proposed can also help to
262 highlight areas that require more research in the subject of nutrition therapy and ALS.

263

264 **ETHICS AND DISSEMINATION**

265 Ethical approval and human consent are not required because this is a protocol for systematic
266 review and only secondary data will be used. Findings will be published in a peer-reviewed
267 journal and presented at conferences. In case of any changes in this protocol, amendments will
268 be updated in PROSPERO and explanations of these modifications will be described in the final
269 report of this review.

270

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273 University of Rio Grande do Norte (UFRN) and its researchers who are part of the revELA
274 project.

275

276 **CONTRIBUTORS**

277 MDCV, LLL, and GP conceptualized and designed the protocol. The protocol manuscript was
278 written by MDCV and LLL. It was critically reviewed by GP, GCBSM, KMDC, SHLV, and
279 JBN. The search strategy was developed by MDCV, LLL, SHLV, GP, and GCBSM. MDCV,
280 KMDC, and LLL will lead the study selection. MDCV, LLL, and KMDC will be responsible for
281 data extraction. Statistical analysis will be performed by MDCV, SHLV, LLL, GCBSM, and GP.
282 JBN will be the third party and will host consensus meetings at each stage in case of
283 disagreement. All authors read, reviewed, and approved the final protocol.

284

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290

291 **COMPETING INTERESTS**

292 None declared.

293

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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	X		OK*
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		X	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X		26
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X		OK*
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X		277-284
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		X	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	X		286-290
Sponsor	5b	Provide name for the review funder and/or sponsor	X		286-290
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		X	NA
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X		58-73
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X		74-76
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	X		104-127

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
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	X		104-127
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	X		129-146
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X		148-158
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)	X		148-155
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	X		157-160; 168-171
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	X		161-168
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X		161-168
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	X		173-179
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X		181-185
	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)	X		187-201
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X		203-206
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X		182-185
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X		200-201
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X		208-213

* The title is included in the Step 1 of the submission process at BMJ Open's author dashboard. The title is in accordance with PRISMA-P recommendations.

Supplemental Material [Draft of Search Strategy]

Database	Equations	
PubMed	1	"amyotrophic lateral sclerosis" OR "motor neuron disease" AND "nutrition" AND "guideline"
	2	"amyotrophic lateral sclerosis" OR "motor neuron disease" AND "nutrition therapy" AND "dietary supplements"

For peer review only

BMJ Open

Nutritional therapy in amyotrophic lateral sclerosis: Protocol for a systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-064086.R1
Article Type:	Protocol
Date Submitted by the Author:	06-Jul-2022
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Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Nutrition and metabolism, Neurology, Evidence based practice
Keywords:	NUTRITION & DIETETICS, Neuromuscular disease < NEUROLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Manuscripts

Nutritional therapy in amyotrophic lateral sclerosis: Protocol for a systematic review and meta-analysis

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Keywords: amyotrophic lateral sclerosis, nutrition therapy, quality of health care

Word count (excluding title page, abstract, references, figures, and tables): 2,787

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1 ABSTRACT

2 **Introduction:** Amyotrophic Lateral Sclerosis (ALS) is a complex neurodegenerative disease
3 characterized by the degeneration of motor neurons. Nutritional interventions in ALS are essential
4 and must be based on scientific evidence to provide quality of health care, improve the quality of
5 life, and increase survival time. Therefore, this protocol of systematic reviews and meta-analyses
6 aims to present a synthesis of evidence-based recommendations to support adequate nutrition
7 therapy for patients with ALS.

8 **Methods and analysis:** The search will be performed using the following databases: PubMed,
9 Excerpta Medica Database (Embase), Scopus, SciELO, Web of Science, LILACS, Cochrane
10 Central Register of Controlled Trials (CENTRAL), ScienceDirect, ProQuest, and Google Scholar.
11 We will include clinical practice guidelines, treatment protocols, systematic reviews, and clinical
12 trials according to the three research questions to be answered related to nutrition therapy and
13 interventions in ALS patients. This protocol will be developed in accordance with the Preferred
14 Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P). To evaluate
15 the methodological quality of the studies, AGREE II, Cochrane Risk of Bias (RoB 2.0), and
16 ROBINS-I tools will be used. In addition, The Grading of Recommendations Assessment,
17 Development and Evaluation (short GRADE) will be used to assess the quality of evidence and
18 the strength of the recommendations. The findings will be summarized and presented descriptively
19 according to the Cochrane Collaboration Handbook and the standard statistical meta-analysis
20 techniques.

21 **Ethics and dissemination:** Ethical approval and human consent are not required because this is a
22 protocol for systematic review and only secondary data will be used. Findings will be published
23 in a peer-reviewed journal and presented at conferences. In case of any changes in this protocol,

24 amendments will be updated in PROSPERO and the modifications will be explained in the final
25 report of this review.

26 **PROSPERO registration number:** CRD42021233088.

28 **Keywords:** amyotrophic lateral sclerosis, nutrition therapy, quality of health care

30 **Strengths and limitations of this study:**

- 31 • This protocol encompasses two systematic reviews.
- 32 • This protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-
33 Analyses Protocols (PRISMA-P) statement guidelines.
- 34 • The methodological quality of the studies will be performed using the AGREE II statement.
- 35 • The methodological quality and risk of bias of clinical trials will be accomplished using
36 the Cochrane Risk of Bias (RoB 2.0) and ROBINS-I tools for randomized and non-
37 randomized studies, respectively.
- 38 • Meta-analysis may not be possible for certain outcomes due to a limited number of eligible
39 studies.

41 **INTRODUCTION**

42 ALS is a multisystemic neurodegenerative disease characterized by progressive cell death of
43 upper and lower motor neurons.[1, 2] Worldwide ALS prevalence varies from 1.57 cases per
44 100,000 to 9.62 per 100,000. Its incidence varies from 0.42 per 100,000 to 2.76 per 100,000
45 people/year. Both ALS prevalence and incidence are higher in developed regions.[3] Clinical
46 signs of the disease have a low incidence before age 50 years, with a peak around age 85 years

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3 47 followed by a marked decrease in incidence. However, the onset of this disease is rarely possible
4
5 48 in early adulthood.[4] The severity of the disease points to a short median survival of 3 to 4 years
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8 49 after the initial diagnosis.[5-8]
9

10 50 Malnutrition is a frequent condition in patients with ALS, with prevalence ranging from 16 to
11
12 51 53%.[9] The Body Mass Index (BMI) is an important anthropometric parameter for diagnosing
13
14 52 malnutrition among these patients. BMI reduction is related to faster disease progression and
15
16 53 increased risk of mortality.[10] Marin et al.[11] demonstrated that 5% of body weight loss
17
18 54 increases the risk of death by 30% in patients with ALS. Thus, nutritional care is essential for
19
20 55 maintaining adequate nutritional status, which positively affects these patients' functional
21
22 56 capacity, quality of life, and survival time.[12-14]
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26 57 Several risk factors such as dysphagia, anorexia, gastrointestinal disorders, cognitive
27
28 58 impairment, apathy, psychological disorders, and inadequate energy and nutrient intake
29
30 59 contribute to malnutrition in patients with ALS. In addition, hypermetabolism may be present
31
32 60 and can increase the risk of malnutrition or aggravate this condition, especially in the absence of
33
34 61 nutritional care.[15, 16] Therefore, evidence-based nutritional interventions for ALS are of the
35
36 62 utmost importance and must consider the different stages of the disease.[17]
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40 63 Clinical Practice Guidelines (CPGs) have been developed to provide scientific evidence to
41
42 64 support clinical decision-making of health professionals and establish standards of care for many
43
44 65 conditions.[18, 19] CPGs focused on all aspects of nutritional therapy for ALS are still lacking.
45
46 66 Existent guidelines on this matter only address some nutritional aspects, most of them related to
47
48 67 gastrostomy and dysphagia. Many other aspects of nutritional therapy have not been covered,
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50 68 such as energy and nutrient requirements, modified consistency diet, micronutrients and
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52 69 bioactive compounds supplementation, and nutrition advice for comorbidities in ALS patients.
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3 70 Considering this gap and aiming to provide broader guidance on nutrition therapy for ALS
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5 71 patients, it is essential to gather and synthesize recommendations on this subject, based on
6
7 72 available scientific evidence of clinical protocols and guidelines. Also, based on the effectiveness
8
9 73 of nutritional interventions verified through clinical trials. We believe that a synthesis of
10
11 74 recommendations on nutrition therapy in ALS will help and guide the nutrition care process and
12
13 75 benefit the patients.[20, 21]
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17 76 Given the information above, this protocol will seek to answer the following questions: **RQ1**
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19 77 - What are the evidence-based nutritional recommendations to maintain or restore the nutritional
20
21 78 status of patients with ALS? **RQ2** - What is the effect of a diet rich in energy and protein in
22
23 79 people with ALS? **RQ3** - What are the effects of supplementing isolated micronutrients or
24
25 80 bioactive compounds in people with ALS?
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28 81 Therefore, this protocol aims to build an outline of upcoming systematic reviews and meta-
29
30 82 analyses to present a synthesis of evidence-based recommendations to support adequate nutrition
31
32 83 therapy and improve the nutritional status of patients with ALS.
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36 37 85 **METHODS AND ANALYSIS**

38 39 86 **Protocol Registration**

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42 87 This protocol was registered on the International Prospective Register of Systematic Reviews
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44 88 (PROSPERO) database on April 12, 2021 (CRD42021233088). This protocol is in line with
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46 89 international ethical parameters and because it is a study with secondary data, there is no need to
47
48 90 seek approval from a research ethics committee. Also, it was developed in accordance with the
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50 91 Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P)
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52 92 statement guidelines.[22] The PRISMA-P checklist used to prepare this protocol has been
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93 provided as an online supplemental file. To report the systematic review, the PRISMA statement
94 with a 27-item checklist and descriptive flow diagram will be used.[23] This present protocol
95 encompasses two systematic reviews and meta-analyses. The first one will be a review of
96 protocols/guidelines aimed to answer the RQ1. The second one will be a review of clinical trials
97 aimed to answer RQ2 and RQ3. The information regarding methods and analysis are described
98 according to the research questions.

100 **Selection Criteria**

101 For RQ1, we will include CPGs, treatment protocols, and systematic reviews. For RQ2 and RQ3,
102 we will only include clinical trials with control groups.

104 **Participants**

105 For all RQ's we will include studies comprised of adults (aged 18 and over) and seniors of both
106 sexes with a clinical diagnosis of ALS as defined, probable, or possible.

108 **Types of interventions**

109 For RQ1, we will include studies involving nutrition therapy recommendations to maintain or
110 restore the nutritional status of patients with ALS. For RQ2, we will include studies
111 implementing a diet rich in energy and/or protein as an intervention. For RQ3, we will include
112 studies supplementing single micronutrients or bioactive compounds as an intervention.

114 **Outcomes measures**

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3 115 For RQ1, only the summary of the nutritional recommendations for recovery or maintenance of
4
5 116 the nutritional status in ALS patients will be performed, with no outcomes to be measured. For
6
7 117 the RQ2, the outcome will be the change of body mass index, percentage of weight loss,
8
9 118 progression rate of total revised ALS Functional Rating Scale (ALSFRS-R), and mortality rate.
10
11 119 For the RQ3, the outcome will be the antioxidant effect, ALSFRS-R progression rate, and
12
13 120 mortality rate.
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19 122 **Inclusion Criteria**

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21 123 For RQ1, the inclusion criteria are evidence-based nutritional recommendations to maintain or
22
23 124 restore the nutritional status of patients diagnosed with definite, probable, or possible ALS. For
24
25 125 RQ2 and RQ3, the inclusion criteria are adults and elderly patients, of both sexes, diagnosed with
26
27 126 definite, probable, or possible ALS.
28
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33 128 **Exclusion Criteria**

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35 129 For all RQ's we will exclude studies with other neurodegenerative diseases or without nutritional
36
37 130 recommendations. No restrictions of time and language will be applied in our search.
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42 132 **Search strategy**

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44 133 A comprehensive electronic search will be performed in the following databases: PubMed,
45
46 134 Excerpta Medica Database (Embase), Scopus, SciELO, Web of Science, LILACS, Cochrane
47
48 135 Central Register of Controlled Trials (CENTRAL), ScienceDirect, ProQuest, and Google
49
50 136 Scholar. The search strategy will include the following descriptors (MeSH): “Amyotrophic
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52 137 Lateral Sclerosis”, “Motor Neuron Disease”, “Nutrition”, “Nutritional Assessment”, “Nutrition
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3 138 Therapy”, “Diet”, “Dietary Supplements”, “Deglutition Disorders”, “Guideline”, and “Clinical
4
5 139 Protocols”. In addition, the Emtree terms “Diet Therapy”, “Dysphagia”, and “Practice
6
7 140 Guideline” will be included for the Embase database. A draft of our search strategy has been
8
9 141 provided as an online supplemental file.
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143 **Searches of other resources**

144 To ensure the comprehensiveness of this research, we will supplement searches by hand-
145 searching in the reference lists of retrieved studies or relevant reviews. To identify unpublished
146 studies and assess publication bias, we will also examine *ClinicalTrials.gov* and
147 *ensaiosclinicos.gov.br* for registered clinical trials using interventions such as high-energy and/or
148 high-protein diet and supplementation of micronutrients or bioactive compounds in people with
149 ALS.
150

151 **Study selection**

152 For all identified studies, at least 2 authors (MDCV and LLL) will independently select and
153 review titles and abstracts using the Rayyan QCRI® tool. Papers that meet the inclusion criteria
154 will be ordered for a full review. Any disagreement will be resolved by discussion with a third
155 reviewer (SHLV). A manual search will be performed if any relevant studies are found using the
156 defined search strategies. All investigators will then review the full text of all eligible studies.
157 The information on the phases of the selection process will be described through PRISMA flow
158 diagram.[23]
159

160 **Data extraction**

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2
3 161 The data extraction will be done in a standardized way, using Microsoft Excel by 2 independent
4
5 162 authors (MDCV and LLL). Discrepancies between the data extraction will be resolved by
6
7 163 consensus. The study characteristics will be collated according to the research questions. For
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9
10 164 RQ1, the following data will be extracted: general information about the guideline (title,
11
12 165 responsible organization, year of publication, and funding); nutritional recommendations
13
14 166 addressed; and the stratification of the level of evidence used. For RQ2 and RQ3, the following
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16 167 data will be extracted: general information (title, authors, journal, year, country); study
17
18 168 characteristics (study design, study duration); sample characteristics (sample size, mean age,
19
20 169 ALS subtype, ALSFRS-R); intervention (type of intervention, duration, diet characteristics,
21
22 170 energy and/or protein amount); outcomes (changes in body mass index, percentage of weight
23
24 171 loss, progression rate of functional status, mortality rate); and statistical results. If study reports
25
26 172 are incomplete or missing data, corresponding authors will be contacted. If we do not receive
27
28 173 clarification, the requested data will be excluded from our analysis and will be commented in the
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31 174 Discussion section.
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38 **Evaluation of methodological quality**

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40 177 Two independent authors (SHLV and MDCV) will evaluate the methodological quality of the
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42 178 studies using the AGREE II statement. This instrument assesses six domains: 1. Scope and
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44 179 purpose, 2. Stakeholder involvement, 3. Rigour of development, 4. Clarity of presentation, 5.
45
46 180 Applicability, and 6. Editorial independence.[24] To assess the methodological quality and risk
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48 181 of bias of clinical trials, the Cochrane Risk of Bias (RoB 2.0) and ROBINS-I tools will be used
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50 182 for randomized and non-randomized studies, respectively.[25, 26]
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184 **Data synthesis**

185 For the first systematic review (RQ1), the findings and main recommendations will be
186 narratively summarized. For the second systematic review (RQ2 and RQ3), meta-analysis will
187 be performed, if possible. If meta-analysis is not possible, we will conduct a systematic review
188 with narrative analysis tabling the results.

189

190 **Assessment of heterogeneity**

191 To assess the heterogeneity, we plan to calculate the standard chi-square statistic, which is a
192 quantitative measure of inconsistency between the studies. Next, the I^2 index will be calculated
193 to quantify heterogeneity. The I^2 statistic describes the percentage of variation across studies due
194 to heterogeneity rather than chance. No heterogeneity is observed when I^2 is 0%, and the
195 variability can be explained by chance alone. A value of $I^2 > 50\%$ indicates high heterogeneity.

196

197 **Meta-analysis**

198 If there is the possibility of meta-analysis, standard statistical techniques will be used. If
199 substantial heterogeneity occurs, we will perform subgroup analysis and meta-regression to
200 identify possible associated cofactors such as disease onset (bulbar or spinal), age at onset,
201 disease duration, and clinical stages of ALS (early, middle, late, and end). In addition, the
202 random effects model will be used in the synthesis of data from the included studies. Publication
203 bias will be assessed using a funnel plot and its asymmetry will be verified by linear regression.

204

205 **Subgroup analysis**

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2
3 206 For the RQ1 the analysis of subgroups is not applicable. If sufficient data are available for the
4
5 207 RQ2 and RQ3, the subgroup analysis will consider disease onset (bulbar or spinal), age of onset,
6
7 208 disease duration, and clinical stages of ALS (early, middle, late, and end). These stages are
8
9
10 209 classified as follow: stage 1 for symptom onset or functional involvement of one Central System
11
12 210 Nervous (CSN) region (**early**), stage 2 for diagnosis or functional involvement of two CSN
13
14 211 regions (**middle**), stage 3 for functional involvement of three CSN regions (**late**), stage 4 for
15
16 212 need for gastrostomy or non-invasive ventilation (**end**), and stage 5 for death.[27, 28]
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21 214 **Assessment of quality of evidence (GRADE)**

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23
24 215 Two independent authors (MDCV and LLL) will assess the quality of the evidence and the
25
26 216 strength of the recommendations provided by the selected studies. For this purpose, we will use
27
28 217 the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)[29] for
29
30 218 decision-making in health, which classifies the quality of evidence into four levels (high,
31
32 219 moderate, low, and very low) and the strength of the evidence into two levels (strong or weak).
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37 221 **Patient and public involvement**

38 222 No patients or the public will be directly engaged in this research, as it is conducted using
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40 223 secondary data.
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46 225 **DISCUSSION**

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49 226 This study aims to gather and synthesize recommendations for nutritional intervention and
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51 227 treatment based on available scientific evidence from clinical protocols and guidelines. Also, the
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53 228 effectiveness of interventions will be verified through clinical trials.
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229 Weight loss, low BMI, and malnutrition are frequent in ALS patients. According to the
230 guideline conducted by Burgos et al.,[30] the BMI reduction in ALS patients is associated with
231 shortened survival and high risk of mortality.

232 A systematic review states that there is no cure or effective treatment for ALS to date.
233 Multidisciplinary care is the basis for its treatment, including nutritional support as well as
234 respiratory and symptom management during the disease. Furthermore, the review highlights
235 that dietary intervention can help to improve nutrition status. For example, gastrostomy is
236 indicated if oral intake is insufficient or is no longer safe.[31]

237 Dorst et al. found that high-energy supplementation effectively stabilizes the body weight of
238 patients with ALS and no side effects were detected. The authors also observed a positive impact
239 on the survival of the patients. Thus, the use of high-energy supplementation was suggested.[32]
240 In a cohort study, Traynor et al.[33] demonstrated that ALS patients who received
241 multidisciplinary care had a better prognosis than patients who received general care through a
242 neurology clinic.

243 Scientific entities specialized in ALS recognize nutrition as integral part of care during the
244 course of the disease and address some nutritional recommendations.[34, 35] Nutrition therapy
245 seeks to prevent malnutrition, maintain adequate nutritional status, promote hemodynamic
246 stability, reduce the rate of disease progression, and positively impact the quality of life and
247 survival of ALS patients.[36] Thus, identifying consistent recommendations for nutrition
248 intervention in ALS is of the utmost importance and will contribute to more assertive patient
249 care.[37-40] Nevertheless, systematic reviews and guidelines about ALS nutritional therapy are
250 scarce and some of them present gaps because they do not discuss specific aspects regarding
251 nutritional treatment and management that should be implemented in this type of patient.

252 For example, the recommendations by Garcia et al.[41] describe the nutritional aspects of
253 ALS and nutritional management with recommendations for high energy intake and those related
254 to enteral and parenteral nutrition. However, it does not address percentages of macronutrients
255 distribution, micronutrients requirements, or adjuvant nutritional supplements.

256 In a review paper about nutrition management in ALS, Greenwood et al.[39] prioritize the
257 quantitative recommendation of protein but do not determine recommendations for lipids,
258 carbohydrates, fibers, micronutrients, bioactive compounds, and nutritional supplements. The
259 pieces of information we gathered show how these two systematic reviews proposed by our
260 group are needed and can be helpful in assisting the nutrition care of ALS patients with robust
261 recommendations based on scientific evidence.

262 In this sense, the development of updated systematic reviews with meta-analyses and
263 synthesized recommendations on nutrition therapy of patients with ALS can reduce the
264 nutritional risk and positively influence their quality of life and survival time. Furthermore, it
265 will support the first Brazilian guideline of nutrition therapy in ALS, which will guide the
266 clinical nutrition practice with greater safety and efficiency. Thus, we believe this protocol is
267 relevant and it will benefit the scientific community, health care professionals, caregivers, and
268 especially patients with ALS. In addition, the systematic reviews proposed can also help to
269 highlight areas that require more research in the subject of nutrition therapy and ALS.

270

271 **ETHICS AND DISSEMINATION**

272 Ethical approval and human consent are not required because this is a protocol for systematic
273 review and only secondary data will be used. Findings will be published in a peer-reviewed
274 journal and presented at conferences. In case of any changes in this protocol, amendments will

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3 275 be updated in PROSPERO and explanations of these modifications will be described in the final
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5 276 report of this review.
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10 278 **ACKNOWLEDGMENTS**

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13
14 280 University of Rio Grande do Norte (UFRN) and its researchers who are part of the revELA
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16 281 project.
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21 283 **CONTRIBUTORS**

22
23 284 MDCV, LLL, and GP conceptualized and designed the protocol. The protocol manuscript was
24
25 285 written by MDCV and LLL. It was critically reviewed by GP, GCBSM, KMDC, SHLV, and
26
27 286 JBN. The search strategy was developed by MDCV, LLL, SHLV, GP, and GCBSM. MDCV,
28
29 287 KMDC, and LLL will lead the study selection. MDCV, LLL, and KMDC will be responsible for
30
31 288 data extraction. Statistical analysis will be performed by MDCV, SHLV, LLL, GCBSM, and GP.
32
33 289 JBN will be the third party and will host consensus meetings at each stage in case of
34
35 290 disagreement. All authors read, reviewed, and approved the final protocol.
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39
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48 296 University of Rio Grande do Norte - LAIS/UFRN).
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3 298 **COMPETING INTERESTS**
4

5 299 None declared.
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10 301 **REFERENCES**
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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	X		OK*
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		X	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X		26
Contact					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X		OK*
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X		277-284
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		X	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	X		286-290
Sponsor	5b	Provide name for the review funder and/or sponsor	X		286-290
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		X	NA
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X		58-73
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X		74-76
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	X		104-127

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
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	X		104-127
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	X		129-146
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X		148-158
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)	X		148-155
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	X		157-160; 168-171
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	X		161-168
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X		161-168
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	X		173-179
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X		181-185
	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)	X		187-201
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X		203-206
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X		182-185
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X		200-201
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X		208-213

* The title is included in the Step 1 of the submission process at BMJ Open's author dashboard. The title is in accordance with PRISMA-P recommendations.

Supplemental Material [Draft of Search Strategy]

Database	Research Question (QR)	Equations
PubMed	RQ1*	"amyotrophic lateral sclerosis" OR "motor neuron disease" AND "nutrition" AND "guideline"
PubMed	RQ2**	"amyotrophic lateral sclerosis" OR "motor neuron disease" AND "diet therapy" OR "diet, high fat" OR "diet, high protein"
PubMed	RQ3***	"amyotrophic lateral sclerosis" OR "motor neuron disease" AND "dietary supplements"
<p>*RQ1 - What are the evidence-based nutritional recommendations to maintain or restore the nutritional status of patients with ALS? **RQ2 - What is the effect of a diet rich in energy and protein in people with ALS? ***RQ3 - What are the effects of supplementing isolated micronutrients or bioactive compounds in people with ALS?</p>		

BMJ Open

Nutritional therapy in amyotrophic lateral sclerosis: Protocol for a systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-064086.R2
Article Type:	Protocol
Date Submitted by the Author:	02-Aug-2022
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Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Nutrition and metabolism, Neurology, Evidence based practice
Keywords:	NUTRITION & DIETETICS, Neuromuscular disease < NEUROLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

SCHOLARONE™
Manuscripts

Nutritional therapy in amyotrophic lateral sclerosis: Protocol for a systematic review and meta-analysis

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Keywords: amyotrophic lateral sclerosis, nutrition therapy, quality of health care

Word count (excluding title page, abstract, references, figures, and tables): 2,787

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1 ABSTRACT

2 **Introduction:** Amyotrophic Lateral Sclerosis (ALS) is a complex neurodegenerative disease
3 characterized by the degeneration of motor neurons. Nutritional interventions in ALS are essential
4 and must be based on scientific evidence to provide quality of health care, improve the quality of
5 life, and increase survival time. Therefore, this protocol of systematic reviews and meta-analyses
6 aims to present a synthesis of evidence-based recommendations to support adequate nutrition
7 therapy for patients with ALS.

8 **Methods and analysis:** The search will be performed using the following databases: PubMed,
9 Excerpta Medica Database (Embase), Scopus, SciELO, Web of Science, LILACS, Cochrane
10 Central Register of Controlled Trials (CENTRAL), ScienceDirect, ProQuest, and Google Scholar.
11 We will include clinical practice guidelines, treatment protocols, systematic reviews, and clinical
12 trials according to the three research questions to be answered related to nutrition therapy and
13 interventions in ALS patients. This protocol will be developed in accordance with the Preferred
14 Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P). To evaluate
15 the methodological quality of the studies, AGREE II, Cochrane Risk of Bias (RoB 2.0), and
16 ROBINS-I tools will be used. In addition, The Grading of Recommendations Assessment,
17 Development and Evaluation (short GRADE) will be used to assess the quality of evidence and
18 the strength of the recommendations. The findings will be summarized and presented descriptively
19 according to the Cochrane Collaboration Handbook and the standard statistical meta-analysis
20 techniques.

21 **Ethics and dissemination:** Ethical approval and human consent are not required because this is a
22 protocol for systematic review and only secondary data will be used. Findings will be published
23 in a peer-reviewed journal and presented at conferences. In case of any changes in this protocol,

24 amendments will be updated in PROSPERO and the modifications will be explained in the final
25 report of this review.

26 **PROSPERO registration number:** CRD42021233088.

28 **Keywords:** amyotrophic lateral sclerosis, nutrition therapy, quality of health care

30 **Strengths and limitations of this study:**

- 31 • This protocol encompasses two systematic reviews.
- 32 • This protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-
33 Analyses Protocols (PRISMA-P) statement guidelines.
- 34 • The methodological quality of the studies will be performed using the AGREE II statement.
- 35 • The methodological quality and risk of bias of clinical trials will be accomplished using
36 the Cochrane Risk of Bias (RoB 2.0) and ROBINS-I tools for randomized and non-
37 randomized studies, respectively.
- 38 • Meta-analysis may not be possible for certain outcomes due to a limited number of eligible
39 studies.

41 **INTRODUCTION**

42 ALS is a multisystemic neurodegenerative disease characterized by progressive cell death of
43 upper and lower motor neurons.[1, 2] Worldwide ALS prevalence varies from 1.57 cases per
44 100,000 to 9.62 per 100,000. Its incidence varies from 0.42 per 100,000 to 2.76 per 100,000
45 people/year. Both ALS prevalence and incidence are higher in developed regions.[3] Clinical
46 signs of the disease have a low incidence before age 50 years, with a peak around age 85 years

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3 47 followed by a marked decrease in incidence. However, the onset of this disease is rarely possible
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5 48 in early adulthood.[4] The severity of the disease points to a short median survival of 3 to 4 years
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8 49 after the initial diagnosis.[5-8]
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10 50 Malnutrition is a frequent condition in patients with ALS, with prevalence ranging from 16 to
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12 51 53%.[9] The Body Mass Index (BMI) is an important anthropometric parameter for diagnosing
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14 52 malnutrition among these patients. BMI reduction is related to faster disease progression and
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16 53 increased risk of mortality.[10] Marin et al.[11] demonstrated that 5% of body weight loss
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18 54 increases the risk of death by 30% in patients with ALS. Thus, nutritional care is essential for
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20 55 maintaining adequate nutritional status, which positively affects these patients' functional
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22 56 capacity, quality of life, and survival time.[12-14]
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26 57 Several risk factors such as dysphagia, anorexia, gastrointestinal disorders, cognitive
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28 58 impairment, apathy, psychological disorders, and inadequate energy and nutrient intake
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30 59 contribute to malnutrition in patients with ALS. In addition, hypermetabolism may be present
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32 60 and can increase the risk of malnutrition or aggravate this condition, especially in the absence of
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34 61 nutritional care.[15, 16] Therefore, evidence-based nutritional interventions for ALS are of the
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36 62 utmost importance and must consider the different stages of the disease.[17]
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40 63 Clinical Practice Guidelines (CPGs) have been developed to provide scientific evidence to
41
42 64 support clinical decision-making of health professionals and establish standards of care for many
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44 65 conditions.[18, 19] CPGs focused on all aspects of nutritional therapy for ALS are still lacking.
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46 66 Existent guidelines on this matter only address some nutritional aspects, most of them related to
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48 67 gastrostomy and dysphagia. Many other aspects of nutritional therapy have not been covered,
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50 68 such as energy and nutrient requirements, modified consistency diet, micronutrients and
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52 69 bioactive compounds supplementation, and nutrition advice for comorbidities in ALS patients.
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3 70 Considering this gap and aiming to provide broader guidance on nutrition therapy for ALS
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5 71 patients, it is essential to gather and synthesize recommendations on this subject, based on
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7 72 available scientific evidence of clinical protocols and guidelines. Also, based on the effectiveness
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9 73 of nutritional interventions verified through clinical trials. We believe that a synthesis of
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11 74 recommendations on nutrition therapy in ALS will help and guide the nutrition care process and
12
13 75 benefit the patients.[20, 21]
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17 76 Given the information above, this protocol will seek to answer the following questions: **RQ1**
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19 77 - What are the evidence-based nutritional recommendations to maintain or restore the nutritional
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21 78 status of patients with ALS? **RQ2** - What is the effect of a diet rich in energy and protein in
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23 79 people with ALS? **RQ3** - What are the effects of supplementing isolated micronutrients or
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25 80 bioactive compounds in people with ALS?
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28 81 Therefore, this protocol aims to build an outline of upcoming systematic reviews and meta-
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30 82 analyses to present a synthesis of evidence-based recommendations to support adequate nutrition
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32 83 therapy and improve the nutritional status of patients with ALS.
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36 37 85 **METHODS AND ANALYSIS**

38 39 86 **Protocol Registration**

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41
42 87 This protocol was registered on the International Prospective Register of Systematic Reviews
43
44 88 (PROSPERO) database on April 12, 2021 (CRD42021233088). This protocol is in line with
45
46 89 international ethical parameters and because it is a study with secondary data, there is no need to
47
48 90 seek approval from a research ethics committee. Also, it was developed in accordance with the
49
50 91 Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P)
51
52 92 statement guidelines.[22] The PRISMA-P checklist used to prepare this protocol has been
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93 provided as an online supplemental file. To report the systematic review, the PRISMA statement
94 with a 27-item checklist and descriptive flow diagram will be used.[23] This present protocol
95 encompasses two systematic reviews and meta-analyses. The first one will be a review of
96 protocols/guidelines aimed to answer the RQ1. The second one will be a review of clinical trials
97 aimed to answer RQ2 and RQ3. The information regarding methods and analysis are described
98 according to the research questions.

100 **Selection Criteria**

101 For RQ1, we will include CPGs, treatment protocols, and systematic reviews. For RQ2 and RQ3,
102 we will only include clinical trials with control groups.

104 **Participants**

105 For all RQ's we will include studies comprised of adults (aged 18 and over) and seniors of both
106 sexes with a clinical diagnosis of ALS as definite, probable, or possible, according to the revised
107 El Escorial criteria.

109 **Types of interventions**

110 For RQ1, we will include studies involving nutrition therapy recommendations to maintain or
111 restore the nutritional status of patients with ALS. For RQ2, we will include studies
112 implementing a diet rich in energy and/or protein as an intervention. For RQ3, we will include
113 studies supplementing single micronutrients or bioactive compounds as an intervention.

115 **Outcomes measures**

1
2
3 116 For RQ1, only the summary of the nutritional recommendations for recovery or maintenance of
4
5 117 the nutritional status in ALS patients will be performed, with no outcomes to be measured. For
6
7 118 the RQ2, the outcome will be the change of body mass index, percentage of weight loss,
8
9 119 progression rate of total revised ALS Functional Rating Scale (ALSFRS-R), and mortality rate.
10
11 120 For the RQ3, the outcome will be the antioxidant effect, ALSFRS-R progression rate, and
12
13 121 mortality rate.
14
15 122

19 123 **Inclusion Criteria**

20
21 124 For RQ1, the inclusion criteria are evidence-based nutritional recommendations to maintain or
22
23 125 restore the nutritional status of patients diagnosed with definite, probable, or possible ALS. For
24
25 126 RQ2 and RQ3, the inclusion criteria are adults and elderly patients, of both sexes, diagnosed with
26
27 127 definite, probable, or possible ALS.
28
29 128

33 129 **Exclusion Criteria**

34
35 130 For all RQ's we will exclude studies with other neurodegenerative diseases or without nutritional
36
37 131 recommendations. No restrictions of time and language will be applied in our search.
38
39 132

42 133 **Search strategy**

43
44 134 A comprehensive electronic search will be performed in the following databases: PubMed,
45
46 135 Excerpta Medica Database (Embase), Scopus, SciELO, Web of Science, LILACS, Cochrane
47
48 136 Central Register of Controlled Trials (CENTRAL), ScienceDirect, ProQuest, and Google
49
50 137 Scholar. The search strategy will include the following descriptors (MeSH): “Amyotrophic
51
52 138 Lateral Sclerosis”, “Motor Neuron Disease”, “Nutrition”, “Nutritional Assessment”, “Nutrition
53
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3 139 Therapy”, “Diet”, “Dietary Supplements”, “Deglutition Disorders”, “Guideline”, and “Clinical
4
5 140 Protocols”. In addition, the Emtree terms “Diet Therapy”, “Dysphagia”, and “Practice
6
7 141 Guideline” will be included for the Embase database. A draft of our search strategy has been
8
9 142 provided as an online supplemental file.
10
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12 143
13

14 144 **Searches of other resources**

15
16
17 145 To ensure the comprehensiveness of this research, we will supplement searches by hand-
18
19 146 searching in the reference lists of retrieved studies or relevant reviews. To identify unpublished
20
21 147 studies and assess publication bias, we will also examine *ClinicalTrials.gov* and
22
23 148 *ensaiosclinicos.gov.br* for registered clinical trials using interventions such as high-energy and/or
24
25 149 high-protein diet and supplementation of micronutrients or bioactive compounds in people with
26
27 150 ALS.
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31 151 32 33 152 **Study selection**

34
35 153 For all identified studies, at least 2 authors (MDCV and LLL) will independently select and
36
37 154 review titles and abstracts using the Rayyan QCRI® tool. Papers that meet the inclusion criteria
38
39 155 will be ordered for a full review. Any disagreement will be resolved by discussion with a third
40
41 156 reviewer (SHLV). A manual search will be performed if any relevant studies are found using the
42
43 157 defined search strategies. All investigators will then review the full text of all eligible studies.
44
45 158 The information on the phases of the selection process will be described through PRISMA flow
46
47 159 diagram.[23]
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51 160 52 53 161 **Data extraction**

1
2
3 162 The data extraction will be done in a standardized way, using Microsoft Excel by 2 independent
4
5 163 authors (MDCV and LLL). Discrepancies between the data extraction will be resolved by
6
7 164 consensus. The study characteristics will be collated according to the research questions. For
8
9
10 165 RQ1, the following data will be extracted: general information about the guideline (title,
11
12 166 responsible organization, year of publication, and funding); nutritional recommendations
13
14 167 addressed; and the stratification of the level of evidence used. For RQ2 and RQ3, the following
15
16 168 data will be extracted: general information (title, authors, journal, year, country); study
17
18 169 characteristics (study design, study duration); sample characteristics (sample size, mean age,
19
20 170 ALS subtype, ALSFRS-R); intervention (type of intervention, duration, diet characteristics,
21
22 171 energy and/or protein amount); outcomes (changes in body mass index, percentage of weight
23
24 172 loss, progression rate of functional status, mortality rate); and statistical results. If study reports
25
26 173 are incomplete or missing data, corresponding authors will be contacted. If we do not receive
27
28 174 clarification, the requested data will be excluded from our analysis and will be commented in the
29
30 175 Discussion section.
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38 **Evaluation of methodological quality**

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40 178 Two independent authors (SHLV and MDCV) will evaluate the methodological quality of the
41
42 179 studies using the AGREE II statement. This instrument assesses six domains: 1. Scope and
43
44 180 purpose, 2. Stakeholder involvement, 3. Rigour of development, 4. Clarity of presentation, 5.
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46 181 Applicability, and 6. Editorial independence.[24] To assess the methodological quality and risk
47
48 182 of bias of clinical trials, the Cochrane Risk of Bias (RoB 2.0) and ROBINS-I tools will be used
49
50 183 for randomized and non-randomized studies, respectively.[25, 26]
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185 **Data synthesis**

186 For the first systematic review (RQ1), the findings and main recommendations will be
187 narratively summarized. For the second systematic review (RQ2 and RQ3), meta-analysis will
188 be performed, if possible. If meta-analysis is not possible, we will conduct a systematic review
189 with narrative analysis tabling the results.

190

191 **Assessment of heterogeneity**

192 To assess the heterogeneity, we plan to calculate the standard chi-square statistic, which is a
193 quantitative measure of inconsistency between the studies. Next, the I^2 index will be calculated
194 to quantify heterogeneity. The I^2 statistic describes the percentage of variation across studies due
195 to heterogeneity rather than chance. No heterogeneity is observed when I^2 is 0%, and the
196 variability can be explained by chance alone. A value of $I^2 > 50\%$ indicates high heterogeneity.

197

198 **Meta-analysis**

199 If there is the possibility of meta-analysis, standard statistical techniques will be used. If
200 substantial heterogeneity occurs, we will perform subgroup analysis and meta-regression to
201 identify possible associated cofactors such as disease onset (bulbar or spinal), age at onset,
202 disease duration, and clinical stages of ALS (early, middle, late, and end). In addition, the
203 random effects model will be used in the synthesis of data from the included studies. Publication
204 bias will be assessed using a funnel plot and its asymmetry will be verified by linear regression.

205

206 **Subgroup analysis**

207 For the RQ1 the analysis of subgroups is not applicable. If sufficient data are available for the
208 RQ2 and RQ3, the subgroup analysis will consider disease onset (bulbar or spinal), age of onset,
209 disease duration, and clinical stages of ALS (early, middle, late, and end). These stages are
210 classified as follow: stage 1 for symptom onset or functional involvement of one Central
211 Nervous System (CNS) region (**early**), stage 2 for diagnosis or functional involvement of two
212 CNS regions (**middle**), stage 3 for functional involvement of three CNS regions (**late**), stage 4
213 for need for gastrostomy or non-invasive ventilation (**end**), and stage 5 for death.[27, 28]

215 **Assessment of quality of evidence (GRADE)**

216 Two independent authors (MDCV and LLL) will assess the quality of the evidence and the
217 strength of the recommendations provided by the selected studies. For this purpose, we will use
218 the Grading of Recommendations, Assessment, Development and Evaluation (GRADE)[29] for
219 decision-making in health, which classifies the quality of evidence into four levels (high,
220 moderate, low, and very low) and the strength of the evidence into two levels (strong or weak).

222 **Patient and public involvement**

223 No patients or the public will be directly engaged in this research, as it is conducted using
224 secondary data.

226 **DISCUSSION**

227 This study aims to gather and synthesize recommendations for nutritional intervention and
228 treatment based on available scientific evidence from clinical protocols and guidelines. Also, the
229 effectiveness of interventions will be verified through clinical trials.

230 Weight loss, low BMI, and malnutrition are frequent in ALS patients. According to the
231 guideline conducted by Burgos et al.,[30] the BMI reduction in ALS patients is associated with
232 shortened survival and high risk of mortality.

233 A systematic review states that there is no cure or effective treatment for ALS to date.
234 Multidisciplinary care is the basis for its treatment, including nutritional support as well as
235 respiratory and symptom management during the disease. Furthermore, the review highlights
236 that dietary intervention can help to improve nutrition status. For example, gastrostomy is
237 indicated if oral intake is insufficient or is no longer safe.[31]

238 Dorst et al. found that high-energy supplementation effectively stabilizes the body weight of
239 patients with ALS and no side effects were detected. The authors also observed a positive impact
240 on the survival of the patients. Thus, the use of high-energy supplementation was suggested.[32]
241 In a cohort study, Traynor et al.[33] demonstrated that ALS patients who received
242 multidisciplinary care had a better prognosis than patients who received general care through a
243 neurology clinic.

244 Scientific entities specialized in ALS recognize nutrition as integral part of care during the
245 course of the disease and address some nutritional recommendations.[34, 35] Nutrition therapy
246 seeks to prevent malnutrition, maintain adequate nutritional status, promote hemodynamic
247 stability, reduce the rate of disease progression, and positively impact the quality of life and
248 survival of ALS patients.[36] Thus, identifying consistent recommendations for nutrition
249 intervention in ALS is of the utmost importance and will contribute to more assertive patient
250 care.[37-40] Nevertheless, systematic reviews and guidelines about ALS nutritional therapy are
251 scarce and some of them present gaps because they do not discuss specific aspects regarding
252 nutritional treatment and management that should be implemented in this type of patient.

253 For example, the recommendations by Garcia et al.[41] describe the nutritional aspects of
254 ALS and nutritional management with recommendations for high energy intake and those related
255 to enteral and parenteral nutrition. However, it does not address percentages of macronutrients
256 distribution, micronutrients requirements, or adjuvant nutritional supplements.

257 In a review paper about nutrition management in ALS, Greenwood et al.[39] prioritize the
258 quantitative recommendation of protein but do not determine recommendations for lipids,
259 carbohydrates, fibers, micronutrients, bioactive compounds, and nutritional supplements. The
260 pieces of information we gathered show how these two systematic reviews proposed by our
261 group are needed and can be helpful in assisting the nutrition care of ALS patients with robust
262 recommendations based on scientific evidence.

263 In this sense, the development of updated systematic reviews with meta-analyses and
264 synthesized recommendations on nutrition therapy of patients with ALS can reduce the
265 nutritional risk and positively influence their quality of life and survival time. Furthermore, it
266 will support the first Brazilian guideline of nutrition therapy in ALS, which will guide the
267 clinical nutrition practice with greater safety and efficiency. Thus, we believe this protocol is
268 relevant and it will benefit the scientific community, health care professionals, caregivers, and
269 especially patients with ALS. In addition, the systematic reviews proposed can also help to
270 highlight areas that require more research in the subject of nutrition therapy and ALS.

271

272 **ETHICS AND DISSEMINATION**

273 Ethical approval and human consent are not required because this is a protocol for systematic
274 review and only secondary data will be used. Findings will be published in a peer-reviewed
275 journal and presented at conferences. In case of any changes in this protocol, amendments will

276 be updated in PROSPERO and explanations of these modifications will be described in the final
277 report of this review.

278

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281 University of Rio Grande do Norte (UFRN) and its researchers who are part of the revELA
282 project.

283

284 **CONTRIBUTORS**

285 MDCV, LLL, and GP conceptualized and designed the protocol. The protocol manuscript was
286 written by MDCV and LLL. It was critically reviewed by GP, GCBSM, KMDC, SHLV, and
287 JBN. The search strategy was developed by MDCV, LLL, SHLV, GP, and GCBSM. MDCV,
288 KMDC, and LLL will lead the study selection. MDCV, LLL, and KMDC will be responsible for
289 data extraction. Statistical analysis will be performed by MDCV, SHLV, LLL, GCBSM, and GP.
290 JBN will be the third party and will host consensus meetings at each stage in case of
291 disagreement. All authors read, reviewed, and approved the final protocol.

292

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297 University of Rio Grande do Norte - LAIS/UFRN).

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3 299 **COMPETING INTERESTS**
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5 300 None declared.
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Supplemental Material [Draft of Search Strategy]

Database	Research Question (QR)	Equations
PubMed	RQ1*	"amyotrophic lateral sclerosis" OR "motor neuron disease" AND "nutrition" AND "guideline"
PubMed	RQ2**	"amyotrophic lateral sclerosis" OR "motor neuron disease" AND "diet therapy" OR "diet, high fat" OR "diet, high protein"
PubMed	RQ3***	"amyotrophic lateral sclerosis" OR "motor neuron disease" AND "dietary supplements"
<p>*RQ1 - What are the evidence-based nutritional recommendations to maintain or restore the nutritional status of patients with ALS? **RQ2 - What is the effect of a diet rich in energy and protein in people with ALS? ***RQ3 - What are the effects of supplementing isolated micronutrients or bioactive compounds in people with ALS?</p>		

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	X		OK*
Update	1b	If the protocol is for an update of a previous systematic review, identify as such		X	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	X		26
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	X		OK*
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	X		277-284
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		X	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	X		286-290
Sponsor	5b	Provide name for the review funder and/or sponsor	X		286-290
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol		X	NA
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	X		58-73
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	X		74-76
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	X		104-127

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
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	X		104-127
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	X		129-146
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	X		148-158
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)	X		148-155
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	X		157-160; 168-171
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	X		161-168
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	X		161-168
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	X		173-179
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	X		181-185
	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)	X		187-201
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	X		203-206
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	X		182-185
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	X		200-201
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	X		208-213

* The title is included in the Step 1 of the submission process at BMJ Open's author dashboard. The title is in accordance with PRISMA-P recommendations.