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Protocol for a prospective cohort study on the feasibility of application of nutritional ultrasound in the diagnosis and follow-up of patients with nutritional risk at hospital discharge: Study on body composition and function (DRECO).

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1 **Protocol for a prospective cohort study on the feasibility of application of nutritional**
2 **ultrasound in the diagnosis and follow-up of patients with nutritional risk at hospital**
3 **discharge: Study on body composition and function (DRECO).**

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16 **ABSTRACT**

17 **Background:** Nutritional ultrasound is an emerging technique in clinical nutrition for the
18 morphological and structural study of muscle mass. Currently, all definitions of malnutrition
19 include the measurement of muscle mass, however, there is no single way to assess it. It is
20 necessary to develop new techniques to identify muscle involvement in malnutrition that are
21 valid, standardized, reliable, accurate and profitable.

22 **Objective:** To value the new muscle ultrasound techniques aimed to measure muscle and
23 functional status, to make a more accurate diagnosis and a better prediction of complications
24 and morbidity and mortality in patients at nutritional risk. Primary outcome: to assess the
25 feasibility of ultrasound or muscle ultrasound techniques in both nutritional diagnosis and
26 follow-up in a nutritional intervention program.

27 **Methods and analysis:** DRECO (Disease-Related caloric-protein malnutrition EChOgraphy)
28 is a prospective, multicenter (25 Spanish hospitals), uncontrolled clinical study in standard
29 clinical practice to value the usefulness of nutritional ultrasound (muscle ultrasound) in the
30 nutritional diagnosis and follow-up, over 3 to 6 months, after standard nutritional clinical
31 practice intervention and physical activity, to control their disease-related malnutrition. 1000
32 patients are expected to be included in.

33 **Discussion:** This study will standardize nutritional ultrasound measures. It will validate and
34 define specific cut-off values for nutritional ultrasound and correlate it with already well-known
35 nutritional tools such as SGA (Subjective Global Assessment) or GLIM (Global Leadership
36 Initiative on Malnutrition) criteria. Thus, muscle ultrasound will become not only a tool to

37 diagnose malnutrition, but it will be integrated in the daily practice to evaluate nutritional
38 interventions.

39 **Ethics and dissemination Ethical:** All DRECO study materials have been approved by each
40 of the IRB/IEC of all the sites enrolled (either approval of the own IRB/IEC or validating the
41 approval of the IRB/IEC of another hospital). The study has been registered with
42 ClinicalTrials.gov, on June 27th, 2022. Results from this study will be presented at scientific
43 conferences and in peer-reviewed scientific journals.

44 **Trial registration number:** NCT05433831

45 **Strengths and limitations of this study**

46 DRECO strengths

- 47 • Multicentre, prospective, medium-term study in which a large sample (1000
48 patients) is expected to be recruited.
- 49 • Carried by a senior pool of researchers with wide experience in clinical nutrition and
50 dietetics.
- 51 • Validation of classical tools and new morpho functional assessment techniques
52 (ultrasound and bioelectrical impedance) are proposed.

53 DRECO limitations

- 54 • Non-randomized clinical practice study, so it will not be possible to adequately
55 analyze the effect of nutritional intervention.
- 56 • It is restricted to patients upon hospital discharge, so it cannot be generalized to the
57 entire population of people at risk of malnutrition.

58 **Keywords:** nutritional ultrasound; nutritional biomarker; ultrasound cut-off values; disease-
59 related malnutrition; GLIM; SGA; body composition; sarcopenia; quadriceps femoris muscle;
60 abdominal muscle area, muscle mass.

61 **INTRODUCTION**

62 Disease-related malnutrition (DRM) can occur when there is a deficient supply of energy,
63 protein and/or other nutrients, depending on the nutritional needs of everyone at different
64 times of their life cycle or health or disease circumstances. This deficiency induces effects on
65 body composition and tissue and organ function and results in clinical consequences:
66 increased morbidity and mortality associated with different disease processes (1).

67 In 2019, the GLIM criteria were published (2), providing a different vision of how to assess
68 the malnourished patient. These criteria are divided into both phenotypic and etiological
69 criterion:

70 - Phenotypic criterion

- 71 • Weight loss (%): >5% within past 6 months, or >10% beyond 6 months
- 72 • Low body mass index (kg/m²): <20 if < 70 years, or <22 if >70 years. Asia: <18.5 if <
73 70 years, or <20 if >70 years

- 1
2
3 74 ● Reduced muscle mass: Reduced by validated body composition measuring
4 75 techniques
5
6 76 - Etiological criterion
7
8 77 ● 50% of ER (energy requirements) > 1 week, or any reduction for >2 weeks, or any
9 78 chronic GI (gastrointestinal) condition
10
11 79 that adversely impacts food assimilation or absorption
12
13 80 ● Inflammation: Acute disease/injury or chronic disease-related

14 81 There are techniques for nutritional assessment using assessment tools aimed at morpho
15 82 functional diagnosis of malnutrition (3), in addition to the classical nutritional parameters, such
16 83 as weight loss, BMI (body mass index), folds, circumferences, albumin, lymphocytes,
17 84 cholesterol and intake. New advanced parameters are being incorporated into clinical
18 85 nutrition and their incorporation into clinical practice is of increasing interest, such as
19 86 measures derived from bioelectrical impedance (BIA) and phase angle (PhA), dynamometry,
20 87 functional tests, CRP/prealbumin ratio and muscle ultrasound (see Figure 1).

21 88 Figure 1. Update of nutritional evolution parameters. Reproduced with permission from the
22 89 authors (3).

23 90 From a scientific point of view, the following nutritional assessment techniques are being
24 91 incorporated:

25 92 Muscle ultrasound

26 93 The application of ultrasound for the morphological and structural study of muscle mass is an
27 94 emerging technique. Currently, there are different validation studies on the measurement
28 95 technique. The ultrasound technique determines the surface area of the muscle in transverse
29 96 and longitudinal position. With ultrasound analysis, it is possible to measure key parameters
30 97 of muscle architecture, such as muscle volume and muscle fascicle length. Although there
31 98 are different muscle structures that can be evaluated, many of the studies focus on the
32 99 quadriceps rectus femoris or on combinations of various muscle groups involving large
33 100 muscle bundles with functional importance to the patient in terms of gait. Measurement of the
34 101 rectus femoris of the quadriceps is one of the most referenced measurements due to its
35 102 correlation with strength and tests of execution or functional performance. It is necessary to
36 103 develop new techniques to identify muscle involvement in malnutrition that are valid,
37 104 standardised, reliable, accurate and profitable. Currently, all definitions of malnutrition include
38 105 the measurement of muscle mass involvement, however, there is no single way to assess it.
39 106 The classic imaging techniques such as DEXA (dual-energy x-ray absorptiometry), CT
40 107 (computerised tomography) and MRI (magnetic resonance imaging) are considered the gold
41 108 standard, but they have difficulties in their clinical application under normal practice
42 109 conditions. Ultrasound has the advantage of being inexpensive, portable, and does not
43 110 involve ionising radiation. Several studies have confirmed the reliability of this technique to

1
2
3 111 measure the size of the quadriceps muscle in a healthy population (4). Studies on the
4 112 reliability of rectus femoris ultrasound have been published with an intraclass coefficient of
5 113 variation (ICC) of 0.97 (95% CI: 0.92-0.99) for the test-retest reliability of ultrasound.

6
7
8 114 The American Society for Parenteral and Enteral Nutrition (ASPEN), among the criteria for
9 115 the diagnosis of malnutrition in adults, recommends including an evaluation of fat and muscle
10 116 deposits. Specialists must incorporate techniques that properly help to identify the loss of
11 117 muscle and fat mass for a correct diagnosis of malnutrition. Implementing these evaluation
12 118 techniques and instruments is challenging and remains a work in progress (5). Muscle
13 119 ultrasonography correlates with body composition measurement techniques such as BIA and
14 120 anthropometry in patients with cancer (6). In adults with cystic fibrosis muscle ultrasound
15 121 measurements, particularly the mean muscular area rectus anterior (MARA), are related to
16 122 the nutritional status and respiratory function of these patients. (7)

17
18
19 123 The Global Leadership Initiative on Malnutrition (GLIM) has recently appointed a working
20 124 group to provide consensus-based guidance on assessment of skeletal muscle mass and its
21 125 role in the malnutrition diagnostic and assessment process. They support the use of US
22 126 (ultrasound), particularly in settings where its practical applicability provides potential for
23 127 patient follow-up through repeated measurements, but it requires standardisation through
24 128 experienced operators, and repeated measurements performed by the same individual. They
25 129 also encourage further validation studies for the US (8).

26 130 Bioelectrical impedance (BIA)

27 131 BIA is used as a tool to obtain data that helps to better understand the patient's nutritional
28 132 status, being a non-invasive, inexpensive, and easily transportable technique. Vector
29 133 analysis and phase angle provide direct data, not being necessary to be later adjusted using
30 134 formulas or mathematical models, as it is needed with simple or multifrequency bioelectrical
31 135 impedance or multifrequency (9). This method is based on the analysis of the two
32 136 bioimpedance vectors: resistance (R) and capacitive reactance (Xc). Resistance is defined
33 137 as the opposition to a flow of electric current through a circuit component, medium, or
34 138 substance, providing information about biological fluids, and therefore, related to tissue
35 139 hydration. A decrease in the resistance/height ratio will indicate swelling or third space;
36 140 conversely, an increased ratio will indicate dehydration. Reactance is the effect on an
37 141 electrical current caused by a material's ability to store energy in cell membranes, so it is
38 142 related to the cell mass and the integrity of its membranes. A decrease in Xc indicates loss
39 143 of cell mass. This cell mass is the sum of all metabolically active cells, being the central
40 144 parameter in the evaluation of nutritional status since the reduction of cell mass is typically
41 145 related to malnutrition (10).

42
43
44 146 A recent study conducted by Fernandez-Jimenez, *et al* found that a low SPhA (standardised
45 147 phase angle)-malnutrition value (SPhA < -0.3) was significantly associated with a higher

1
2
3 148 mortality hazards ratio (HR 7.87, 95% CI 2.56–24.24, $p < 0.001$). This biological marker could
4 149 therefore be incorporated among the screening tools and mortality risk assessment in this
5 150 population (11).

8 151 Dynamometry

9 152 Dynamometry is one of the 6 criteria to define malnutrition according to ASPEN (12). It is
10 153 extremely sensitive to nutritional status changes, so it is particularly useful to track nutritional
11 154 therapy or interventions results, even in the short and medium term. It has mostly been used
12 155 to predict post-surgical complications including elderly patients (13). Results obtained are
13 156 compared to the population averages by age and sex. Sanchez et al (14) presented reference
14 157 values for hand dynamometry using a Jamar hand dynamometer for a Spanish population,
15 158 providing cut-off points to define malnutrition. They concluded that hand dynamometry is
16 159 associated with lean mass, which supports its usefulness in nutritional assessment.

17 160 Although the new GLIM consensus-based guidance on assessment of skeletal muscle mass
18 161 do not include dynamometry as a marker of muscle mass (8), the authors hereby signing this
19 162 article have previously studied dynamometry as a marker of muscle mass suggesting that
20 163 GLIM criterion and dynamometry are associated to a higher mortality rate in both hospitalised
21 164 and outpatient oncology patients (15, 16).

22 165 Functional tests

23 166 These tests are a series of physical activities related to mobility, walking or balance. Their
24 167 results are related to those of scales that assess instrumental activities of daily living (IADL).
25 168 The most common are the "Timed Up and Go test" (TUG), the "Gait Speed Test" (GST) and
26 169 the "Short Physical Performance Battery (SPPB)" test that includes 3 tests (balance, gait
27 170 speed and get up and walk) (17).

28 171 Besides, the decrease in physical performance, evaluated by the SPPB test or hand grip
29 172 strength, has been shown to be elevated in patients with colorectal cancer prior to surgery
30 173 and it was related to an increase in postoperative complications and mortality (18).

31 174 **STUDY OBJECTIVES**

32 175 The objective of this study is to value the new muscle ultrasound techniques aimed to
33 176 measure muscle and functional status, to make a more accurate diagnosis and a better
34 177 prediction of complications and morbidity and mortality in patients at nutritional risk. This main
35 178 objective is developed in primary and secondary objectives as it follows:

36 179 **Primary objective**

- 37 180 ● To assess the feasibility of ultrasound or muscle ultrasound techniques in both nutritional
38 181 diagnosis and follow-up, over 3 to 6 months, in a nutritional intervention programme.

39 182 **Secondary objectives**

- 40 183 ● To determine the association between muscle morphological parameters (nutritional
41 184 ultrasound of the leg (area, circumference, axis and adipose tissue), total abdominal and

- 185 pre-peritoneal parameters measured by nutritional ultrasound and the nutritional and
186 functional status of the patient, as well as their prognostic value in hospitalised patients.
- 187 ● To establish an association between ultrasound as a diagnostic value of malnutrition as
188 compared to the diagnostic gold standard (SGA and GLIM criteria).
 - 189 ● To determine the ultrasound cut-off points associated with the diagnosis of malnutrition
190 and sarcopenia using the following tools:
 - 191 ○ Measurement of body composition using impedance techniques (Report: Phase
192 angle, body cell mass (BCM), hydration, fat free mass (FFM) and lean mass index.
 - 193 ○ Muscle strength and capacity to perform physical activity after the intervention:
194 dynamometry and Timed Up and Go test (TUG).
 - 195 ○ Criteria for sarcopenia.
 - 196 ○ To assess association with inflammatory activity markers: High-sensitivity C-
197 reactive protein (CRP)/prealbumin.
 - 198 ● To assess ultrasound changes in patient follow-up.
 - 199 ● To establish an association of ultrasound results as predictors of morbidity and mortality
200 (stay, mortality at 3 and 6 months, readmissions and in-hospital complications).

202 **METHODS AND ANALYSIS**

203 **Study design and setting**

204 DRECO (Disease-Related caloric-protein malnutrition EChOgraphy) is a prospective,
205 multicentre, uncontrolled clinical study in standard clinical practice to value the usefulness of
206 nutritional ultrasound (muscle ultrasound) in the nutritional diagnosis and follow-up of patients
207 over a period of 3 to 6 consecutive months, after standard nutritional clinical practice
208 intervention, and physical activity to control their disease-related malnutrition.

209 The study may be considered non-interventional since patients will undergo nutritional
210 interventions and the standard treatment planned by their physician for treatment according
211 to his/her standard clinical practice, and the only addition to the standard measurement and
212 follow-up techniques of the patient will be the performance of a muscle ultrasound
213 measurement using equipment provided to the centre for this purpose.

214 **Patients and public involvement**

215 Patients or the public will not be involved in the design, or conduct, or reporting, or
216 dissemination plans of our research.

217 **Recruitment**

218 Patients over 18 years of age who, in the first week of hospital admission in medical-surgical
219 areas, excluding critical patients, have an assessment of risk of malnutrition according to the
220 MUST and SARC-F screening test using R-MAPP. [(MUST: Malnutrition Universal Screening
221 Tool; SARC-F is an acronym of 5 domains included in the questionnaire: 1) Strength, 2)

222 Assistance with walking, 3) Rising from a chair, 4) Climbing stairs, and 5) Falls; R-MAPP
223 (Remote consultation on MAInutrition in the Primary Practice)].

224 If the results show a moderate or high risk of malnutrition, these patients will be invited to
225 participate in the study, and will undergo the morpho functional assessment, an ultrasound
226 study and the Subjective Global Assessment (SGA). This study is registered under
227 ClinicalTrials.gov (NCT05433831).

228 Figure 2 shows the schedule of enrolment, interventions, and assessments.

229 **Inclusion criteria**

- 230 ● Patients admitted to hospital who in the first week of admission have moderate or high
231 risk of malnutrition according to the MUST and SARC-F screening test using R-
232 MAPP.
- 233 ● Patients aged 18 to 85 years.
- 234 ● Patient who agrees to participate in the study and signs the informed consent.

235 **Exclusion criteria**

- 236 ● Hepatic impairment - AST/ALT (aspartate aminotransferase/alanine
237 aminotransferase) 3 x upper limit of normal.
- 238 ● Chronic kidney failure - GFR (glomerular filtration rate) <45 mL/min).
- 239 ● Patients with previous ICU (intensive care unit) stay during the study admission.
- 240 ● Cancer patients on palliative treatment or ECOG (Eastern Cooperative Oncology
241 Group) ≥ 3 .
- 242 ● Orthopaedic disease that does not allow adequate walking.
- 243 ● Patients with known dementia or others not related to a significant neurological or
244 psychiatric disorder, or any other psychological condition that may interfere with the
245 conduct of the study.
- 246 ● Patients with eating disorders.
- 247 ● Life expectancy of less than 6 months.
- 248 ● Patients unable to adequately complete the clinical laboratory assessments required
249 for the study protocol.

250 **Sample size calculation**

251 There are no previous clinical trials focusing on this objective published in the literature. We
252 report a study in patients with chronic kidney disease on haemodialysis (HD) (19) where
253 measurement of the rectus femoris cross-sectional muscle area (RFCSA) was validated for
254 the diagnosis of malnutrition related to this condition. RFCSA compared to bioimpedance
255 spectroscopy had higher area under the curve (AUC, 0.686 vs. 0.581), sensitivity (72.8% vs.
256 65.8%), and specificity (55.6% vs. 53.9%). The AUC of RFCSA was higher for the risk of
257 protein-energy wasting (PEW) in male (0.74, 95% CI: 0.66 to 0.82) and female patients (0.80,
258 95% CI: 0.70 to 0.90) (both $p < 0.001$). Gender-specific RFCSA values (males < 6.00 cm²;

259 females <4.47 cm²) indicated that HD patients with lower RFCSA were 8 times more likely to
260 have PEW (AOR = 8.63, 95% CI: 4.80-15.50, p<0.001).

261 Our study aims to establish the feasibility of nutritional ultrasound measurements at different
262 ages in both sexes to apply to patients with nutritional risk worldwide. For this purpose, the
263 electronic CRF will be programmed with the sample distributed by quotas to cover 50% men
264 and 50% women, as well as 10-year age ranges. Age-stratified sampling is designed to obtain
265 representative results of different ages and could be associated with the results of VGS, BIA,
266 and dynamometry. Variability of measurements should be adjusted for sex, age and
267 anthropometric parameters such as height.

268 It is estimated that 1,000 patients with nutritional risk will be discharged from 20-25 healthcare
269 centres throughout Spain and that at least 60% of the population will complete the 3-to-6-
270 month follow-up of the study. Due to the special pandemic situation, a higher-than-expected
271 drop-out rate is expected at 6 months than under normal conditions (40% are estimated not
272 to complete the 6-month follow-up for any reason).

273 **Study conduct**

274 The physicians participating in the study will be responsible for assessing the suitability of
275 inclusion for each patient.

276 Patients will be consecutively recruited by the physician as they are assessed daily in their
277 clinical practice at the hospital and found to have a risk of malnutrition according to the
278 MUST/SARC-F (R-MAPP) screening test.

279 Before inclusion, the investigator must check the inclusion and exclusion criteria and obtain
280 their informed consent.

281 The physician will be responsible for applying nutritional intervention and physical activity
282 treatment according to standard clinical practice, as well as for clinical monitoring of patients.
283 The treatment prescribed to each patient is not the objective of this study and is how the
284 patient will experience changes that must be recorded with the different techniques described
285 and with the muscle ultrasound involved in this study.

286 All physicians participating in the study must have been previously trained in the use of the
287 ultrasound equipment and materials provided for the study, as well as in the use of the
288 electronic CRF for data entry designed for this study.

289 Nutritional ultrasound techniques and measurements (ultrasound with 4-10 cm linear tube).

290 The equipment provided for the study is UProbe L6C Ultrasound Scanner (linear transducer
291 7.5-10 kHz) that allows depths up to 100 mm. Manufactured by Guangzhou Sonostar
292 Technologies Co., Ltd. PR China.

293 **Quadriceps rectus femoris ultrasound (see Figure 3)**

294 The measurement technique is determined for the patient lying supine with knees extended
295 and relaxed.

1
2
3 296 Measurement technique:

- 4 297 • In the lower third of the imaginary line between the antero-superior iliac spine and the
5 superior border of the patella.
6 298
7
8 299 • Correction of leg angle, it is important to focus the image on the rectus femoris.
9
10 300 • In malnourished patients, loss of muscle tone causes the muscle to move to the sides
11 301 • To minimize variability, measurements must be repeated three times.

12 302 Figure 3 – Comparison of longitudinal and transversal sections of the QRF muscle area
13 ultrasound. Functional measures and main anatomical structures are represented.

14 303
15 304 **Abdominal ultrasound (see Figure 4)**

16 305 Total, superficial, and pre-peritoneal adipose tissue are measured (centimetres) for the
17 patient lying down.
18 306

19 307 Measurement technique:

- 20 308 • The transducer is placed between the xiphoid process and the umbilicus in the midline
21 (in patients with surgery without navel, this would be 10 cm from the xiphoid
22 appendix).
23 309
24 310
25 311 • Images are taken during non-forced expiration, in a transverse plane with a variable
26 probe depth of 4-10 cm, perpendicular to the skin.
27 312
28 313 • To minimize variability, measurements must be repeated three times.

29 314 Measurement planes:

- 30 315 • Measurement of subcutaneous adipose tissue: the superficial and deep layers are
31 differentiated.
32 316
33 317 • Visceral adipose tissue measurement: it is measured in a transverse position.
34 Measure the distance between the boundary of the parietal peritoneum to the *linea*
35 *alba* on the inner side at the junction of the two-rectus abdominis muscles.
36 318
37 319

38 320 Figure 4 - Comparison of longitudinal and transversal sections of the abdominal area
39 ultrasound. Functional measures and main anatomical structures are represented.
40 321

41 322 Follow-up period

42 323 The planned follow-up period for each patient will be 3 to 6 months from the inclusion visit.
43 324 The investigating physician will perform at least one first inclusion visit, and a follow-up visit
44 at 3 and 6 months for each patient.
45 325

46 326 Study duration

47 327 The study is planned to last 18 months to detect patients at risk of malnutrition, recruitment,
48 field work, monitoring and data analysis.
49 328

50 329 An estimated 2-3 months will be needed to plan the coordination and distribution of the work
51 in the hospitalisation and outpatient clinic areas for the selection of candidate patients. It will
52 take 6 to 9 months to recruit patients. From the start of the study, the database will be
53 completed, and preliminary analyses will be performed. The final analysis will be performed
54 330
55 331
56 332

333 when the follow-up is completed together with writing of the related work that will require 4 to
334 6 months to complete.

335 Outcome measures

336 A list of the outcomes of interest is provided in Table 1.

337

338 Table 1. Study outcomes.

PRIMARY OUTCOMES	
Nutritional ultrasound measurements: ultrasound with 4-10 cm linear probe *	
	<ul style="list-style-type: none"> Abdominal ultrasound: total, superficial and pre-peritoneal adipose tissue (measured in centimetres) Muscle ultrasound: Area, circumference, axes and adipose tissue (measured in centimetres)
SECONDARY OUTCOMES	
Sociodemographic data:	
	<ul style="list-style-type: none"> Age Sex Educational level Toxic habits Medical history Risk of sarcopenia and moderate to high malnutrition based on MUST and SARC-F screening test using R-MAPP
Subjective Global Assessment (SGA) questionnaire	
Anthropometric data:	
	<ul style="list-style-type: none"> Current body weight (measured or estimated) Usual weight Adjusted weight (adjusted weight in obese subjects, dry weight without oedema in malnourished subjects) Height (measured or estimated) BMI Arm circumference
Bioelectrical impedance data (model (50 kHz): **	
	<ul style="list-style-type: none"> TBW (total body water, L) ECW (extracellular water, L) ICW (intracellular water, L) FFM (lean mass, kg) FM (fat mass, kg) BCM (body cell mass, kg) ASMM (appendicular skeletal muscle mass, kg) SMI (skeletal muscle mass index, kg) Percent hydration Body fat (%)
Blood biochemistry data (at baseline visit, at 3 and 6 months):	
	<ul style="list-style-type: none"> Albumin Prealbumin C-reactive protein Total cholesterol Lymphocytes
Bioelectrical impedance data (model (50 kHz): **	
	<ul style="list-style-type: none"> Age Sex Educational level Toxic habits Medical history Risk of sarcopenia and moderate to high malnutrition based on MUST and SARC-F screening test using R-MAPP
Functional parameters	
	<ul style="list-style-type: none"> Timed Up and Go test (TUG): patient sits in a chair and is told to get up (timing starts), walks 3 metres, comes back and sits in the initial chair (timing ends). Interpretation: <20 seconds: normal, > 20 seconds: increased risk of falling. Dynamometry. Three measurements of the dominant hand will be made recording the mean and maximum, measured in kilograms. Jamar® dynamometers are most used in international studies and have several grip positions.
Current patient status	

	<ul style="list-style-type: none"> • Hospital stays, mortality at 3 and 6 months, hospital readmissions and complications, if occurring, and their consequences (resolved/unresolved) must be recorded in the form.
Adherence	
	<ul style="list-style-type: none"> • Attendance to study follow-up visits.

*The equipment provided for the study is the UProbe L6C Ultrasound Scanner (linear transducer 7.5-10 kHz) that allows depths up to 100 mm. Manufactured by Guangzhou Sonostar Technologies Co., Ltd. PR China.

**Each healthcare center could use the BIA device they already owned. The most used device among all participants was AKERN branded.

345 **Data analysis plan**

346 Data analysis will be performed using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA).

347 Quantitative variables will be expressed as mean \pm standard deviation. The comparison
348 between qualitative variables will be performed using the Chi-square test with Fisher's
349 correction when necessary. Quantitative variables will be analysed using a Kolmogorov-
350 Smirnov test. Differences between quantitative variables will be analysed using Student's t
351 or ANOVA tests (for two or more samples, respectively) and non-parametric tests (Mann-
352 Whitney or Kruskal-Wallis) will be used when the variables to be analysed do not follow a
353 normal distribution.

354 Kappa coefficient will be used to assess agreement between techniques in diagnosis of
355 malnutrition.

356 The association between variables will be studied using Spearman or Pearson correlations
357 according to normality.

358 Several cut-off points will be estimated for prediction of diagnosis of malnutrition and
359 sarcopenia using ultrasound by ROC curves.

360 The significant associations between muscle ultrasound parameters and the objective clinical
361 variables in the univariate analysis will then be analysed in multivariate logistic regression
362 models which also control other confounding variables. To assess which nutritional tool best
363 predicts the risk of mortality during admission (and re-admission), we will perform multivariate
364 logistic regression models, in which the dependent variable will be in-hospital mortality (or re-
365 admission) based on the different tools applied (e.g. ultrasound, phase angle, SGA criteria,
366 GLIM, LMI), also controlling for sex, the presence of previous comorbidities and other
367 variables showing association in the univariate study.

368 For all calculations, a probability p less than 0.05 for two tails will be considered significant.

369 Recording of adverse reactions

370 Adverse reactions reporting is not the objective of the study. The investigator should proceed
371 as usual and through the channels established in the healthcare system if any adverse effect
372 occurs during follow-up. It will only be recorded in the follow-up if the patient must leave the
373 study for this reason for statistical purposes.

1
2
3 374 Handling of missing data

4 375 No formal imputation will be made for the different analyses; therefore, all estimates will be
5
6 376 obtained using all available data (available data only, ADO).

7
8 377 Since the study will be recorded using an electronic CRF (case report form), the necessary
9
10 378 consistency filters and alerts for missing data will be programmed to validate and store the
11
12 379 information, to minimise missing data and prevent the entry of incorrect or out of range data.

13 380 **ETHICS**

14 381 **General aspects**

15 382 This study will be conducted in accordance with current regulations, accepted international
16
17 383 ethical standards of Good Clinical Practice (CPMP/ICH/135/95), the principles laid down in
18
19 384 the latest version of the Declaration of Helsinki, RD 1591/2009 and Circular No. 07/2004
20
21 385 regulating clinical research with medical devices.

22 386 **Informed consent**

23 387 Before inclusion in the study and after considering the suitability of patient inclusion, all
24
25 388 participating physicians must offer the patient information about the study using a patient
26
27 389 information sheet, invite the patient to participate in it, answer their questions and request
28
29 390 completion of the informed consent form that will be kept in their own file.

30 391 **Evaluation by an Ethics Committee**

31 392 All DRECO study materials have been approved by each of the IRB/IEC of all the sites
32
33 393 enrolled (either approval of the own IRB/IEC or validating the approval of the IRB/IEC of
34
35 394 another hospital).

36 395 **Confidentiality**

37 396 The study data will be entered into an automated file owned by the sponsor. The analysis of
38
39 397 study results will be made from an anonymised database, that is, dissociated, with no
40
41 398 personal data, so that no subject can be identified or identifiable. This study database will be
42
43 399 extracted from the electronic CRF and will include data from physician records, impedance
44
45 400 recordings, and muscle ultrasound images. Data from different sources will be linked from
46
47 401 the patient code and will not include personal data. All data in the file owned by the sponsor
48
49 402 will be treated confidentially. The sponsor undertakes not to transfer data to third parties.

49 403 **Dissemination**

50 404 Results from this study will be presented at international and national scientific conferences,
51
52 405 and in peer-reviewed scientific journals.

53 406 **DISCUSSION**

54
55 407 There is a growing interest in the literature on the evaluation of muscle mass by ultrasound
56
57 408 (20). Its current clinical utility focuses on measuring the involvement of muscle mass to
58
59 409 assess the nutritional status of a patient (21). The further step that it is being investigated in
60
410 this clinical study, is that muscle ultrasound becomes not only a tool to assess the diagnosis

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3 411 of malnutrition but to integrate it in the routine clinical practices to evaluate nutritional
4 412 interventions.

6 413 The evaluation of the nutritional ultrasound should enable clinical decisions based on its
7
8 414 results to permit the adjustment and individualization of the nutritional therapeutic and
9
10 415 physical exercise plan, along with functional recovery (20).

11 416 To the best of our knowledge, this is going to be the largest study (sample size=1,000) using
12
13 417 nutritional ultrasound in patients with nutritional risk. Current scientific evidence is limited,
14
15 418 and it is expected that such a large population will allow us to validate and define specific cut-
16
17 419 off values for nutritional ultrasound and get its correlation with already well-known nutritional
18 420 tools such as SGA or GLIM criteria (22).

19 421 The emerging field of ultrasound assessment of muscle mass only highlights the need for a
20
21 422 standardisation of measurement technique as Perkisas, *et al* outline in their recently
22
23 423 published 2022 SARCUS update. This update provides the approach of muscle assessment
24
25 424 according to the most recent literature and anatomical landmarks for 39 different muscles.
26
27 425 Besides, the discussion about 4 new muscle parameters that are added to the 5 that were
28
29 426 previously considered is also presented (23) and some of these parameters have been
30
31 427 correlated with PhA (24) and they will be analysed in our present protocol. Our ongoing study
32
33 428 is intended to standardize these outstanding technique measures, to apply this technique
34
35 429 widely soon.

36 430 **Author Contributions:** All authors have identified the research question and were
37
38 431 responsible for the conception and design of the protocol and the study. JM.G.A., D.B. D.L.R,
39
40 432 and G.O. are conducting study investigation. G.G.R has managed funding acquisition. All
41
42 433 authors have been involved in drafting the manuscript and revising it critically for intellectual
43
44 434 content. All authors read and approved the final manuscript.

45 435 **Funding:** This study will be conducted thanks to a research grant from Abbott Laboratories.

46 436 **Conflicts of Interest:** JM.G.A., D.B. D.L.R, and G.O declare no conflict of interest. G.G.R is
47
48 437 an employee of Abbott Laboratories.

49 438 **Institutional Review Board Statement:** The study was conducted in accordance with the
50
51 439 Declaration of Helsinki, and approved by the following Ethical Committees: Comité de Ética
52
53 440 de la Investigación Provincial De Málaga, Portal de Ética de la Investigación Biomédica de
54
55 441 Andalucía (PEIBA), Comité de Ética de la Investigación con medicamentos Área De Salud
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57 442 Valladolid, Comité de Ética de la Investigación con medicamentos Hospital Universitario La
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59 443 Paz, Comité de Ética de la Investigación con medicamentos Hospital Universitario 12 de
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444 Octubre, Comité de Ética de la Investigación con medicamentos Hospital General
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446 Universitario Gregorio Marañón, Comité de Ética de la Investigación con medicamentos del
Complejo Hospitalario Universitario de Canarias (Provincia de Santa Cruz de Tenerife),

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3 447 Comité de Ética de la Investigación con medicamentos del Complejo Hospitalario
4 448 Universitario de Las Palmas, Comité de Ética de la Investigación con medicamentos y
5 449 Comisión de Proyectos de Investigación del Hospital Universitari Vall d'Hebron, Comité de
6 450 Ética de la Investigación con medicamentos del Consorcio Hospital General Universitario de
7 451 Valencia, Comité de Ética de la Investigación con medicamentos de la Clínica de Navarra,
8 452 Comité de Ética de la Investigación con medicamentos del Hospital de Basurto and Comité
9 453 de Ética de la Investigación con Medicamentos del Hospital Universitario y Politécnico la Fe
10 454 de Valencia. This study is registered at clinicaltrials.gov (NCT05433831), registered on June
11 455 27th, 2022. <https://clinicaltrials.gov/ct2/show/NCT05433831>.

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18 456 **Informed Consent Statement:** All participants are provided with a participant information
19 457 sheet and are required to provide written consent.

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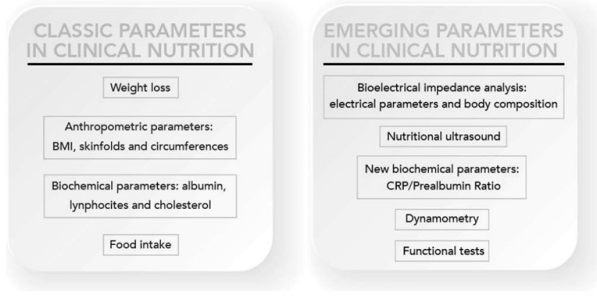


Figure 1. Update of nutritional evolution parameters. Reproduced with permission from the authors
338x190mm (96 x 96 DPI)

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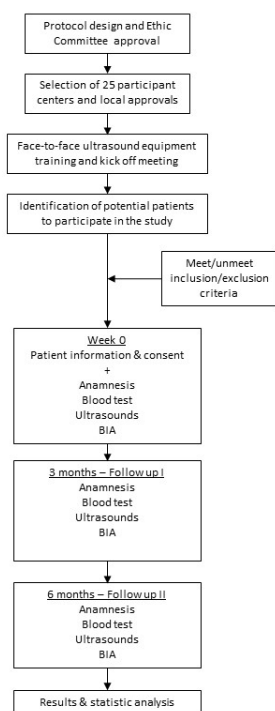


Figure 2 shows the schedule of enrolment, interventions, and assessments.

190x338mm (96 x 96 DPI)

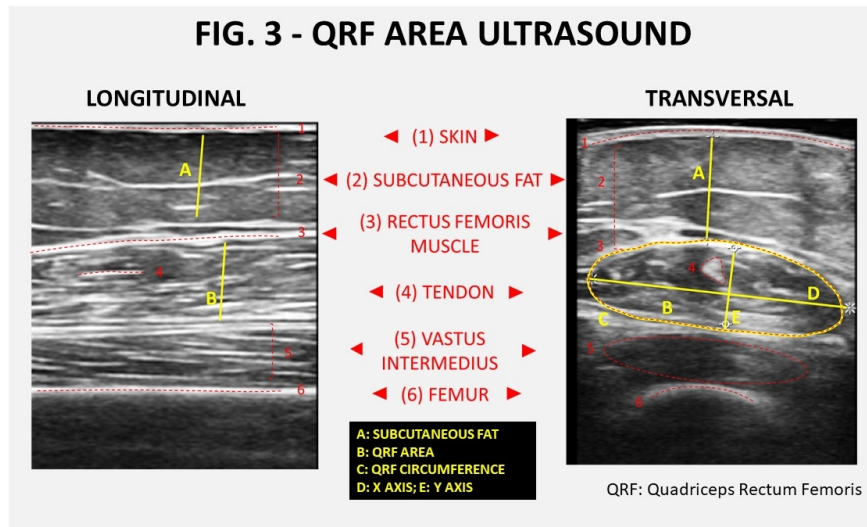
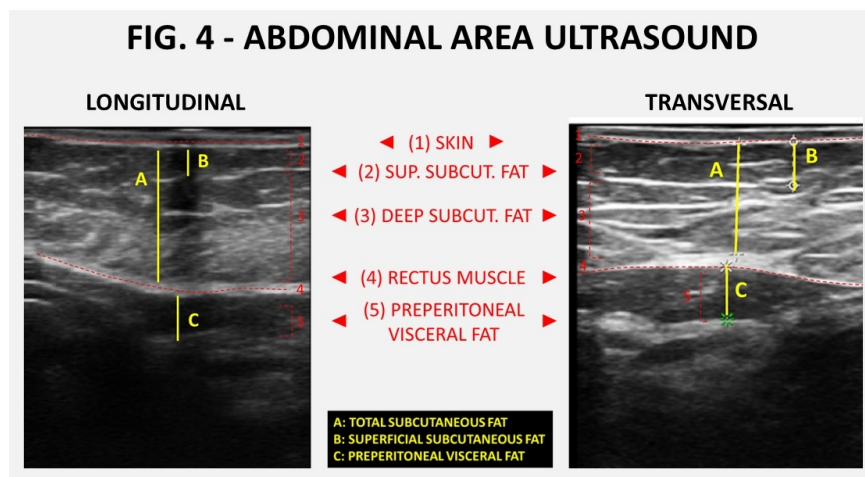


Figure 3 – Comparison of longitudinal and transversal sections of the QRF muscle area ultrasound. Functional measures and main anatomical structures are represented.

338x190mm (96 x 96 DPI)



25 Figure 4 - Comparison of longitudinal and transversal sections of the QRF muscle area ultrasound. Functional
26 measures and main anatomical structures are represented.

27 338x190mm (96 x 96 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

	Reporting Item	Page Number
Administrative information		
Title	<u>#1</u> Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

1 2 3 4 5 6	Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
7 8 9 10 11	Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
12 13 14	Protocol version	#3	Date and version identifier	NA
15 16 17 18 19	Funding	#4	Sources and types of financial, material, and other support	12
20 21 22 23 24 25 26 27	Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1; 12
28 29 30 31 32 33 34 35 36 37	Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
38 39 40 41 42 43 44 45 46 47 48 49 50 51	Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1;12
52 53 54 55 56 57 58 59 60	Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team,	1;12

and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)

Introduction

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	NA
Objectives	#7	Specific objectives or hypotheses	5-6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	

Methods:

Participants, interventions, and outcomes

1 2 3 4 5 6 7 8 9	Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7
10 11 12 13 14 15 16 17 18 19 20	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
21 22 23 24 25 26 27	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
28 29 30 31 32 33 34 35 36 37	Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	NO DRUG INTERVENTION
38 39 40 41 42 43 44 45 46 47	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	NO DRUG INTERVENTION
48 49 50 51 52	Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
53 54 55 56 57 58 59 60	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg,	10 – TABLE 1

1 systolic blood pressure), analysis metric (eg,
 2 change from baseline, final value, time to event),
 3 method of aggregation (eg, median, proportion),
 4 and time point for each outcome. Explanation of
 5 the clinical relevance of chosen efficacy and harm
 6 outcomes is strongly recommended
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15	Participant timeline	#13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7 – FIGURE 2
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27	Sample size	#14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	7-8
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39	Recruitment	#15 Strategies for achieving adequate participant enrolment to reach target sample size	7-8
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44	Methods:		NO
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46	Assignment of		CONTROLLED
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48	interventions (for		TRIAL
49			
50	controlled trials)		
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1	Allocation:	#16a	Method of generating the allocation sequence	NA
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3	sequence		(eg, computer-generated random numbers), and	
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5	generation		list of any factors for stratification. To reduce	
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7			predictability of a random sequence, details of	
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9			any planned restriction (eg, blocking) should be	
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11			provided in a separate document that is	
12				
13			unavailable to those who enrol participants or	
14				
15			assign interventions	
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17	Allocation	#16b	Mechanism of implementing the allocation	NA
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19	concealment		sequence (eg, central telephone; sequentially	
20				
21	mechanism		numbered, opaque, sealed envelopes),	
22				
23			describing any steps to conceal the sequence	
24				
25			until interventions are assigned	
26				
27	Allocation:	#16c	Who will generate the allocation sequence, who	NA
28				
29	implementation		will enrol participants, and who will assign	
30				
31			participants to interventions	
32				
33	Blinding (masking)	#17a	Who will be blinded after assignment to	NA
34				
35			interventions (eg, trial participants, care	
36				
37			providers, outcome assessors, data analysts),	
38				
39			and how	
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41	Blinding (masking):	#17b	If blinded, circumstances under which unblinding	NA
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43	emergency		is permissible, and procedure for revealing a	
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45	unblinding		participant's allocated intervention during the trial	
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Methods: Data**collection,****management, and****analysis**

Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10

1	Statistics: outcomes	#20a	Statistical methods for analysing primary and	10
2			secondary outcomes. Reference to where other	
3			details of the statistical analysis plan can be	
4			found, if not in the protocol	
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11	Statistics: additional	#20b	Methods for any additional analyses (eg,	10
12	analyses		subgroup and adjusted analyses)	
13				
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16	Statistics: analysis	#20c	Definition of analysis population relating to	10
17	population and		protocol non-adherence (eg, as randomised	
18	missing data		analysis), and any statistical methods to handle	
19			missing data (eg, multiple imputation)	
20				
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26	Methods:			NA
27				
28	Monitoring			
29				
30				
31				
32	Data monitoring:	#21a	Composition of data monitoring committee	
33	formal committee		(DMC); summary of its role and reporting	
34			structure; statement of whether it is independent	
35			from the sponsor and competing interests; and	
36			reference to where further details about its	
37			charter can be found, if not in the protocol.	
38			Alternatively, an explanation of why a DMC is not	
39			needed	
40				
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50				
51	Data monitoring:	#21b	Description of any interim analyses and stopping	
52	interim analysis		guidelines, including who will have access to	
53			these interim results and make the final decision	
54			to terminate the trial	
55				
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1	Harms	#22	Plans for collecting, assessing, reporting, and	
2			managing solicited and spontaneously reported	
3			adverse events and other unintended effects of	
4			trial interventions or trial conduct	
5				
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10				
11	Auditing	#23	Frequency and procedures for auditing trial	
12			conduct, if any, and whether the process will be	
13			independent from investigators and the sponsor	
14				
15				
16				
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18				
19	Ethics and			
20				
21	dissemination			
22				
23				
24	Research ethics	#24	Plans for seeking research ethics committee /	11
25			institutional review board (REC / IRB) approval	
26	approval			
27				
28				
29	Protocol	#25	Plans for communicating important protocol	11
30			modifications (eg, changes to eligibility criteria,	
31	amendments		outcomes, analyses) to relevant parties (eg,	
32			investigators, REC / IRBs, trial participants, trial	
33			registries, journals, regulators)	
34				
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36				
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41				
42	Consent or assent	#26a	Who will obtain informed consent or assent from	13
43			potential trial participants or authorised	
44			surrogates, and how (see Item 32)	
45				
46				
47				
48				
49	Consent or assent:	#26b	Additional consent provisions for collection and	NA
50			use of participant data and biological specimens	
51	ancillary studies		in ancillary studies, if applicable	
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1	Confidentiality	#27	How personal information about potential and	11
2			enrolled participants will be collected, shared, and	
3			maintained in order to protect confidentiality	
4			before, during, and after the trial	
5				
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11	Declaration of	#28	Financial and other competing interests for	12
12	interests		principal investigators for the overall trial and	
13			each study site	
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19	Data access	#29	Statement of who will have access to the final trial	11
20			dataset, and disclosure of contractual	
21			agreements that limit such access for	
22			investigators	
23				
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29	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care,	NA
30	trial care		and for compensation to those who suffer harm	
31			from trial participation	
32				
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35				
36	Dissemination	#31a	Plans for investigators and sponsor to	11
37	policy: trial results		communicate trial results to participants,	
38			healthcare professionals, the public, and other	
39			relevant groups (eg, via publication, reporting in	
40			results databases, or other data sharing	
41			arrangements), including any publication	
42			restrictions	
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53	Dissemination	#31b	Authorship eligibility guidelines and any intended	NA
54	policy: authorship		use of professional writers	
55				
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1 Dissemination [#31c](#) Plans, if any, for granting public access to the full NA
 2
 3 policy: reproducible protocol, participant-level dataset, and statistical
 4
 5 research code
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 7

8 Appendices

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 11
 12 Informed consent [#32](#) Model consent form and other related NA
 13
 14 materials documentation given to participants and
 15
 16 authorised surrogates
 17
 18

19
 20 Biological [#33](#) Plans for collection, laboratory evaluation, and NA
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 22 specimens storage of biological specimens for genetic or
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 24 molecular analysis in the current trial and for
 25
 26 future use in ancillary studies, if applicable
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 30 None The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative
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 33
 34 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with
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 36 [Penelope.ai](#)
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BMJ Open

Protocol for a prospective cohort study on the feasibility of application of nutritional ultrasound in the diagnosis and follow-up of patients with nutritional risk at hospital discharge: Study on body composition and function (DRECO).

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1 **Protocol for a prospective cohort study on the feasibility of application of nutritional**
2 **ultrasound in the diagnosis and follow-up of patients with nutritional risk at hospital**
3 **discharge: Study on body composition and function (DRECO).**

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21 **ABSTRACT**

22 **Introduction:** Nutritional ultrasound is an emerging technique in clinical nutrition for the
23 morphological and structural study of muscle mass. Currently, all definitions of malnutrition
24 include the measurement of muscle mass, however, there is no single way to assess it. It is
25 necessary to develop new techniques to identify muscle involvement in malnutrition that are
26 valid, standardized, reliable, accurate and profitable.

27 **Objective:** To value the new muscle ultrasound techniques aimed to measure muscle and
28 functional status, to make a more accurate diagnosis and a better prediction of complications
29 and morbidity and mortality in patients at nutritional risk. Primary outcome: to assess the
30 feasibility of ultrasound or muscle ultrasound techniques in both nutritional diagnosis and
31 follow-up in a nutritional intervention program.

32 **Methods and analysis:** DRECO (Disease-Related caloric-protein malnutrition EChOgraphy)
33 is a prospective, multicenter (25 Spanish hospitals), uncontrolled clinical study in standard
34 clinical practice to value the usefulness of nutritional ultrasound (muscle ultrasound) in the
35 nutritional diagnosis and follow-up, over 3 to 6 months, after standard nutritional clinical

36 practice intervention and physical activity, to control their disease-related malnutrition. 1000
37 patients are expected to be included in.

38 **Discussion:** This study will standardize nutritional ultrasound measures. It will validate and
39 define specific cut-off values for nutritional ultrasound and correlate it with already well-known
40 nutritional tools such as SGA (Subjective Global Assessment) or GLIM (Global Leadership
41 Initiative on Malnutrition) criteria. Thus, muscle ultrasound will become not only a tool to
42 diagnose malnutrition, but it will be integrated in the daily practice to evaluate nutritional
43 interventions.

44 **Ethics and dissemination Ethical:** All DRECO study materials have been approved by each
45 of the IRB/IEC of all the sites enrolled (either approval of the own IRB/IEC or validating the
46 approval of the IRB/IEC of another hospital). The study has been registered with
47 ClinicalTrials.gov, on June 27th, 2022. Results from this study will be presented at scientific
48 conferences and in peer-reviewed scientific journals.

49 **Trial registration number:** NCT05433831

50 **Strengths and limitations of this study**

51 DRECO strengths

- 52 • Multicentre, prospective, medium-term study in which a large sample (1000
53 patients) is expected to be recruited.
- 54 • First study designed as a real-world study to evaluate the feasibility of nutritional
55 ultrasound, led by senior researchers wide experienced in clinical nutrition.
- 56 • Validation of classical tools and new morpho functional assessment techniques
57 (ultrasound and bioelectrical impedance) are proposed.

58 DRECO limitations

- 59 • Non-randomized clinical practice study, so it will not be possible to adequately
60 analyze the effect of nutritional intervention.
- 61 • It is restricted to patients upon hospital discharge, so it cannot be generalized to the
62 entire population of people at risk of malnutrition.

63 **Keywords:** nutritional ultrasound; nutritional biomarker; ultrasound cut-off values; disease-
64 related malnutrition; GLIM; SGA; body composition; sarcopenia; quadriceps femoris muscle;
65 abdominal muscle area, muscle mass.

66 **1. INTRODUCTION**

67 Disease-related malnutrition (DRM) can occur when there is a deficient supply of energy,
68 protein and/or other nutrients, depending on the nutritional needs of everyone at different
69 times of their life cycle or health or disease circumstances. This deficiency induces effects on
70 body composition and tissue and organ function and results in clinical consequences:
71 increased morbidity and mortality associated with different disease processes (1).

1
2
3 72 In 2019, the GLIM criteria were published (2), providing a different vision of how to assess
4 73 the malnourished patient. These criteria are divided into both phenotypic and etiological
5 74 criterion:

6 75 - Phenotypic criterion

- 7 76
- 8 77 • Weight loss (%): >5% within past 6 months, or >10% beyond 6 months
 - 9 78 • Low body mass index (kg/m²): <20 if < 70 years, or <22 if >70 years. Asia: <18.5 if <
10 79 70 years, or <20 if >70 years
 - 11 80 • Reduced muscle mass: Reduced by validated body composition measuring
12 81 techniques

13 82 - Etiological criterion

- 14 83 • 50% of ER (energy requirements) > 1 week, or any reduction for >2 weeks, or any
15 84 chronic GI (gastrointestinal) condition
16 85 that adversely impacts food assimilation or absorption
- 17 86 • Inflammation: Acute disease/injury or chronic disease-related

18 87 There are techniques for nutritional assessment using assessment tools aimed at morpho
19 88 functional diagnosis of malnutrition (3), in addition to the classical nutritional parameters, such
20 89 as weight loss, BMI (body mass index), folds, circumferences, albumin, lymphocytes,
21 90 cholesterol and intake. New advanced parameters are being incorporated into clinical
22 91 nutrition and their incorporation into clinical practice is of increasing interest, such as
23 92 measures derived from bioelectrical impedance (BIA) and phase angle (PhA), dynamometry,
24 93 functional tests, CRP/prealbumin ratio and muscle ultrasound (see Figure 1).

25 94 Figure 1. Update of nutritional evolution parameters. Reproduced with permission from the
26 95 authors (3).

27 96 From a scientific point of view, the following nutritional assessment techniques are being
28 97 incorporated:

29 98 Muscle ultrasound

30 99 The application of ultrasound for the morphological and structural study of muscle mass is an
31 100 emerging technique. Currently, there are different validation studies on the measurement
32 101 technique. The ultrasound technique determines the surface area of the muscle in transverse
33 102 and longitudinal position. With ultrasound analysis, it is possible to measure key parameters
34 103 of muscle architecture, such as muscle volume and muscle fascicle length. Although there
35 104 are different muscle structures that can be evaluated, many of the studies focus on the
36 105 quadriceps rectus femoris or on combinations of various muscle groups involving large
37 106 muscle bundles with functional importance to the patient in terms of gait. Measurement of the
38 107 rectus femoris of the quadriceps is one of the most referenced measurements due to its
39 108 correlation with strength and tests of execution or functional performance. It is necessary to
40 develop new techniques to identify muscle involvement in malnutrition that are valid,

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2
3 109 standardised, reliable, accurate and profitable. Currently, all definitions of malnutrition include
4 110 the measurement of muscle mass involvement, however, there is no single way to assess it.
5
6 111 The classic imaging techniques such as DEXA (dual-energy x-ray absorptiometry), CT
7 112 (computerised tomography) and MRI (magnetic resonance imaging) are considered the gold
8
9 113 standard, but they have difficulties in their clinical application under normal practice
10 114 conditions. Ultrasound has the advantage of being inexpensive, portable, and does not
11 115 involve ionising radiation. Several studies have confirmed the reliability of this technique to
12 116 measure the size of the quadriceps muscle in a healthy population (4). Studies on the
13 117 reliability of rectus femoris ultrasound have been published with an intraclass coefficient of
14 118 variation (ICC) of 0.97 (95% CI: 0.92-0.99) for the test-retest reliability of ultrasound.

15
16 119 The American Society for Parenteral and Enteral Nutrition (ASPEN), among the criteria for
17 120 the diagnosis of malnutrition in adults, recommends including an evaluation of fat and muscle
18 121 deposits. Specialists must incorporate techniques that properly help to identify the loss of
19 122 muscle and fat mass for a correct diagnosis of malnutrition. Implementing these evaluation
20 123 techniques and instruments is challenging and remains a work in progress (5). Muscle
21 124 ultrasonography correlates with body composition measurement techniques such as BIA and
22 125 anthropometry in patients with cancer (6). In adults with cystic fibrosis muscle ultrasound
23 126 measurements, particularly the mean muscular area rectus anterior (MARA), are related to
24 127 the nutritional status and respiratory function of these patients. (7)

25
26 128 The Global Leadership Initiative on Malnutrition (GLIM) has recently appointed a working
27 129 group to provide consensus-based guidance on assessment of skeletal muscle mass and its
28 130 role in the malnutrition diagnostic and assessment process. They support the use of US
29 131 (ultrasound), particularly in settings where its practical applicability provides potential for
30 132 patient follow-up through repeated measurements, but it requires standardisation through
31 133 experienced operators, and repeated measurements performed by the same individual. They
32 134 also encourage further validation studies for the US (8).

33 135 Bioelectrical impedance (BIA)

34
35 136 BIA is used as a tool to obtain data that helps to better understand the patient's nutritional
36 137 status, being a non-invasive, inexpensive, and easily transportable technique. Vector
37 138 analysis and phase angle provide direct data, not being necessary to be later adjusted using
38 139 formulas or mathematical models, as it is needed with simple or multifrequency bioelectrical
39 140 impedance or multifrequency (9). This method is based on the analysis of the two
40 141 bioimpedance vectors: resistance (R) and capacitive reactance (Xc). Resistance is defined
41 142 as the opposition to a flow of electric current through a circuit component, medium, or
42 143 substance, providing information about biological fluids, and therefore, related to tissue
43 144 hydration. A decrease in the resistance/height ratio will indicate swelling or third space;
44 145 conversely, an increased ratio will indicate dehydration. Reactance is the effect on an

1
2
3 146 electrical current caused by a material's ability to store energy in cell membranes, so it is
4 147 related to the cell mass and the integrity of its membranes. A decrease in Xc indicates loss
5 148 of cell mass. This cell mass is the sum of all metabolically active cells, being the central
6 149 parameter in the evaluation of nutritional status since the reduction of cell mass is typically
7 150 related to malnutrition (10).

8 151 A recent study conducted by Fernandez-Jimenez, *et al* found that a low SPhA (standardised
9 152 phase angle)-malnutrition value (SPhA < -0.3) was significantly associated with a higher
10 153 mortality hazards ratio (HR 7.87, 95% CI 2.56–24.24, $p < 0.001$). This biological marker could
11 154 therefore be incorporated among the screening tools and mortality risk assessment in this
12 155 population (11).

13 156 Dynamometry

14 157 Dynamometry is one of the 6 criteria to define malnutrition according to ASPEN (12). It is
15 158 extremely sensitive to nutritional status changes, so it is particularly useful to track nutritional
16 159 therapy or interventions results, even in the short and medium term. It has mostly been used
17 160 to predict post-surgical complications including elderly patients (13). Results obtained are
18 161 compared to the population averages by age and sex. Sanchez et al (14) presented reference
19 162 values for hand dynamometry using a Jamar hand dynamometer for a Spanish population,
20 163 providing cut-off points to define malnutrition. They concluded that hand dynamometry is
21 164 associated with lean mass, which supports its usefulness in nutritional assessment.

22 165 Although the new GLIM consensus-based guidance on assessment of skeletal muscle mass
23 166 do not include dynamometry as a marker of muscle mass (8), the authors hereby signing this
24 167 article have previously studied dynamometry as a marker of muscle mass suggesting that
25 168 GLIM criterion and dynamometry are associated to a higher mortality rate in both hospitalised
26 169 and outpatient oncology patients (15, 16).

27 170 Functional tests

28 171 These tests are a series of physical activities related to mobility, walking or balance. Their
29 172 results are related to those of scales that assess instrumental activities of daily living (IADL).
30 173 The most common are the "Timed Up and Go test" (TUG), the "Gait Speed Test" (GST) and
31 174 the "Short Physical Performance Battery (SPPB)" test that includes 3 tests (balance, gait
32 175 speed and get up and walk) (17).

33 176 Besides, the decrease in physical performance, evaluated by the SPPB test or hand grip
34 177 strength, has been shown to be elevated in patients with colorectal cancer prior to surgery
35 178 and it was related to an increase in postoperative complications and mortality (18).

36 179 **1.1. STUDY OBJECTIVES**

37 180 The objective of this study is to value the new muscle ultrasound techniques aimed to
38 181 measure muscle and functional status, to make a more accurate diagnosis and a better
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3 182 prediction of complications and morbidity and mortality in patients at nutritional risk. This main
4 183 objective is developed in primary and secondary objectives as it follows:

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6 184 **1.1.1. Primary objective**

- 7
8 185 ● To assess the feasibility of ultrasound or muscle ultrasound techniques in both nutritional
9 186 diagnosis and follow-up, over 3 to 6 months, in a nutritional intervention programme.

10
11 187 **1.1.2. Secondary objectives**

- 12 188 ● To determine the association between muscle morphological parameters (nutritional
13 189 ultrasound of the leg (area, circumference, axis and adipose tissue), total abdominal and
14 190 pre-peritoneal parameters measured by nutritional ultrasound and the nutritional and
15 191 functional status of the patient, as well as their prognostic value in hospitalised patients.
16 192 ● To establish an association between ultrasound as a diagnostic value of malnutrition as
17 193 compared to the diagnostic gold standard (SGA and GLIM criteria).
18 194 ● To determine the ultrasound cut-off points associated with the diagnosis of malnutrition
19 195 and sarcopenia using the following tools:
20 196 ○ Measurement of body composition using impedance techniques (Report: Phase
21 197 angle, body cell mass (BCM), hydration, fat free mass (FFM) and lean mass index.
22 198 ○ Muscle strength and capacity to perform physical activity after the intervention:
23 199 dynamometry and Timed Up and Go test (TUG).
24 200 ○ Criteria for sarcopenia.
25 201 ○ To assess association with inflammatory activity markers: High-sensitivity C-
26 202 reactive protein (CRP)/prealbumin.
27 203 ● To assess ultrasound changes in patient follow-up.
28 204 ● To establish an association of ultrasound results as predictors of morbidity and mortality
29 205 (stay, mortality at 3 and 6 months, readmissions and in-hospital complications).

30
31 206 **2. PATIENT PARTICIPANT INVOLVEMENT AND FEASIBILITY OF STUDY DESIGN**

32 207 DRECO (Disease-Related caloric-protein malnutrition EChOgraphy) is a prospective,
33 208 multicentre, uncontrolled clinical study in standard clinical practice to value the usefulness of
34 209 nutritional ultrasound (muscle ultrasound) in the nutritional diagnosis and follow-up of patients
35 210 over a period of 3 to 6 consecutive months, after standard nutritional clinical practice
36 211 intervention, and physical activity to control their disease-related malnutrition.

37 212 The study may be considered non-interventional since patients will undergo nutritional
38 213 interventions and the standard treatment planned by their physician for treatment according
39 214 to his/her standard clinical practice, and the only addition to the standard measurement and
40 215 follow-up techniques of the patient will be the performance of a muscle ultrasound
41 216 measurement using equipment provided to the centre for this purpose.

42 217 Patients over 18 years of age who, in the first week of hospital admission in medical-surgical
43 218 areas, excluding critical patients, have an assessment of risk of malnutrition according to the

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3 219 MUST and SARC-F screening test using R-MAPP. [(MUST: Malnutrition Universal Screening
4 220 Tool; SARC-F is an acronym of 5 domains included in the questionnaire: 1) Strength, 2)
5 221 Assistance with walking, 3) Rising from a chair, 4) Climbing stairs, and 5) Falls; R-MAPP
6 222 (Remote consultation on MAInutrition in the Primary Practice)].

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8
9 223 If the results show a moderate or high risk of malnutrition, these patients will be invited to
10 224 participate in the study, and will undergo the morpho functional assessment, an ultrasound
11 225 study and the Subjective Global Assessment (SGA). This study is registered under
12 226 ClinicalTrials.gov (NCT05433831).

13
14
15 227 Figure 2 shows the schedule of enrolment, interventions, and assessments.

16 228 **2.1. Inclusion criteria**

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18
19 229 ● Patients admitted to hospital who in the first week of admission have moderate or high
20 230 risk of malnutrition according to the MUST and SARC-F screening test using R-
21 231 MAPP.
22
23 232 ● Patients aged 18 to 85 years.
24
25 233 ● Patient who agrees to participate in the study and signs the informed consent.

26 234 **2.2. Exclusion criteria**

- 27
28 235 ● Hepatic impairment - AST/ALT (aspartate aminotransferase/alanine
29 236 aminotransferase) 3 x upper limit of normal.
30
31 237 ● Chronic kidney failure - GFR (glomerular filtration rate) <45 mL/min).
32
33 238 ● Patients with previous ICU (intensive care unit) stay during the study admission.
34
35 239 ● Cancer patients on palliative treatment or ECOG (Eastern Cooperative Oncology
36 240 Group) ≥ 3 .
37
38 241 ● Orthopaedic disease that does not allow adequate walking.
39
40 242 ● Patients with known dementia or others not related to a significant neurological or
41 243 psychiatric disorder, or any other psychological condition that may interfere with the
42 244 conduct of the study.
43
44 245 ● Patients with eating disorders.
45
46 246 ● Life expectancy of less than 6 months.
47
48 247 ● Patients unable to adequately complete the clinical laboratory assessments required
49 248 for the study protocol.

50 249 **2.3. Sample size calculation**

51
52 250 There are no previous clinical trials focusing on this objective published in the literature. We
53 251 report a study in patients with chronic kidney disease on haemodialysis (HD) (19) where
54 252 measurement of the rectus femoris cross-sectional muscle area (RFCSA) was validated for
55 253 the diagnosis of malnutrition related to this condition. RFCSA compared to bioimpedance
56 254 spectroscopy had higher area under the curve (AUC, 0.686 vs. 0.581), sensitivity (72.8% vs.
57 255 65.8%), and specificity (55.6% vs. 53.9%). The AUC of RFCSA was higher for the risk of

256 protein-energy wasting (PEW) in male (0.74, 95% CI: 0.66 to 0.82) and female patients (0.80,
257 95% CI: 0.70 to 0.90) (both $p < 0.001$). Gender-specific RFCSA values (males $< 6.00 \text{ cm}^2$;
258 females $< 4.47 \text{ cm}^2$) indicated that HD patients with lower RFCSA were 8 times more likely to
259 have PEW (AOR = 8.63, 95% CI: 4.80-15.50, $p < 0.001$).

260 Our study aims to establish the feasibility of nutritional ultrasound measurements at different
261 ages in both sexes to apply to patients with nutritional risk worldwide. For this purpose, the
262 electronic CRF will be programmed with the sample distributed by quotas to cover 50% men
263 and 50% women, as well as 10-year age ranges. Age-stratified sampling is designed to obtain
264 representative results of different ages and could be associated with the results of VGS, BIA,
265 and dynamometry. Variability of measurements should be adjusted for sex, age and
266 anthropometric parameters such as height.

267 It is estimated that 1,000 patients with nutritional risk will be discharged from 20-25 healthcare
268 centres throughout Spain and that at least 60% of the population will complete the 3-to-6-
269 month follow-up of the study. Due to the special pandemic situation, a higher-than-expected
270 drop-out rate is expected at 6 months than under normal conditions (40% are estimated not
271 to complete the 6-month follow-up for any reason).

272 **2.4. Study conduct**

273 The physicians participating in the study will be responsible for assessing the suitability of
274 inclusion for each patient.

275 Patients will be consecutively recruited by the physician as they are assessed daily in their
276 clinical practice at the hospital and found to have a risk of malnutrition according to the
277 MUST/SARC-F (R-MAPP) screening test.

278 Before inclusion, the investigator must check the inclusion and exclusion criteria and obtain
279 their informed consent.

280 The physician will be responsible for applying nutritional intervention and physical activity
281 treatment according to standard clinical practice, as well as for clinical monitoring of patients.

282 The treatment prescribed to each patient is not the objective of this study and is how the
283 patient will experience changes that must be recorded with the different techniques described
284 and with the muscle ultrasound involved in this study.

285 All physicians participating in the study must have been previously trained in the use of the
286 ultrasound equipment and materials provided for the study, as well as in the use of the
287 electronic CRF for data entry designed for this study.

288 Throughout the entire study, monthly meetings are held with all participants on Thursdays at
289 8:30 a.m., and on Fridays at 8:30 a.m. with the study's central committee. The objective of
290 these meetings is to monitor the status of the study at each participating center, to resolve
291 doubts, and to make sure that all techniques and measurements are properly made according
292 to previous training.

2.4.1. Nutritional ultrasound techniques and measurements

US accuracy highly depends on the skills of the technician. Point training using rectus femoris phantom have shown to improve the accuracy of measurements. (20) Before starting the study, a training session was held. All study participants were required to attend, and they had the opportunity to practice with the same ultrasound machine that was going to be used in the study in phantom patients. Besides, several videos explaining detailed measurements technique were recorded. These videos were proactively shared with all researchers and available anytime at the study on-line electronic data capture (EDC) platform.

Beyond, once the study finishes, all DICOM images gathered will be analysed to develop a semi-automated algorithm that helps diagnose the patient's nutritional status. Subsequently, once the algorithm is available, the individual and manual US measurements will be contrasted with the data showed by the automatic algorithm, thus minimizing the inter and intra observer correlation. This work will have its own analysis and publication plan.

Abdominal and anterior thigh muscle measurements are performed using a commercially available portable ultrasound system with a 4-10 cm linear tube (UProbe L6C Ultrasound Scanner, Guangzhou Sonostar Technologies Co., Ltd., Guangzhou, Guangdong, P.R. China). The funder of the study provided an ultrasound machine to each of the participants hospitals.

2.4.1a. Quadriceps rectus femoris (QRF) ultrasound (see Figure 3)

With the patient lying supine with knees extended and relaxed, ultrasound measurements of unilateral (right side) quadriceps rectus femoris is performed at each participating center by an experienced medical sonographer blinded to the clinical data and other results of nutritional assessment. The acquisition site is located two-thirds of the way along the femur length, measured between the anterior superior iliac spine and the upper edge of the patella. The transducer is placed perpendicular to the long axis of the thigh with excessive use of contact gel and minimal pressure to avoid compression of the muscle. All parameters are taken as an average of three consecutive measurements in the dominant leg. We measure the transversal axis of the cross-sectional area (CSA) in cm^2 , the X-axis and Y-axis in mm, which corresponded to the linear measurement of the distance between the muscular limits of the rectus femoris (lateral and anteroposterior), the X-axis/Y-axis ratio, and the total fat tissue in mm. All US parameters were also standardized divided by height squared (in cm^2 for rectus femoris). The DICOM images of the QRF ultrasounds will be kept for later analysis.

Figure 3 – Comparison of longitudinal and transversal sections of the QRF muscle area ultrasound. Functional measures and main anatomical structures are represented.

330 **2.4.1b. Abdominal ultrasound (see Figure 4)**

331 The second component of nutritional ultrasound is the evaluation of fat at the level of the
332 abdominal wall. (21) The location of the measurement point is set at the midpoint between
333 the xiphoid appendix and the navel on the midline. The patient remains in a supine position
334 in a situation of relaxation and the image is taken during the unforced expiration, in a
335 transverse plane using the same linear probe perpendicular to the skin. In the cross-
336 section, the anatomical structures that are visualized are ordered from the most superficial
337 layer corresponding to the epidermis, followed by the layer of subcutaneous, superficial,
338 and deep adipose tissue. Then the two muscles of the anterior rectum of the abdomen that
339 join in the central part in the linea alba are identified. (21) We measure both total and
340 superficial subcutaneous adipose tissue and the pre-peritoneal visceral adipose tissue. The
341 DICOM images of the abdominal ultrasounds will be kept for later analysis.

342 Figure 4 - Comparison of longitudinal and transversal sections of the abdominal area
343 ultrasound. Functional measures and main anatomical structures are represented.

344 • **2.4.2 Bioelectrical Impedance (BIA)**

345 Total body BIA (50-kHz frequency) (Tanita BC-420MA BIA analyzer, Tanita Corporation,
346 Arlington Heights, IL, USA) was used to determine phase angle (degrees), total body water
347 (%), fat mass (kg), lean mass (kg), body cell mass (kg), and appendicular skeletal muscle
348 mass (ASMM) (kg).

349 Since interval fluid balance is more sensible to the change of edema, bioelectrical
350 impedance analysis can be affected in edematous patients. (22) Therefore, extreme phase
351 angle values and/or non-coherent reactance/resistance ratios will be discarded, as a control
352 measure, to detect patients with edema and fluid balance change.

353 • **2.4.3 Timed Up and Go test (TUG)**

354 The TUG test was used to assess functionality. A coloured tape was marked 3 m away
355 from an armless chair in which participants were sitting. Participants were asked to walk 3
356 m, turn around the marked tape, and return to the chair as fast as they could. A timer was
357 set as soon as the patient stood up from the chair and was stopped when the patient was
358 seated again. At least one practice trial was performed before the test. Being that a TUG-
359 score of ≥ 20 s is identified as a cut-off point for severe sarcopenia, TUG was considered in
360 this study. (23)

361 • **2.4.4 Handgrip strength test**

362 Handgrip strength was determined using the Jamar dynamometer (J A Preston
363 Corporation, New York, NY, USA). The dominant hand was tested. Three measurements of
364 both media and maximum value were taken. The American Society for Parenteral and
365 Enteral Nutrition has included the assessment of grip strength by dynamometer as one of
366

367 the six criteria to define malnutrition. (24) In this study, the cut-off values defined for the
 368 Spanish population will be considered. (14)

369

370 Although some quality-of-life test, such as SF-36 or ADL test (activities of daily living), were
 371 initially considered in the study protocol, they were finally rejected because, in real clinical
 372 practice, these tests are not used with the patient profile included in this study.

373

374 ● 2.4.5 Follow-up period

375 The planned follow-up period for each patient will be 3 to 6 months from the inclusion visit.

376 The investigating physician will perform at least one first inclusion visit, and a follow-up visit
 377 at 3 and 6 months for each patient. A follow-up period of 6 months was established since it
 378 is common clinical practice in these patients, and with the aim of making the results more
 379 generalizable.

380 It is planned that the same physician attends the three visits to the patient (baseline, 3 and 6
 381 months), to minimise the interpersonal variability in the measurements.

382

383 ● 2.4.6. Study duration

384 The study is planned to last 18 months to detect patients at risk of malnutrition, recruitment,
 385 field work, monitoring and data analysis.

386 An estimated 2-3 months will be needed to plan the coordination and distribution of the work
 387 in the hospitalisation and outpatient clinic areas for the selection of candidate patients. It will
 388 take 6 to 9 months to recruit patients. From the start of the study, the database will be
 389 completed, and preliminary analyses will be performed. The final analysis will be performed
 390 when the follow-up is completed together with writing of the related work that will require 4 to
 391 6 months to complete.

392 2.5. Outcome measures

393 A list of the outcomes of interest is provided in Table 1.

394

395 Table 1. Study outcomes.

PRIMARY OUTCOMES	
Nutritional ultrasound measurements: ultrasound with 4-10 cm linear probe *	
	● Abdominal ultrasound: total, superficial and pre-peritoneal adipose tissue (measured in centimetres)
	● Muscle ultrasound: Area, circumference, axes and adipose tissue (measured in centimetres)
SECONDARY OUTCOMES	
Sociodemographic data:	
	<ul style="list-style-type: none"> ● Age ● Sex ● Educational level ● Toxic habits ● Medical history ● Risk of sarcopenia and moderate to high malnutrition based on MUST and SARC-F screening test using R-MAPP

Subjective Global Assessment (SGA) questionnaire	
Anthropometric data:	
	<ul style="list-style-type: none"> • Current body weight (measured or estimated) • Usual weight • Adjusted weight (adjusted weight in obese subjects, dry weight without oedema in malnourished subjects) • Height (measured or estimated) • BMI • Arm circumference
Bioelectrical impedance data (model (50 kHz): **	
	<ul style="list-style-type: none"> • TBW (total body water, L) • ECW (extracellular water, L) • ICW (intracellular water, L) • FFM (lean mass, kg) • FM (fat mass, kg) • BCM (body cell mass, kg) • ASMM (appendicular skeletal muscle mass, kg) • SMI (skeletal muscle mass index, kg) • Percent hydration • Body fat (%)
Blood biochemistry data (at baseline visit, at 3 and 6 months):	
	<ul style="list-style-type: none"> • Albumin • Prealbumin • C-reactive protein • Total cholesterol • Lymphocytes
Bioelectrical impedance data (model (50 kHz):	
	<ul style="list-style-type: none"> • Age • Sex • Educational level • Toxic habits • Medical history • Risk of sarcopenia and moderate to high malnutrition based on MUST and SARC-F screening test using R-MAPP
Functional parameters	
	<ul style="list-style-type: none"> • Timed Up and Go test (TUG): patient sits in a chair and is told to get up (timing starts), walks 3 metres, comes back and sits in the initial chair (timing ends). Interpretation: <20 seconds: normal, > 20 seconds: increased risk of falling. • Dynamometry. Three measurements of the dominant hand will be made recording the mean and maximum, measured in kilograms. Jamar® dynamometers are most used in international studies and have several grip positions.
Current patient status	
	<ul style="list-style-type: none"> • Hospital stays, mortality at 3 and 6 months, hospital readmissions and complications, if occurring, and their consequences (resolved/unresolved) must be recorded in the form.
Adherence	
	<ul style="list-style-type: none"> • Attendance to study follow-up visits.

*The equipment provided for the study is the UProbe L6C Ultrasound Scanner (linear transducer 7.5-10 kHz) that allows depths up to 100 mm. Manufactured by Guangzhou Sonostar Technologies Co., Ltd. PR China.

2.6. Data analysis plan

Data analysis will be performed using SPSS 22.0 software (SPSS Inc., Chicago, IL, USA). Quantitative variables will be expressed as mean \pm standard deviation. The comparison between qualitative variables will be performed using the Chi-square test with Fisher's correction when necessary. Quantitative variables will be analysed using a Kolmogorov-Smirnov test. Differences between quantitative variables will be analysed using Student's t or ANOVA tests (for two or more samples, respectively) and non-parametric tests (Mann-Whitney or Kruskal-Wallis) will be used when the variables to be analysed do not follow a normal distribution.

1
2
3 409 Kappa coefficient will be used to assess agreement between techniques in diagnosis of
4 410 malnutrition.

5
6 411 The association between variables will be studied using Spearman or Pearson correlations
7 412 according to normality.

8
9 413 The thresholds for translation into clinical practice will be presented as cut-off points that will
10 414 be estimated by AUC ROC curves. Centiles will be also considered.

11
12 415 The significant associations between muscle ultrasound parameters and the objective clinical
13 416 variables in the univariate analysis will then be analysed in multivariate logistic regression
14 417 models which also control other confounding variables. To assess which nutritional tool best
15 418 predicts the risk of mortality during admission (and re-admission), we will perform multivariate
16 419 logistic regression models, in which the dependent variable will be in-hospital mortality (or re-
17 420 admission) based on the different tools applied (e.g. ultrasound, phase angle, SGA criteria,
18 421 GLIM, LMI), also controlling for sex, the presence of previous comorbidities and other
19 422 variables showing association in the univariate study.

20
21 423 For all calculations, a probability p less than 0.05 for two tails will be considered significant.

22
23 424 • **2.6.1. Recording of adverse reactions**

24
25 425 Adverse reactions reporting is not the objective of the study. The investigator should proceed
26 426 as usual and through the channels established in the healthcare system if any adverse effect
27 427 occurs during follow-up. It will only be recorded in the follow-up if the patient must leave the
28 428 study for this reason for statistical purposes.

29
30 429 • **2.6.2. Handling of missing data**

31
32 430 No formal imputation will be made for the different analyses; therefore, all estimates will be
33 431 obtained using all available data (available data only, ADO).

34
35 432 Since the study will be recorded using an electronic CRF (case report form), the necessary
36 433 consistency filters and alerts for missing data will be programmed to validate and store the
37 434 information, to minimise missing data and prevent the entry of incorrect or out of range data.

38
39 435 **3. ETHICS**

40
41 436 **3.1. General aspects**

42
43 437 This study will be conducted in accordance with current regulations, accepted international
44 438 ethical standards of Good Clinical Practice (CPMP/ICH/135/95), the principles laid down in
45 439 the latest version of the Declaration of Helsinki, RD 1591/2009 and Circular No. 07/2004
46 440 regulating clinical research with medical devices.

47
48 441 **3.2. Informed consent**

49
50 442 Before inclusion in the study and after considering the suitability of patient inclusion, all
51 443 participating physicians must offer the patient information about the study using a patient
52 444 information sheet, invite the patient to participate in it, answer their questions and request
53 445 completion of the informed consent form that will be kept in their own file.

446 **3.3. Evaluation by an Ethics Committee**

447 All DRECO study materials have been approved by each of the IRB/IEC of all the sites
448 enrolled (either approval of the own IRB/IEC or validating the approval of the IRB/IEC of
449 another hospital).

450 **3.4. Confidentiality**

451 The study data will be entered into an automated file owned by the sponsor. The analysis of
452 study results will be made from an anonymised database, that is, dissociated, with no
453 personal data, so that no subject can be identified or identifiable. This study database will be
454 extracted from the electronic CRF and will include data from physician records, impedance
455 recordings, and muscle ultrasound images. Data from different sources will be linked from
456 the patient code and will not include personal data. All data in the file owned by the sponsor
457 will be treated confidentially. The sponsor undertakes not to transfer data to third parties.

458 **3.5. Dissemination**

459 Results from this study will be presented at international and national scientific conferences,
460 and in peer-reviewed scientific journals.

461 **3.6. Patient and Public Involvement**

462 Patients and/or the public were not involved in the design, or conduct, or reporting, or
463 dissemination plans of this research.

464 **4. DISCUSSION**

465 There is a growing interest in the literature on the evaluation of muscle mass by ultrasound
466 (21). Its current clinical utility focuses on measuring the involvement of muscle mass to
467 assess the nutritional status of a patient (25). The further step that it is being investigated in
468 this clinical study, is that muscle ultrasound becomes not only a tool to assess the diagnosis
469 of malnutrition but to integrate it in the routine clinical practices to evaluate nutritional
470 interventions.

471 The evaluation of the nutritional ultrasound should enable clinical decisions based on its
472 results to permit the adjustment and individualization of the nutritional therapeutic and
473 physical exercise plan, along with functional recovery (21).

474 To the best of our knowledge, this is going to be the largest study (sample size=1,000) using
475 nutritional ultrasound in patients with nutritional risk. Current scientific evidence is limited,
476 and it is expected that such a large population will allow us to validate and define specific cut-
477 off values for nutritional ultrasound and get its correlation with already well-known nutritional
478 tools such as SGA or GLIM criteria (26).

479 This study stands out for the use of several morphofunctional assessment techniques in
480 patients with disease-related malnutrition in real clinical practice. Beyond its large sample, it
481 is the first study with this design, as a real-world study, to evaluate the feasibility of nutritional
482 ultrasound.

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2
3 483 The emerging field of ultrasound assessment of muscle mass only highlights the need for a
4 484 standardisation of measurement technique as Perkisas, *et al* outline in their recently
5 485 published 2022 SARCUS update. This update provides the approach of muscle assessment
6 486 according to the most recent literature and anatomical landmarks for 39 different muscles.
7
8 487 Besides, the discussion about 4 new muscle parameters that are added to the 5 that were
9 488 previously considered is also presented (27) and some of these parameters have been
10 489 correlated with PhA (28) and they will be analysed in our present protocol. Our ongoing study
11 490 is intended to standardize these outstanding technique measures, to apply this technique
12 491 widely soon. Recruited patients were at risk of malnutrition so the results will be very
13 492 interesting for routine clinical practice and nutritional care, in this patient profile, easily
14 493 generalizable and free to use with publication.

15 494 **Author Contributions:** All authors have identified the research question and were
16 495 responsible for the conception and design of the protocol and the study. JM.G.A., D.B. D.L.R,
17 496 and G.O. are conducting study investigation. G.G.R has managed funding acquisition. All
18 497 authors have been involved in drafting the manuscript and revising it critically for intellectual
19 498 content. All authors read and approved the final manuscript.

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21 500 **Conflicts of Interest:** JM.G.A., D.B. D.L.R, and G.O declare no conflict of interest. G.G.R is
22 501 an employee of Abbott Laboratories.

23 502 **Institutional Review Board Statement:** The study was conducted in accordance with the
24 503 Declaration of Helsinki, and approved by the following Ethical Committees: Comité de Ética
25 504 de la Investigación Provincial De Málaga, Portal de Ética de la Investigación Biomédica de
26 505 Andalucía (PEIBA), Comité de Ética de la Investigación con medicamentos Área De Salud
27 506 Valladolid, Comité de Ética de la Investigación con medicamentos Hospital Universitario La
28 507 Paz, Comité de Ética de la Investigación con medicamentos Hospital Universitario 12 de
29 508 Octubre, Comité de Ética de la Investigación con medicamentos Hospital General
30 509 Universitario Gregorio Marañón, Comité de Ética de la Investigación con medicamentos del
31 510 Complejo Hospitalario Universitario de Canarias (Provincia de Santa Cruz de Tenerife),
32 511 Comité de Ética de la Investigación con medicamentos del Complejo Hospitalario
33 512 Universitario de Las Palmas, Comité de Ética de la Investigación con medicamentos y
34 513 Comisión de Proyectos de Investigación del Hospital Universitari Vall d'Hebron, Comité de
35 514 Ética de la Investigación con medicamentos del Consorcio Hospital General Universitario de
36 515 Valencia, Comité de Ética de la Investigación con medicamentos de la Clínica de Navarra,
37 516 Comité de Ética de la Investigación con medicamentos del Hospital de Basurto and Comité
38 517 de Ética de la Investigación con Medicamentos del Hospital Universitario y Politécnico la Fe

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3 518 de Valencia. This study is registered at clinicaltrials.gov (NCT05433831), registered on June
4 519 27th, 2022. <https://clinicaltrials.gov/ct2/show/NCT05433831>.

5
6 520 **Informed Consent Statement:** All participants are provided with a participant information
7 521 sheet and are required to provide written consent.

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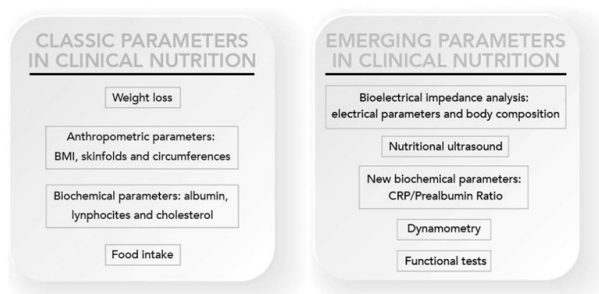


Figure 1. Update of nutritional evolution parameters. Reproduced with permission from the authors

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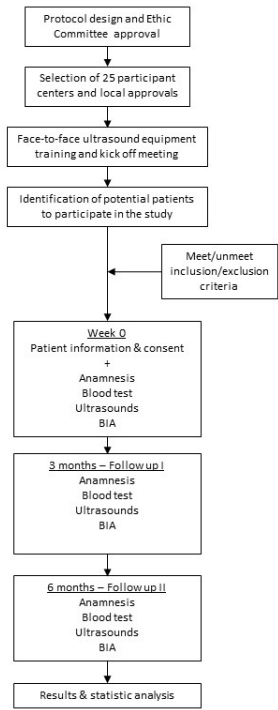


Figure 2 shows the schedule of enrolment, interventions, and assessments.

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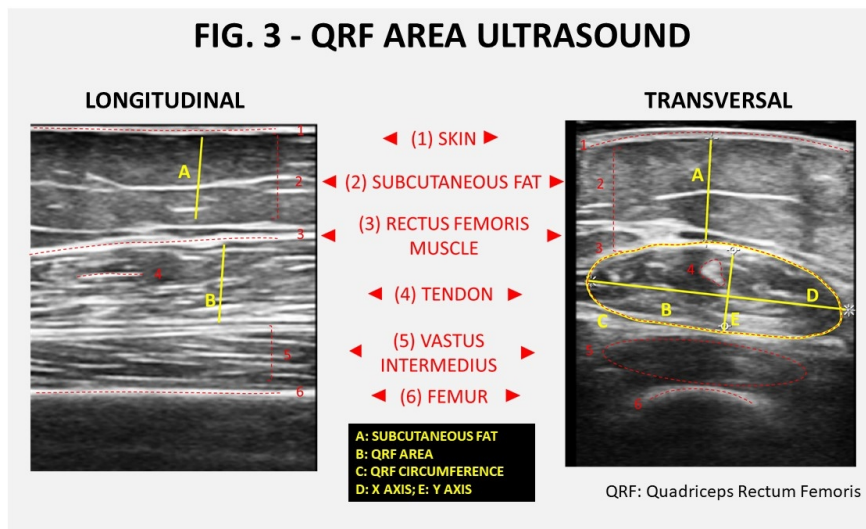


Figure 3 – Comparison of longitudinal and transversal sections of the QRF muscle area ultrasound. Functional measures and main anatomical structures are represented.

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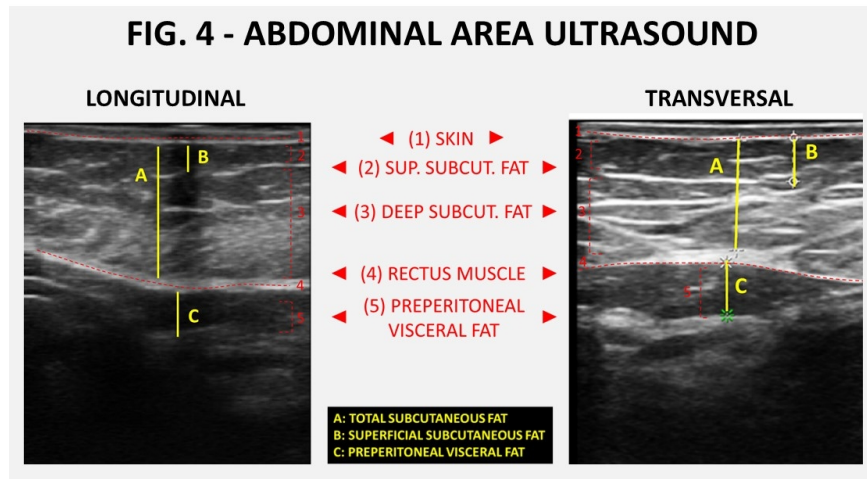


Figure 4 - Comparison of longitudinal and transversal sections of the QRF muscle area ultrasound. Functional measures and main anatomical structures are represented.

338x190mm (96 x 96 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

	Reporting Item	Page Number
Administrative information		
Title	#1 Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

1	Trial registration	#2a	Trial identifier and registry name. If not yet	2
2			registered, name of intended registry	
3				
4				
5				
6	Trial registration:	#2b	All items from the World Health Organization Trial	2
7	data set		Registration Data Set	
8				
9				
10				
11				
12	Protocol version	#3	Date and version identifier	NA
13				
14				
15	Funding	#4	Sources and types of financial, material, and	12
16			other support	
17				
18				
19				
20	Roles and	#5a	Names, affiliations, and roles of protocol	1; 12
21	responsibilities:		contributors	
22				
23	contributorship			
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28	Roles and	#5b	Name and contact information for the trial	1
29	responsibilities:		sponsor	
30				
31	sponsor contact			
32				
33	information			
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37				
38	Roles and	#5c	Role of study sponsor and funders, if any, in	1;12
39	responsibilities:		study design; collection, management, analysis,	
40			and interpretation of data; writing of the report;	
41	sponsor and funder		and the decision to submit the report for	
42			publication, including whether they will have	
43			ultimate authority over any of these activities	
44				
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52	Roles and	#5d	Composition, roles, and responsibilities of the	1;12
53	responsibilities:		coordinating centre, steering committee, endpoint	
54			adjudication committee, data management team,	
55	committees			
56				
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and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)

Introduction

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	NA
Objectives	#7	Specific objectives or hypotheses	5-6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	

Methods:

Participants, interventions, and outcomes

1	Study setting	#9	Description of study settings (eg, community	6-7
2			clinic, academic hospital) and list of countries	
3			where data will be collected. Reference to where	
4			list of study sites can be obtained	
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11	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If	7
12			applicable, eligibility criteria for study centres and	
13			individuals who will perform the interventions (eg,	
14			surgeons, psychotherapists)	
15				
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21	Interventions:	#11a	Interventions for each group with sufficient detail	8
22			to allow replication, including how and when they	
23	description		will be administered	
24				
25				
26				
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28				
29	Interventions:	#11b	Criteria for discontinuing or modifying allocated	NO DRUG
30			interventions for a given trial participant (eg, drug	INTERVENTION
31	modifications		dose change in response to harms, participant	
32			request, or improving / worsening disease)	
33				
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39	Interventions:	#11c	Strategies to improve adherence to intervention	NO DRUG
40			protocols, and any procedures for monitoring	INTERVENTION
41	adherence		adherence (eg, drug tablet return; laboratory	
42			tests)	
43				
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49	Interventions:	#11d	Relevant concomitant care and interventions that	NA
50			are permitted or prohibited during the trial	
51	concomitant care			
52				
53				
54	Outcomes	#12	Primary, secondary, and other outcomes,	10 – TABLE 1
55			including the specific measurement variable (eg,	
56				
57				
58				
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1 systolic blood pressure), analysis metric (eg,
 2 change from baseline, final value, time to event),
 3 method of aggregation (eg, median, proportion),
 4 and time point for each outcome. Explanation of
 5 the clinical relevance of chosen efficacy and harm
 6 outcomes is strongly recommended

15	Participant timeline	#13	Time schedule of enrolment, interventions 16 (including any run-ins and washouts), 17 assessments, and visits for participants. A 18 schematic diagram is highly recommended (see 19 Figure)	7 – FIGURE 2
27	Sample size	#14	Estimated number of participants needed to 28 achieve study objectives and how it was 29 determined, including clinical and statistical 30 assumptions supporting any sample size 31 calculations	7-8
39	Recruitment	#15	Strategies for achieving adequate participant 40 enrolment to reach target sample size	7-8
45	Methods:			NO
47	Assignment of			CONTROLLED
49	interventions (for			TRIAL
51	controlled trials)			

1	Allocation:	#16a	Method of generating the allocation sequence	NA
2				
3	sequence		(eg, computer-generated random numbers), and	
4				
5	generation		list of any factors for stratification. To reduce	
6				
7				
8			predictability of a random sequence, details of	
9				
10			any planned restriction (eg, blocking) should be	
11				
12			provided in a separate document that is	
13				
14			unavailable to those who enrol participants or	
15				
16			assign interventions	
17				
18				
19				
20	Allocation	#16b	Mechanism of implementing the allocation	NA
21				
22	concealment		sequence (eg, central telephone; sequentially	
23				
24	mechanism		numbered, opaque, sealed envelopes),	
25				
26			describing any steps to conceal the sequence	
27				
28			until interventions are assigned	
29				
30				
31				
32	Allocation:	#16c	Who will generate the allocation sequence, who	NA
33				
34	implementation		will enrol participants, and who will assign	
35				
36			participants to interventions	
37				
38				
39				
40	Blinding (masking)	#17a	Who will be blinded after assignment to	NA
41				
42			interventions (eg, trial participants, care	
43				
44			providers, outcome assessors, data analysts),	
45				
46			and how	
47				
48				
49				
50	Blinding (masking):	#17b	If blinded, circumstances under which unblinding	NA
51				
52	emergency		is permissible, and procedure for revealing a	
53				
54	unblinding		participant's allocated intervention during the trial	
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1 **Methods: Data**

2
3 **collection,**

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5 **management, and**

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7 **analysis**

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11 Data collection plan [#18a](#) Plans for assessment and collection of outcome, 10

12
13 baseline, and other trial data, including any
14
15 related processes to promote data quality (eg,
16
17 duplicate measurements, training of assessors)
18
19 and a description of study instruments (eg,
20
21 questionnaires, laboratory tests) along with their
22
23 reliability and validity, if known. Reference to
24
25 where data collection forms can be found, if not in
26
27 the protocol
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32 Data collection plan: [#18b](#) Plans to promote participant retention and 9

33
34 retention complete follow-up, including list of any outcome
35
36 data to be collected for participants who
37
38 discontinue or deviate from intervention protocols
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42 Data management [#19](#) Plans for data entry, coding, security, and 10

43
44 storage, including any related processes to
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46 promote data quality (eg, double data entry;
47
48 range checks for data values). Reference to
49
50 where details of data management procedures
51
52 can be found, if not in the protocol
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1	Statistics: outcomes	#20a	Statistical methods for analysing primary and	10
2			secondary outcomes. Reference to where other	
3			details of the statistical analysis plan can be	
4			found, if not in the protocol	
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11	Statistics: additional	#20b	Methods for any additional analyses (eg,	10
12	analyses		subgroup and adjusted analyses)	
13				
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15				
16	Statistics: analysis	#20c	Definition of analysis population relating to	10
17	population and		protocol non-adherence (eg, as randomised	
18	missing data		analysis), and any statistical methods to handle	
19			missing data (eg, multiple imputation)	
20				
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26	Methods:			NA
27				
28	Monitoring			
29				
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31				
32	Data monitoring:	#21a	Composition of data monitoring committee	
33	formal committee		(DMC); summary of its role and reporting	
34			structure; statement of whether it is independent	
35			from the sponsor and competing interests; and	
36			reference to where further details about its	
37			charter can be found, if not in the protocol.	
38			Alternatively, an explanation of why a DMC is not	
39			needed	
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51	Data monitoring:	#21b	Description of any interim analyses and stopping	
52	interim analysis		guidelines, including who will have access to	
53			these interim results and make the final decision	
54			to terminate the trial	
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1	Harms	#22	Plans for collecting, assessing, reporting, and	
2			managing solicited and spontaneously reported	
3			adverse events and other unintended effects of	
4			trial interventions or trial conduct	
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11	Auditing	#23	Frequency and procedures for auditing trial	
12			conduct, if any, and whether the process will be	
13			independent from investigators and the sponsor	
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19	Ethics and			
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21	dissemination			
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24	Research ethics	#24	Plans for seeking research ethics committee /	11
25			institutional review board (REC / IRB) approval	
26	approval			
27				
28				
29	Protocol	#25	Plans for communicating important protocol	11
30			modifications (eg, changes to eligibility criteria,	
31	amendments		outcomes, analyses) to relevant parties (eg,	
32			investigators, REC / IRBs, trial participants, trial	
33			registries, journals, regulators)	
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42	Consent or assent	#26a	Who will obtain informed consent or assent from	13
43			potential trial participants or authorised	
44			surrogates, and how (see Item 32)	
45				
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49	Consent or assent:	#26b	Additional consent provisions for collection and	NA
50			use of participant data and biological specimens	
51	ancillary studies		in ancillary studies, if applicable	
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1	Confidentiality	#27	How personal information about potential and	11
2			enrolled participants will be collected, shared, and	
3			maintained in order to protect confidentiality	
4			before, during, and after the trial	
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11	Declaration of	#28	Financial and other competing interests for	12
12	interests		principal investigators for the overall trial and	
13			each study site	
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19	Data access	#29	Statement of who will have access to the final trial	11
20			dataset, and disclosure of contractual	
21			agreements that limit such access for	
22			investigators	
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29	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care,	NA
30	trial care		and for compensation to those who suffer harm	
31			from trial participation	
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36	Dissemination	#31a	Plans for investigators and sponsor to	11
37	policy: trial results		communicate trial results to participants,	
38			healthcare professionals, the public, and other	
39			relevant groups (eg, via publication, reporting in	
40			results databases, or other data sharing	
41			arrangements), including any publication	
42			restrictions	
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53	Dissemination	#31b	Authorship eligibility guidelines and any intended	NA
54	policy: authorship		use of professional writers	
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1 Dissemination [#31c](#) Plans, if any, for granting public access to the full NA
 2
 3 policy: reproducible protocol, participant-level dataset, and statistical
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 5 research code
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 7

8 Appendices

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 11
 12 Informed consent [#32](#) Model consent form and other related NA
 13
 14 materials documentation given to participants and
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 16 authorised surrogates
 17
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 20 Biological [#33](#) Plans for collection, laboratory evaluation, and NA
 21
 22 specimens storage of biological specimens for genetic or
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 24 molecular analysis in the current trial and for
 25
 26 future use in ancillary studies, if applicable
 27
 28

29
 30 None The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative
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