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Effectiveness and cost-effectiveness of a Lifestyle Modification Program in the prevention and treatment of subclinical, mild and moderate depression in primary care. A randomized clinical trial protocol

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Abstract

Introduction:

Major depression is a highly prevalent pathology that is currently the second most common cause of disease-induced disability in our society. The onset and continuation of depression may be related to a wide variety of biological and psychosocial factors, many of which are linked to different lifestyle aspects. Therefore, health systems must design and implement health promotion and lifestyle modification programs, taking into account personal factors and facilitators. The main objective of this work is to analyze the utility and cost-effectiveness of an adjunctive treatment program for subclinical, mild or moderate depression in Primary Care patients, based on healthier lifestyle recommendations. Secondary objectives include the analysis of the effectiveness of the intervention in comorbid chronic pathology and the measurement of the influence of personal factors on lifestyle modification.

Methods and analysis:

A randomized, multicenter pragmatic clinical trial with 3 parallel groups consisting of primary healthcare patients suffering from subclinical, mild or moderate depression. The following

interventions will be used: 1. Usual antidepressant treatment with psychological advice and/or psychotropic drugs prescribed by the General Practitioner (treatment-as-usual, TAU). 2. TAU + Lifestyle Modification Program (LMP). A program to be imparted in 6 weekly 90-minute group sessions, intended to improve the following aspects: behavioral activation + daily physical activity + adherence to the Mediterranean diet pattern + sleep hygiene + careful exposure to sunlight. 3. TAU + LMP + ICTs: healthy lifestyle recommendations (TAU+LMP intervention) + monitoring using ICTs (a wearable smartwatch). The primary outcome will be the depressive symptomatology and the secondary outcomes will be the quality of life, the use of health and social resources, personal variables related to program adherence (patient activation in their own health, self-efficacy, sense of coherence, health literacy and procrastination) and chronic comorbid pathology. Data will be collected before and after the intervention, with 6- and 12-month follow-ups.

Ethics and dissemination: This study has been approved by the Research Ethics Committee of Aragón (CEICA) (Approval Number: C.P. - C.I. PI18/286) and the Research Ethics Committee of the Balearic Islands (IB3950/19 PI)**.** Data distribution will be anonymous. Results will be disseminated via conferences and papers published in peer-reviewed, open-access journals.

Trial registration number: ClinicalTrials.gov Identifier: NCT03951350

Strengths and limitations of this study:

- The intervention has the potential to be highly scalable and sustainable for the Spanish National Health Service.
- Increased motivation, upon introducing self-registers for everyone and a group that will be monitored using wearable smartwatches.
- Most healthcare professionals can implement the intervention groups.
- Some individuals may refuse to participate in group intervention. Difficulty of the entire group attending a session set on one specific date and time.

Keywords: Depression, Lifestyle modifications, Diet, Exercise, Sunlight exposure, Sleep patterns

Introduction:

Depression is considered to be the principle cause of disability worldwide, and it contributes to the overall global burden of morbidity and mortality. By 2030, it is expected to be the main contributor to the burden of morbidity (1–3). Approximately 25-35% of all primary care patients suffer from psychiatric disorders, and over 80% of these patients suffer from depression or anxiety disorders (4,5). In Spanish primary healthcare centers (PHC centers) the prevalence of depression ranges from 9.6% to 20.2% (6,7). Furthermore, depression generates great disability and high economic and social costs (8).

The prevalence of depression in Spain is 13% over one's lifetime and 4% per year (13).Indeed, comorbidity with other chronic conditions is also high (64.9% to 71.0%) (diabetes, hypertension, cardiovascular diseases and cancer, among others) (9–11) as well as with other psychiatric diseases such as anxiety disorders (40% to 66%) (12).

Despite the negative impact of depression on people's lives and the existence of numerous treatment interventions (14), these often are not appropriately used in PHC services (6),

mainly due to physician time or resource limitations (7). Thus, pharmacological (15) treatment is usually recommended, even though research has shown that in subclinical, mild or moderate depression, non-pharmacological interventions are recommended (15,16).

Since options and outcomes for the care of individuals suffering from depression and their access to treatment remains limited (17), it is important to promote cost-effective treatment options. The onset and continuation of depression has been linked to numerous biological and psychosocial factors, many of which are related to distinct lifestyle aspects (18–21). Therefore, many of the strategies promoting a healthier lifestyle could have antidepressant utility (20,22–24). In addition to multimodal studies, others have focused on one aspect of lifestyle modification: daily physical activity (25), adherence to the Mediterranean diet (26,27), sleep hygiene practices (28,29) and careful exposure to sunlight (30,31).

The present study will be framed around the theory of salutogenesis (32), which establishes that an individual's ability to modify our lifestyle is influenced by Psychosocial Generalized Resistance Resources, which consist of personal, interpersonal or contextual resources (money, knowledge, experience, self-esteem, healthy habits, commitment, social support, cultural capital, intelligence, traditions and vision of life) and the Sense of Coherence (way of making sense of the world, which is a major factor in determining how well an individual manages stress and stays healthy).

Moreover, previous studies show that is quite important the use of facilitators (simplicity of guidelines, tailoring through motivational interviewing, prolonged and intense monitoring throughout the different stages of the disorder, and the provision of adequate feedback and social support) (23) to facilitate adherence to lifestyle modification programs. For example, enhanced motivation can be achieved through the use of Information and Communication Technologies (ICTs) and with the social support resulting from intervention group participation (33). Personal factors and facilitators must be taken into account in lifestyle modification interventions, since they may determine the success of health promotion programs.

The main objective of this protocol is to analyze the effectiveness and cost-utility of the healthier lifestyle recommendations as adjunctive treatment for subclinical, mild or moderate depression in PHC patients. The secondary objectives are to analyze the effectiveness and cost-utility of the intervention in comorbid chronic pathology and to measure how personal factors relate to lifestyle modification.

Methods and analysis:

Study design

Randomized multicenter pragmatic clinical trial in 3 parallel groups.

Setting and study sample

We will recruit patients having subclinical, mild or moderate depression (scoring ≥ 10 and ≤ 30 points on the Beck II Self-Applied Depression Inventory (BDI II) (34)) from PHC centers of two Spanish areas (Zaragoza and Mallorca). Inclusion criteria: individuals over the age of 18, both sexes, having a duration of depression symptoms of at least 2 months, who perfectly understand written and spoken Spanish and who have provided their informed consent. Exclusion criteria will be: suffering from another disease that affects the central nervous system (organic brain pathology or having suffered a traumatic brain injury of any severity, dementia); having another psychiatric diagnosis or serious psychiatric illness (substance dependence or abuse, history of schizophrenia or other psychotic disorders, eating disorders)

with the exception of anxious pathology or personality disorders (collected through a medical history and from the Mini-International Neuropsychiatric Interview (MINI) (35)); presence of a serious or uncontrolled medical, infectious or degenerative illness that may interfere with the affective symptoms; the presence of delirium or hallucinations, risk of suicide, pregnancy or lactation; patients who have participated in another clinical trial over the past 6 months or who are currently in psychotherapy; or those who practice mindfulness, yoga, meditation or similar practices over the past 6 months, engaging in formal practice at least once a week; and the presence of any medical, psychological or social problem that could seriously interfere with the patient's participation in the study.

Sample size

Scientific evidence suggests that a 17% reduction in the BDI-II (34) is considered clinically relevant (36). In a previous study conducted by our team with psychiatric outpatients, we found that the average BDI score at the beginning of the study was 24.5 points (SD 9.8) (22), so we consider that a reduction of at least 4.8 points would have clinical significance and would benefit the patient. Accepting an α risk of 0.05 and a β risk of 0.20 in a bilateral contrast, 62 subjects will be required for each group. A maximum follow-up loss rate of 20% has been estimated. The total sample required is 186 subjects. A formula based on the Snedecor's *F* distribution (37) has been used. Therefore, 93 subjects will be recruited from PHC centers in Zaragoza and an additional 93 subjects from PHC centers in Mallorca. It is estimated that approximately 50% of these patients will present some physical or mental comorbidity (11).

Recruitment

General practitioners (GPs) from the PHC centers of Zaragoza and Mallorca will be invited to refer patients who are suspected of suffering from depression. GPs will explain the characteristics of the study to their patients and if they agree to participate, they will be asked to provide a phone number to be contacted by a team researcher during the next week. The researcher will phone patients, establish an appointment, in which he will explain them the study, providing them the Patient Information Sheet and signed the Informed Consent. To ensure that they fulfill the inclusion criteria, the researcher will administrate the BDI-II (34) and the MINI (35). If participants meet the criteria, the researcher will administer the baseline questionnaires at the same appointment. Recruitment and baseline assessments will be carried out until the final sample size has been achieved. All information collected will be treated in accordance with the provisions of current legislation on the protection of personal data.

Randomization and allocation

Once baseline data has been collected, the participants will be randomized. The randomization will be carried out using blocks of patients from the Zaragoza and Mallorca PHC centers. Since three PHC centers in Zaragoza and three PHC centers in Mallorca will participate, the 31 participants to be recruited from each PHC centers will be randomized into each of the three arms (Figure 1). The outcome assessor and data analyst will be blinded.

[Figure 1 about here]

Intervention development and evaluation

Patients allocated in the first arm (control group) will follow the usual treatment provided by their GP (treatment-as-usual, TAU).

Patients allocated in the second arm (1st intervention group) will follow the TAU and the Lifestyle Modification Program (LMP). This program will consist of 6 weekly group sessions (lasting 90 minutes each) led by an experienced psychologist and complemented by PowerPoint presentations.

Patients allocated in the third arm (2nd intervention group) will follow TAU and LMP and will be monitored using a wearable smart wristwatch that will track their daily sleep patterns and physical activity (LMP+ICTs).

The group sessions will consist of the following content:

1) Presentation of the project and psychoeducation on depression: Presentation of the project and a review of the study objectives. Definition, symptoms, causes, consequences of depression and, also, how lifestyles and social environment changes influence the symptomatology of depression.

2) Behavior activation: a psychologist will provide information on the importance of establishing, maintaining and monitoring activities. For the LMP+ICTs group, they will also learn how to use the smart wristwatch, ensuring all participants are able to use it.

3) Sleep hygiene habits and careful exposure to sunlight: recommendations on healthy sleep habits, factors influencing sleep quality and possible solutions. The benefits of careful exposure to sunlight and recommendations of when to do so and for how long. Responding to questions regarding the previous session.

4) Physical activity: the benefits of engaging in regular physical activity. Benefits of regular physical activity. Personalized recommendations about what physical exercise may be practiced, how and when to do so. Responding to questions regarding the previous session.

5) Adherence to the Mediterranean diet: explanations about the Mediterranean diet, food groups and their characteristics, as well as the most beneficial foods for physical and mental health, how to cook it and food-related habits. Responding to questions regarding the previous session

6) Summary of previous sessions with practical final suggestions: personalized experiences and doubts of the participants throughout the course. Recommendations for daily healthy lifestyle practices for the future and farewell.

At the end of each session, the participants will receive a paper with self-registration tables. They will complete the tables with the information on their daily routines regarding the modification of lifestyles on which they have been instructed. They will be asked about when they wake up and when they go to bed, the duration of their sleep, the time spent exposed to sunlight, the diet pattern, the physical activity and sports practiced, the social support, and the subjective perception of satisfaction after these activities. A qualitative study associated with this study will be included to analyze the participants' difficulties in following the intervention.

Outcomes and measures

We will collect patient data using the questionnaires administered in baseline, immediately after the intervention and at six and 12-month follow-up.

Primary outcome

Severity of depression

The primary outcome will be measured using the BDI-II (34). This is a self-report inventory for measuring the severity of depression, consisting of 21 multiple-choice questions with each answer being scored on a scale ranged from 0 to 3. It was translated and validated into Spanish with a reliability of .89 (38). The standardized cutoffs are: 0–13: minimal depression; 14–19: mild depression; 20–28: moderate depression; 29–63: severe depression.

Secondary outcomes

Health-related quality of life

Health-related quality of life will be measured using the European Quality of Life-5 Dimensions questionnaire (EQ-5D) (39,40). EQ-5D scores will be used to calculate the quality-adjusted life year (QALY) during the monitoring period by adjusting the length of time affected by the health result by the utility value. It contains five health dimensions (mobility, selfcare, usual activities, pain/discomfort and anxiety/depression) and each of these has three levels (no problems, slight problems or moderate and severe problems). The EQ records the patient's self-rated health on a vertical visual analogue scale of 20 centimeters (VAS), where the endpoints are labeled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgment. Patients mark the point on the vertical line that best reflects their assessment of their current global health status (41). Cronbach's Alpha coefficient has been calculated in research with disease-specific populations. We highlight Seoane et al. (42), in which the overall alpha value was .788. The only study with a general population, it provides an overall mean estimate of the Minimum Important Difference (MID) for the EQ-5D, which is .074 (43).

Comorbidity with chronic diseases

Comorbidity with chronic diseases will be determined according to the International Classification of Diseases (ICD-10) (44): diabetes (glucose concentration (mg/dl), glycated hemoglobin (%), creatinine), arterial hypertension and diseases of lipid metabolism. In patients with chronic heart disease, coagulation variables will be added. They will be collected from the last blood test or control measurements of the clinical history, taken by their GP or nurse (assuming they were taken over the past 3 months). Otherwise, their GP will be asked for a blood control test. It is estimated that approximately 50% of these patients will present some comorbidity (11). Anthropometric measures will also be collected (weight, size and perimeter of the waist).

Social support

It will be measured by the Medical Outcomes Study Social Support Survey (MOS-SS) (45). It is a self-report instrument consisting of four subscales (emotional/informational, tangible, affectionate, and positive social interaction) and an overall functional social support index. It has a good reliability (Cronbach's alpha ≥ .91) and is quite stable over time. It has 19 items, a five-point Likert scale. Higher scores indicate more support. We will use the Spanish validated version (46).

Use of health services

It will be measured using the Client Service Receipt Inventory (CSRI) (47). This data may be used for a wide range of applications, including estimates of the costs of service receipt. To collect information on the entire range of services and supports used by study participants. It retrospectively collects data on the use of services over the past 6 months (e.g., rates of use of individual services, mean intensity of service use, rates of accommodation use over time). We will use the validated Spanish version (48).

Assessment of lifestyle

Physical activity

Physical activity will be measured using the International Physical Activity Questionnaire-Short Form (IPAQ-SF) (49). It assesses the levels of habitual physical activity over the last 7 days. It has 7 items and records the activity of four intensity levels: vigorous-intensity activity, moderate-intensity activity (walking and sitting). We will use the validated Spanish version (50). IPAQ-SF has acceptable validity for the measurement of total and vigorous physical activity and poor validity for moderate activity and good reliability (51).

Adherence to the Mediterranean Diet

Measured using the 14-item Mediterranean Diet Adherence Screener (MEDAS), developed within the PREDIMED study group (52). It includes items on food consumption and intake habits: the use of olive oil as the main source of cooking fat, preference for white meat over red meat, servings of vegetables, portions of fruit, red meat or sausages, servings of animal fat, sugar-sweetened beverages, red wine, legumes, fish, commercial pastries and dressing food with a traditional sauce made of tomatoes, garlic, onion, or leeks sautéed in olive oil. The total score ranges from 0 to 14, with a higher score indicating a better accordance with the Mediterranean diet (53).

Quality and patterns of sleep

Measured using the Pittsburgh Sleep Quality Index (PSQI) (54). To measure sleep quality and patterns in adults. It differentiates between “poor” and “good” sleep by measuring seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the past month. It consists of 19 self-applied questions and 5 questions that request the evaluation of the patient's bedmate or roommate (these are not scored). Answers range from 0 (no difficulty) to 3 (severe difficulty). The overall score ranges from 0 to 21 points. In its Spanish version, the Cronbach’s alpha coefficient is .81, sensitivity of 88.63% and specificity of 74.99%. We will use the validated Spanish version (55).

Personal factors on health behavior

We will assess: 1) self-efficacy (56); 2) activation (57); 3) sense of coherence (58); 4) health literacy (59); and , 5) procrastination (60).

Self-Efficacy

Measured using by the Self-Efficacy Scale (56). To measure General Self-Efficacy subscale (17 items including individuals' beliefs in their ability to perform well in a variety of situations) and Social Self-Efficacy subscale (6 items). It contains 23 items that are rated on a 14-point scale (ranging from strongly agree to strongly disagree). Higher scores indicate higher levels of self-efficacy. It has a Cronbach coefficient alpha of .86 for General Self-efficacy subscale and .71 for

the Social Self-efficacy subscale. The unpublished Spanish version was translated by Godoy in 1990 (61).

Patient activation in their own health

Measured using the Patient Activation Questionnaire (PAM) with regard to the management of their health. It evaluates the patient's perceived knowledge, skills, and confidence to engage in self-management activities. It has 13 items, a Likert scale from 1 (strongly disagree) to 4 (strongly agree). The resulting score (between 0 and 100) places the individual at one of four levels of activation, each of which reveals insight into a range of health-related characteristics, including behaviors and outcomes. Higher scores indicate higher levels of activation (57). This scale is only validated in Spanish for chronic patients. It had an item separation index for the parameters of 6.64 and a reliability of .98 (62).

Sense of coherence

Measured using the Sense of Coherence (SOC) questionnaire by Antonovsky (58). It values the personal disposition towards the assessment of vital experiences. It measures the sense of coherence, comprehensibility, manageability and meaningfulness. It has 13 items scoring between 13 and 91 points. It has consistency rates of between .84 and .93. Higher scores (after reversal of the inverted items) indicate a higher sense of coherence. We will use the validated Spanish version (63).

Health Literacy

Measured using the Health Literacy Europe Questionnaire (HLS-EUQ16) (59). It can indicate that the probability of functional literacy in limited health is high, a possibility of functional literacy in limited health, and a functional health literacy in adequate health. It contains 16 items. Higher scores indicate better health literacy. It presents a high consistency (Cronbach's alpha of .982) in the Spanish validation (64).

Procrastination

Measured using the Irrational Procrastination Scale (IPS) (65). To measure general procrastination (dysfunctional delay). It has 9 items, rated on a 5-point Likert scale, with higher scores (after reversal of the three procrastination-inconsistent items) indicating a higher level of procrastination. Its Cronbach's alpha value is 0.90. We will use the validated Spanish version (60).

Data analysis plan

Clinical effectiveness analysis

The analysis will follow the recommendations established by the CONSORT statement (66) in order to compare the two groups using an intention-to-treat analysis (WOCF method). Initially a descriptive comparison (proportions, means or medians) will be carried out between groups for prognostic variables in order to establish their baseline comparability after randomization. To confirm the main hypothesis, an analysis of the variance of repeated measures will be conducted, including all evaluations over time. For this purpose, the main variable, BDI II score, will be used as a continuous variable. The models will include adjustments for the baseline value of the BDI II and for any other variable that would have shown differences in the baseline measurement. Possible Group per Time interactions will be examined using Mixed Factor Anova. In addition, other linear regression models will be used to compare the differences in

BDI II scores between the groups for each of the time assessments compared to the baseline. Similar analyses will be carried out using the secondary variables (quality of life, effectiveness in chronic diseases, health perception). Comparisons will also be made between the LMP and LMP + ICTs groups regarding adherence to lifestyle modification requirements.

Cost-effectiveness analysis

When the cost-effectiveness of two or more therapeutic options is analyzed, this is carried out by calculating the relationship between the cost of each intervention and its consequences (expressed in the form of QALYs). This relative value is called the incremental cost-effectiveness index (ICEI), and expresses the relationship between the costs and the effects of one option as compared to another. The treatment costs during the 6 months will be modeled using a multivariate gamma regression with logarithmic transformation. The QALYs obtained in the 6 months after the onset of the program will be measured by the area under the curve using the following equation: (6/12 x d0-6) x 0.5. With d0-6 being the effect of increasing change in EQ-5D that the treatment produces during the 6 months. The treatment effect will be estimated using ordinary multivariate regression of least squares, adjusting for baseline differences between groups. The covariates included in the model will be age, gender, years of education, employment and marital status. For the management of uncertainty in the ICEI sample distribution, the non-parametric bootstrapping method will be used with five thousand replications in each comparison. Total costs will be calculated by adding direct and indirect costs. Direct costs will be calculated by adding the costs derived from the medication and the use of health services (consultations to PHC, specialized and emergency, as well as hospital admissions). The medication costs will be calculated by determining the price per milligram during the study period according to the Vademecum of the last year of study, including VAT. The total cost of drug treatment will be calculated by multiplying the price per milligram by the daily dose in milligrams and the number of days the treatment is received. Costs derived from the use of health services will be calculated considering the data from the Oblikue database (67). Indirect costs will be calculated based on the days of leave and multiplying them by the Spanish minimum wage during the study period, 2019-2020.

Analysis of the correlation and the weight of personal factors in the completion of the LMP: for this, a descriptive analysis of these variables (proportions, means or medians) will be used first and then an analysis will be carried out of correlations between personal factors and compliance variables, primary and secondary outcome variable (using the appropriate statistic based on the type of variable and normal distribution of the sample); as well as a linear or logistic regression, depending on the variables.

Execution dates

Initial recruitment of patients: April 2020.

Finalization of patient recruitment: May 2020.

Finalization of patient monitoring period: June 2021.

Publication of results: July 2021.

Partial Patient and Public Involvement: PPI representatives worked with us to refine the research question; however, it was difficult to involve patients in other areas of the study design due to data protection restrictions and the very technical methods required to do a

data linkage analysis. PPI representatives will write a plain language summary and design a leaflet for dissemination to their peers and distributing to patient groups.

Ethics approval: Ethics approval was granted by the Research Ethics Committee of Aragón (CEICA, PI18/286) and the Research Ethics Committee of the Balearic Islands (IB3950/19 PI). The study has been developed in accordance with the Helsinki Declaration. All of the subjects will sign an informed consent form, their data will be anonymized and will only be used for the purposes of the study. Participants and healthcare professionals will be informed about the results. Patients of the TAU group will be invited to participate in the LMP at the end of the study. The Ethics Committee will be notified of any protocol modifications.

Authors' contributions: BOB, MJSR and MGT led the design and developed the study and had the original idea. RMB, MJSR, CN and BOB coordinated the fieldwork. AAL and CCV undertook the fieldwork. AAL, BOB, EG and SBS wrote the first draft of the article. The rest of the signing authors have read the manuscript critically, offering contributions and approving the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: None.

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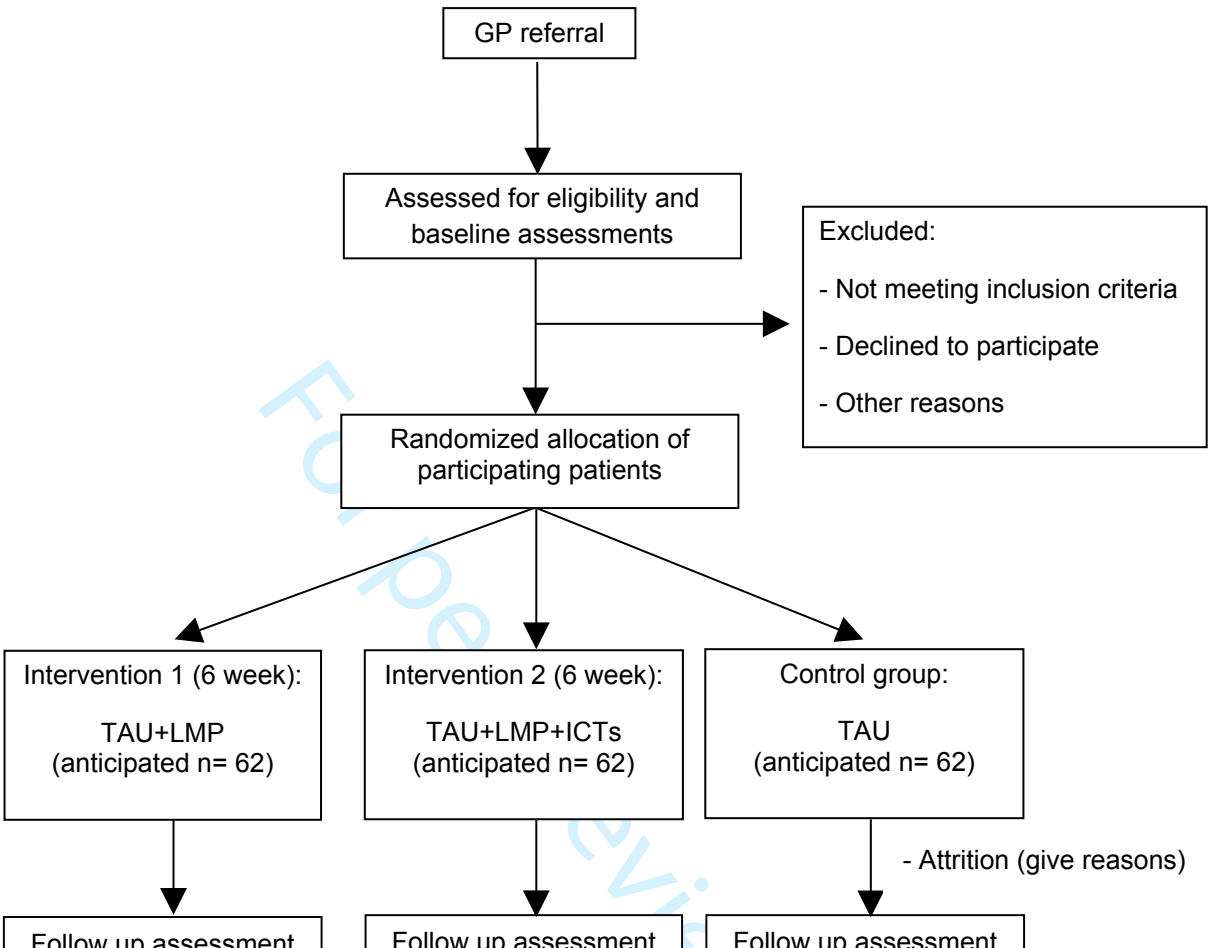
Figure 1: FLOWCHART: Flowchart of the study: randomization, sampling and monitoring of patients.



GP, General Practitioner; TAU, Treatment as Usual; LMP, Lifestyle Mediterranean Program; ICT, Information and Communication Technology; WOCF, Worst Observation Carried Forward

SLEEP DURATION AND SUNLIGHT

Day	Time to get up and go to bed	Sleep duration (hours)	Sunlight exposure (in minutes)
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

SLEEP DURATION AND SUNLIGHT

Day	Time to get up and go to bed	Sleep duration (hours)	Sunlight exposure (in minutes)
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

PHYSICAL ACTIVITY

Day	Activity	Sport	Duration (min)	Company	How do I feel next?
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

SLEEP DURATION AND SUNLIGHT

Day	Time to get up and go to bed	Sleep duration (hours)	Sunlight exposure (in minutes)
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

PHYSICAL ACTIVITY

Day	Activity	Sport	Duration (min)	Company	How do I feel next?
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

MEDITERRANEAN DIET

Day	Breakfast	Snack	Appetizer	Lunch	Snack	Dinner
Monday						
Tuesday						
Wednesday						
Thursday						
Friday						
Saturday						
Sunday						

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1-8
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	8
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page
	5b	Name and contact information for the trial sponsor	8, NA
	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	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA
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	1-2
	6b	Explanation for choice of comparators	2
Objectives	7	Specific objectives or hypotheses	2

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, noninferiority, exploratory)	2-4
Methods: Participants, interventions, and outcomes			
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	3-4
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)	3
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4
	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)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5
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)	5, 9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was	3

		determined, including clinical and statistical assumptions supporting any sample size calculations	
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	3
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	4
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	4
Methods: Data collection, management, and analysis			
Data collection methods	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	5-8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants	NA

		who discontinue or deviate from intervention protocols	
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	4
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8-9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8-9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8-9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility	9

		criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	4
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	9
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	4
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	9
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effectiveness and cost-effectiveness of a Lifestyle Modification Program in the prevention and treatment of subclinical, mild and moderate depression in primary care. A randomized clinical trial protocol.

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Effectiveness and cost-effectiveness of a Lifestyle Modification Program in the prevention and treatment of subclinical, mild and moderate depression in primary care. A randomized clinical trial protocol

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Abstract

Introduction:

Major depression is a highly prevalent pathology that is currently the second most common cause of disease-induced disability in our society. The onset and continuation of depression may be related to a wide variety of biological and psychosocial factors, many of which are linked to different lifestyle aspects. Therefore, health systems must design and implement health promotion and lifestyle modification programs, taking into account personal factors and facilitators. The main objective of this protocol is to analyze the clinical effectiveness, cost-effectiveness and cost-utility of a Lifestyle Modification Program and a Lifestyle Modification Program with ICTs as adjunctive treatment for depression in primary care patients. The secondary objectives are to analyze the clinical effectiveness in the subgroup that presents comorbidity and to analyze the correlation between personal factors on health behavior and lifestyle patterns.

Methods and analysis:

A randomized, multicenter pragmatic clinical trial with 3 parallel groups consisting of primary healthcare patients suffering from subclinical, mild or moderate depression. The following interventions will be used: 1. Usual antidepressant treatment with psychological advice and/or psychotropic drugs prescribed by the General Practitioner (treatment-as-usual, TAU). 2. TAU + Lifestyle Modification Program (LMP). A program to be imparted in 6 weekly 90-minute group sessions, intended to improve the following aspects: behavioral activation + daily physical activity + adherence to the Mediterranean diet pattern + sleep hygiene + careful exposure to sunlight. 3. TAU + LMP + ICTs: healthy lifestyle recommendations (TAU+LMP) + monitoring using ICTs (a wearable smartwatch). The primary outcome will be the depressive symptomatology and the secondary outcomes will be the quality of life, the use of health and social resources, personal factors on health behavior, social support, lifestyle patterns and chronic comorbid pathology. Data will be collected before and after the intervention, with 6- and 12-month follow-ups.

Ethics and dissemination: This study has been approved by the Research Ethics Committee of Aragón (CEICA) (Approval Number: C.P. - C.I. PI18/286) and the Research Ethics Committee of the Balearic Islands (IB3950/19 PI)**.** Data distribution will be anonymous. Results will be disseminated via conferences and papers published in peer-reviewed, open-access journals.

Trial registration number: ClinicalTrials.gov Identifier: NCT03951350

Strengths and limitations of this study:

- The intervention has the potential to be highly scalable and sustainable for the Spanish National Health Service.
- Increased motivation, upon introducing self-registers for everyone and a group that will be monitored using wearable smartwatches.
- Most healthcare professionals can implement the intervention groups.
- Some individuals may refuse to participate in group intervention or may withdraw from the study during the 12-month trial period.
- Difficulty of entire group's attendance to a session held on one specific date and time.

Keywords: Depression, Lifestyle modifications, Diet, Exercise, Sunlight exposure, Sleep patterns

Introduction:

Depression is considered to be the principle cause of disability worldwide, and it contributes to the overall global burden of morbidity and mortality. By 2030, it is expected to be the main contributor to the burden of morbidity (1–3). Approximately 25-35% of all primary care patients suffer from psychiatric disorders, and over 80% of these patients suffer from depression or anxiety disorders (4,5). In Spanish primary healthcare centers (PHCs) the prevalence of depression ranges from 9.6% to 20.2% (6,7). Furthermore, depression generates great disability and high economic and social costs (8).

The prevalence of depression in Spain is 13% over one's lifetime and 4% per year (13). Indeed, comorbidity with other chronic conditions is also high (64.9% to 71.0%) (diabetes, hypertension, cardiovascular diseases and cancer, among others) (10–12) as well as with other psychiatric diseases such as anxiety disorders (40% to 66%) (13).

Despite the negative impact of depression on people's lives and the existence of numerous treatment interventions (14), these often are not appropriately used in PHC services (6), mainly due to physician time or resource limitations (7). Thus, pharmacological (15) treatment is usually recommended, even though research has shown that in subclinical, mild or moderate depression, non-pharmacological interventions are recommended (15,16).

Since options and outcomes for the care of individuals suffering from depression and their access to treatment remains limited (17), it is important to promote cost-effective treatment options. The onset and continuation of depression has been linked to numerous biological and psychosocial factors, many of which are related to distinct lifestyle aspects (18–21). Therefore, many of the strategies promoting a healthier lifestyle could have antidepressant utility (20,22–24). In addition to multimodal studies, others have focused on one aspect of lifestyle modification: daily physical activity (25), adherence to the Mediterranean diet (26,27), sleep hygiene practices (28,29) and careful exposure to sunlight (30,31).

The present study will be framed around the theory of salutogenesis (32), which establishes that an individual's ability to modify our lifestyle is influenced by Psychosocial Generalized Resistance Resources, which consist of personal, interpersonal or contextual resources (money, knowledge, experience, self-esteem, healthy habits, commitment, social support, cultural capital, intelligence, traditions and vision of life) and the Sense of Coherence (way of making sense of the world, which is a major factor in determining how well an individual manages stress and stays healthy).

Moreover, previous studies show that is quite important the use of facilitators (simplicity of guidelines, tailoring through motivational interviewing, prolonged and intense monitoring throughout the different stages of the disorder, and the provision of adequate feedback and social support) (23) to facilitate adherence to lifestyle modification programs. For example, enhanced motivation can be achieved through the use of Information and Communication Technologies (ICTs) and with the social support resulting from intervention group participation (33). Personal factors and facilitators must be taken into account in lifestyle modification interventions, since they may determine the success of health promotion programs.

The main objective of this protocol is to analyze the clinical effectiveness, cost-effectiveness and cost-utility of a Lifestyle Modification Program and a Lifestyle Modification Program with ICTs as adjunctive treatment for depression in primary care patients. The secondary objectives are to

analyze the clinical effectiveness in the subgroup that presents comorbidity and to analyze the correlation between personal factors on health behavior and lifestyle patterns.

Methods and analysis:

Study design

Multicenter pragmatic randomized controlled trial in 3 parallel groups.

Setting and study sample

We will recruit patients having subclinical, mild or moderate depression (scoring ≥ 10 and ≤ 30 points on the Beck II Self-Applied Depression Inventory (BDI II) (34)) from PHCs of two Spanish areas (Zaragoza and Mallorca). Inclusion criteria: individuals over the age of 18, both sexes, having a duration of depression symptoms of at least 2 months, who understand written and spoken Spanish and who have provided their informed consent (supplementary file 1). Exclusion criteria will be: suffering from another disease that affects the brain (organic brain pathology or having suffered a traumatic brain injury of any severity, dementia); having another psychiatric diagnosis or serious psychiatric illness (substance dependence or abuse, history of schizophrenia or other psychotic disorders, eating disorders) with the exception of anxious pathology or personality disorders (collected through a medical history and from the Mini-International Neuropsychiatric Interview (MINI) (35)); presence of a serious or uncontrolled medical, infectious or degenerative illness that may interfere with the affective symptoms; the presence of delirium or hallucinations, risk of suicide, pregnancy or lactation; patients who have participated in another clinical trial over the past 6 months or who are currently in psychotherapy; or those who practice mindfulness, yoga, meditation or similar practices over the past 6 months, engaging in formal practice at least once a week; and the presence of any medical, psychological or social problem that could seriously interfere with the patient's participation in the study.

Sample size

Scientific evidence suggests that a 17% reduction in the BDI-II (34) is considered clinically relevant (36). In a previous study conducted by our team with psychiatric outpatients, we found that the average BDI score at the beginning of the study was 24.5 points (SD 9.8) (22), so we consider that a reduction of at least 4.8 points would have clinical significance and would benefit the patient. Accepting an α risk of 0.05 and a β risk of 0.20 in a bilateral contrast, 62 subjects will be required for each group. A maximum follow-up loss rate of 20% has been estimated. The total sample required is 186 subjects. A formula based on the Snedecor's *F* distribution (37) has been used (see supplementary file 2). Therefore, 93 subjects will be recruited from PHCs in Zaragoza and an additional 93 subjects from PHCs in Mallorca. It is estimated that approximately 50% of these patients will present some physical or mental comorbidity (12).

Recruitment

General practitioners (GPs) from the PHCs of Zaragoza and Mallorca will be invited to refer patients who are suspected of suffering from depression. Most representative PHCs in the area will be invited, based on size, urban or rural area and PHCs with a different socio-demographic profile will be selected. GPs will explain the characteristics of the study to their patients and if they agree to participate, they will be asked to provide a phone number to be contacted by a trained Research Assistant (RA) during the next week. The RA will phone patients, establish an appointment in their PHC, in which he will explain them the study, providing them the Patient Information Sheet and signed the Informed Consent. To ensure that they fulfill the inclusion criteria, the RA will administrate the BDI-II (34) and the MINI (35). If participants meet the criteria, the RA will administer the baseline questionnaires at the same appointment.

Recruitment and baseline assessments will be carried out until the final sample size has been achieved.

Randomization, allocation and masking of study groups

Once baseline data is collected, the participants will be randomized. An independent statistician will perform the individual randomization using a computer-generated random number sequence that employs blocked randomization. The randomization will be carried out using blocks of patients from the Zaragoza and Mallorca PHCs. Since three PHCs in Zaragoza and three PHCs in Mallorca will participate, the 31 participants to be recruited from each PHCs will be randomized, so that 62 patients are randomized into each of the three arms (Figure 1). Given the nature of the interventions, participants will not be blind to their allocation. An RA will phone them to explain their assigned intervention and where they should go and when. The RA will request that participants not inform other researchers of their allocation.

[Figure 1 about here]

Data collection and monitoring

One RA will collect the data and another will perform entry and coding of the identified data. All RA managing the data will be blinded to participant allocation, as well as the RA conducting the outcome assessments and data analysis. All information collected will be treated in accordance with the provisions of current legislation on personal data protection.

The study will not have a formal data monitoring committee since adverse intervention events have not been reported. Any serious unexpected adverse events or outcomes will be discussed by the trial management committee (identical to the authors of this protocol). There are no plans to discontinue or modify interventions, or to improve adherence or promote participant retention. The trial management committee will monitor recruitment, treatment and attrition rates and any concerns related to the study. Reasons for dropping out will be also registered. Concomitant care is permitted and registered as long as it is not one of the exclusion criteria. Group-specific processes will be taken into account and will be evaluated and informed, in accordance with recommendations of the "Mechanisms of Action in Group-based Interventions"(MAGI) framework (38).

Intervention development and evaluation

Patients allocated in the first arm (control group) will follow the usual treatment provided by their GP (treatment-as-usual, TAU).

Patients allocated in the second arm (1st intervention group) will follow the TAU and the Lifestyle Modification Program (LMP). This program will consist of 6 weekly group sessions (lasting 90 minutes each) led by an experienced psychologist and complemented by PowerPoint presentations.

Patients allocated in the third arm (2nd intervention group) will follow TAU and LMP and will be monitored using a wearable smart wristwatch that will track their daily sleep patterns and physical activity (LMP+ICTs).

The group sessions will consist of the following content:

1) Presentation of the project and psychoeducation on depression: Presentation of the project and a review of the study objectives. Definition, symptoms, causes,

consequences of depression and, also, how lifestyles and social environment changes influence the symptomatology of depression.

2) Behavior activation: a psychologist will provide information on the importance of establishing, maintaining and monitoring activities. For the LMP+ICTs group, they will also learn how to use the smart wristwatch, ensuring all participants are able to use it.

3) Sleep hygiene habits and careful exposure to sunlight: recommendations on healthy sleep habits, factors influencing sleep quality and possible solutions. The benefits of careful exposure to sunlight and recommendations of when to do so and for how long. Responding to questions regarding the previous session.

4) Physical activity: the benefits of engaging in regular physical activity. Personalized recommendations about what physical exercise may be practiced, how and when to do so. Responding to questions regarding the previous session.

5) Adherence to the Mediterranean diet: explanations about the Mediterranean diet, food groups and their characteristics, as well as the most beneficial foods for physical and mental health, how to cook it and food-related habits. Responding to questions regarding the previous session

6) Summary of previous sessions with practical final suggestions: personalized experiences and doubts of the participants throughout the course. Recommendations for daily healthy lifestyle practices for the future and farewell.

At the end of each session, the participants will receive a paper with self-registration tables (supplementary file 3). They will complete the tables with the information on their daily routines regarding the modification of lifestyles on which they have been instructed. They will be asked about when they wake up and when they go to bed, the duration of their sleep, the time spent exposed to sunlight, the diet pattern, the physical activity and sports practiced, the social support, and the subjective perception of satisfaction after these activities. A qualitative study associated with this study will be included to analyze the participants' difficulties in following the intervention.

Outcomes and measures

We will collect patient data using the questionnaires administered in baseline, immediately after the intervention (in a period of 2 to 7 days after the last intervention session) and at 6 and 12-month follow-up after the last intervention session (with a margin of ± two weeks) (see Table 1). A blinded RA will phone each patient of the three arms and set up an appointment in their PHC for questionnaire administration. Study outcomes and measures are summarized in Table 1.

Table 1
Study variables

Instrument	Assessment area	Measures
BDI-II (34,39)	Severity of depression	Baseline and follow-up sessions[a]
MINI (35)	Psychiatric diagnosis	Baseline
Gender, age, marital status, education,	Sociodemographic	Baseline and follow-up sessions[a]

occupation, economical level		
Glucose concentration (mg/dL), glycated hemoglobin (%), creatinine, arterial pressure (mmHg) and cholesterol (mg/dL)	Comorbidity with chronic diseases	Baseline and 6 and 12-month follow-up.
EQ-5D (40,41)	Health-related quality of life	Baseline and follow-up sessions[a]
MOS-SS (42,43)	Social support	Baseline and follow-up sessions[a]
CSRI (44,45)	Health and social services use	Baseline and follow-up sessions[a]
IPAQ-SF (46,47)	Physical activity	Baseline and follow-up sessions[a]
MEDAS (48,49)	Adherence to the Mediterranean Diet	Baseline and follow-up sessions[a]
PSQI (50,51)	Quality and patterns of sleep	Baseline and follow-up sessions[a]
Self-Efficacy Scale (52,53)	Self-Efficacy	Baseline and follow-up sessions[a]
PAM (54,55)	Patient activation in their own health	Baseline and follow-up sessions[a]
SOC-13 (56,57)	Sense of coherence	Baseline and follow-up sessions[a]
HLS-EUQ16 (58,59)	Health Literacy	Baseline and follow-up sessions[a]
IPS (60,61)	Procrastination	Baseline and follow-up sessions[a]

BDI-II, Beck II Self-Applied Depression Inventory; MINI, Mini-International Neuropsychiatric Interview; EQ-5D, the European Quality of Life-5 Dimensions questionnaire; MOS-SS, Medical Outcomes Study Social Support Survey; CSRI, Client Service Receipt Inventory; IPAQ-SF, Physical Activity Questionnaire-Short Form; MEDAS, 14-item Mediterranean Diet Adherence Screener; PSQI, Pittsburgh Sleep Quality Index; PAM, Patient Activation Questionnaire; SOC-13, Sense of Coherence questionnaire; HLS-EUQ16, Health Literacy Europe Questionnaire; IPS, Irrational Procrastination Scale.

[a]Follow-up sessions: post-intervention (in a period of 2 to 7 days after the last session of the intervention), 6 and 12-month follow-up (6 and 12-month after the last session of the intervention [± two weeks]).

Sociodemographic data

We will collect information on gender, age, marital status, education, occupation, economical level. These data will be collected through an ad hoc questionnaire.

Primary outcome

Severity of depression

The primary outcome will be measured using the BDI-II (34). This is a self-report inventory for measuring the severity of depression, consisting of 21 multiple-choice questions with each answer being scored on a scale ranged from 0 to 3. It was translated and validated into Spanish with a reliability of .89 (39). The standardized cutoffs are: 0–13: minimal depression; 14–19: mild depression; 20–28: moderate depression; 29–63: severe depression.

Secondary outcomes

Health-related quality of life

Health-related quality of life will be measured using the European Quality of Life-5 Dimensions questionnaire (EQ-5D) (40,62). EQ-5D scores will be used to calculate the quality-adjusted life year (QALY) during the monitoring period by adjusting the length of time affected by the health result by the utility value. It contains five health dimensions (mobility, selfcare, usual activities, pain/discomfort and anxiety/depression) and each of these has three levels (no problems, slight problems or moderate and severe problems). The EQ records the patient's self-rated health on a vertical visual analogue scale of 20 centimeters (VAS), where the endpoints are labeled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgment. Patients mark the point on the vertical line that best reflects their assessment of their current global health status (41). Cronbach's Alpha coefficient has been calculated in research with disease-specific populations. We highlight Seoane et al. (63), in which the overall alpha value was .788. The only study with a general population, it provides an overall mean estimate of the Minimum Important Difference (MID) for the EQ-5D, which is .074 (64).

Comorbidity with chronic diseases

Comorbidity with chronic diseases will be determined according to the International Classification of Diseases (ICD-10) (65): diabetes (glucose concentration (mg/dl), glycated hemoglobin (%), creatinine), arterial hypertension and diseases of lipid metabolism. In patients with chronic heart disease, coagulation variables will be added. They will be collected from the last blood test or control measurements of the clinical history, taken by their GP or nurse (assuming they were taken over the past 3 months). Otherwise, their GP will be asked for a blood control test. It is estimated that approximately 50% of these patients will present some comorbidity (12). Anthropometric measures will also be collected (weight, size and perimeter of the waist).

Social support

It will be measured by the Medical Outcomes Study Social Support Survey (MOS-SS) (66). It is a self-report instrument consisting of four subscales (emotional/informational, tangible, affectionate, and positive social interaction) and an overall functional social support index. It has a good reliability (Cronbach's alpha ≥ .91) and is quite stable over time. It has 19 items, a five-point Likert scale. Higher scores indicate more support. We will use the Spanish validated version (43).

Use of health and social services

It will be measured using the Client Service Receipt Inventory (CSRI) (44). This data may be used for a wide range of applications, including estimates of the costs of service receipt. To collect information on the entire range of services and supports used by study participants. It retrospectively collects data on the use of services over the past 6 months (e.g., rates of use of individual services, mean intensity of service use, rates of accommodation use over time). We will use the validated Spanish version (45).

Assessment of lifestyle

Physical activity

Physical activity will be measured using the International Physical Activity Questionnaire-Short Form (IPAQ-SF) (46). It assesses the levels of habitual physical activity over the last 7 days. It has 7 items and records the activity of four intensity levels: vigorous-intensity activity, moderate-

intensity activity (walking and sitting). We will use the validated Spanish version (47). IPAQ-SF has acceptable validity for the measurement of total and vigorous physical activity and poor validity for moderate activity and good reliability (67).

Adherence to the Mediterranean Diet

Measured using the 14-item Mediterranean Diet Adherence Screener (MEDAS), developed within the PREDIMED study group (48). It includes items on food consumption and intake habits: the use of olive oil as the main source of cooking fat, preference for white meat over red meat, servings of vegetables, portions of fruit, red meat or sausages, servings of animal fat, sugar-sweetened beverages, red wine, legumes, fish, commercial pastries and dressing food with a traditional sauce made of tomatoes, garlic, onion, or leeks sautéed in olive oil. The total score ranges from 0 to 14, with a higher score indicating a better accordance with the Mediterranean diet (49).

Quality and patterns of sleep

Measured using the Pittsburgh Sleep Quality Index (PSQI) (50). To measure sleep quality and patterns in adults. It differentiates between "poor" and "good" sleep by measuring seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the past month. It consists of 19 self-applied questions and 5 questions that request the evaluation of the patient's bedmate or roommate (these are not scored). Answers range from 0 (no difficulty) to 3 (severe difficulty). The overall score ranges from 0 to 21 points. In its Spanish version, the Cronbach's alpha coefficient is .81, sensitivity of 88.63% and specificity of 74.99%. We will use the validated Spanish version (51).

Personal factors on health behavior

We will assess: 1) self-efficacy (52); 2) activation (54); 3) sense of coherence (56); 4) health literacy (58); and , 5) procrastination (61).

Self-Efficacy

Measured using by the Self-Efficacy Scale (52). To measure General Self-Efficacy subscale (17 items including individuals' beliefs in their ability to perform well in a variety of situations) and Social Self-Efficacy subscale (6 items). It contains 23 items that are rated on a 14-point scale (ranging from strongly agree to strongly disagree). Higher scores indicate higher levels of self-efficacy. It has a Cronbach coefficient alpha of .86 for General Self-efficacy subscale and .71 for the Social Self-efficacy subscale. The unpublished Spanish version was translated by Godoy in 1990 (53).

Patient activation in their own health

Measured using the Patient Activation Questionnaire (PAM) with regard to the management of their health (54). It evaluates the patient's perceived knowledge, skills, and confidence to engage in self-management activities. It has 13 items, a Likert scale from 1 (strongly disagree) to 4 (strongly agree). The resulting score (between 0 and 100) places the individual at one of four levels of activation, each of which reveals insight into a range of health-related characteristics, including behaviors and outcomes. Higher scores indicate higher levels of activation (54). This scale is only validated in Spanish for chronic patients. It had an item separation index for the parameters of 6.64 and a reliability of .98 (55).

Sense of coherence

Measured using the Sense of Coherence (SOC-13) questionnaire by Antonovsky (56). It values the personal disposition towards the assessment of vital experiences. It measures the sense of coherence, comprehensibility, manageability and meaningfulness. It has 13 items scoring between 13 and 91 points. It has consistency rates of between .84 and .93. Higher scores (after reversal of the inverted items) indicate a higher sense of coherence. We will use the validated Spanish version (57).

Health Literacy

Measured using the Health Literacy Europe Questionnaire (HLS-EUQ16) (58). It can indicate that the probability of functional literacy in limited health is high, a possibility of functional literacy in limited health, and a functional health literacy in adequate health. It contains 16 items. Higher scores indicate better health literacy. It presents a high consistency (Cronbach's alpha of .982) in the Spanish validation (59).

Procrastination

Measured using the Irrational Procrastination Scale (IPS) (60). To measure general procrastination (dysfunctional delay). It has 9 items, rated on a 5-point Likert scale, with higher scores (after reversal of the three procrastination-inconsistent items) indicating a higher level of procrastination. Its Cronbach's alpha value is 0.90. We will use the validated Spanish version (61).

Data analysis plan

Analysis of the outcomes at baseline

First, descriptive analyses of all the variables (proportions for qualitative variables; means and standard deviation for quantitative variables) will be performed. Then, correlation analysis will be carried out between the questionnaires that evaluate personal factors on health behavior (Self-Efficacy Scale, PAM, SOC-13, HLS-EUQ16 and IPS), social support (MOS-SS) and depression (BDI-II). We will also analyze the correlation between personal factors on health behavior and the questionnaires assessing lifestyle patterns (IPAQ-SF, MEDAS and PSQI). Finally, we will analyze the relation of lifestyle patterns and social support with depression. Inferential statistical analysis will be carried out using the Chi-square test for qualitative variables, and Student's t-test or one-way ANOVA test to assess the potential relationship between qualitative and quantitative variables.

Data collection and statistical analysis will be performed using Excel software, SPSS software (version 25.0) (68) and the R statistical software environment (version 3.6.2) (69).

Clinical effectiveness analysis

The report of the results will follow a pre-specified plan, based on the CONSORT guidelines (70) in order to compare the three groups using an intention-to-treat analysis (ITT) and Multiple Imputation technique (MI) for handling missing data. Initially a descriptive comparison (proportions, means or medians) will be carried out between groups for prognostic variables in order to establish their baseline comparability after randomization. To analyze the clinical effectiveness, a repeated-measure linear regression will be conducted, including all evaluations over time. For this purpose, the main variable, BDI-II score, will be used as a continuous variable. The models will include adjustments for the baseline value of

the BDI-II and for any other variable that would have shown differences in the baseline measurement. Possible Group per Time interactions will be examined using linear regression. Similar analyses will be carried out using the secondary outcomes (personal factors on health behavior and assessment of lifestyle). To counteract the problem of multiple comparisons we will use Bonferroni correction.

Comparisons will also be made between the LMP and LMP + ICTs groups regarding adherence to lifestyle modification requirements. Adherence will be considered as a good or beneficial score on the questionnaires assessing lifestyle patterns (IPAQ-SF, MEDAS and PSQI). In addition, we will compare the LMP and combined LMP+ICTs groups, assuming that they are comparable to each other and the two groups have significant results.

A binary variable regarding comorbidity will be created (comorbidity yes/no). We will determine if the effectiveness of the intervention differs in the subgroup presenting comorbidity and if the pathology improves. Statistical analyses will be selected based on subsample size (parametric or non-parametric tests).

As for the time-point in which we administrate the follow-up questionnaires, we will consider the first follow up assessment (in a period of 2 to 7 days after the last session of the intervention) as the more relevant. We expect to find an immediate effect in the LMP and LMP+ICTs groups after attending group intervention, due to the potential social support received. In the 6 and 12-month follow-up, we expect a beneficial change in the questionnaires assessing lifestyle, reflecting a long-lasting effect.

Cost-effectiveness and cost-utility analysis

The effectiveness of the interventions will be estimated using the difference between the BDI-II baseline score and the score at the 6 and 12-month follow-ups, and utility will be estimated using QALYs at the 6 and 12-month follow-ups. QALYs will be calculated based on these scores using the Spanish EQ-5D tariffs (71). Along with the EQ-5D utility scores, scores recorded on the EQ VAS will also be used as an outcome for the analysis.

Cost effectiveness will be explored through the calculation of incremental cost-effectiveness ratios (ICERs) for the active intervention groups (LMP and LMP+ICTs) using the TAU group as the control. ICER is defined as the ratio between incremental costs and incremental effectiveness. In this way, cost utility will be explored by calculating incremental cost-utility ratios (ICURs), which are defined as the ratio between incremental costs and incremental utilities measured on QALYs. QALYs gained in each evaluation are approximated using the area under-the-curve technique (72).

Total costs will be calculated by adding direct and indirect costs. Direct costs will be calculated by adding the costs derived from the medication and the use of health services and clinical tests. The medication costs will be calculated by determining the price per milligram during the study period according to the Vademecum of the last year of study, including value-added tax (VAT). The total cost of drug treatment will be calculated by multiplying the price per milligram by the daily dose in milligrams and the number of days the treatment is received. Costs derived from the use of health services will be calculated considering the data from the Oblikue database (73). Indirect costs will be calculated based on the sick leave days and multiplying them by the Spanish minimum daily wage during the study period, 2019-2020.

We assume that data will be missing at random (MAR). Only patients with both cost and relevant outcome data at the 6 and 12-month follow-ups will be included in the cost-effectiveness and cost-utility analyses. Notwithstanding this, sensitivity analysis imputing missing 6 and 12-month data will test the robustness of cost-effectiveness and cost-utility results. The imputations will be performed using the "mice" package (74), freely available in cran-R (69).

Discussion

Depression is a significant cause of morbidity having low detection and treatment rates in primary care (75,76). Only 9% of all depressed primary care patients receive adequate treatment, and only 6% achieve remission, making depression an important management issue in primary care (77). An effective treatment for depression that can be implemented in PHCs is brief psychotherapy (6 to 8 sessions programs), which have the advantage of being performed by either mental health professionals or trained non-mental health providers (78). In this case, the promotion of healthy lifestyles will be used to address depressive symptoms, as it has shown efficacy in a number of studies (20–31). To ensure treatment adherence, facilitators should be used, such as the use of ICTs and the group format. They provide monitoring and social support, respectively (33). Organizing group therapies in PHCs generates a range of organizational benefits, in relation to efficient use of facilities, high therapist-to patient ratios and potential reductions to treatment wait-times (79). Moreover, participants are just as likely to engage in group treatment as individual work and the benefits are also maintained over time (80).

The strengths of this study include the design and the wide range of outcome measures. It will provide a wealth of information on the interplay between depression, personal factors on health behavior and lifestyles. Study limitations include the possible attrition of participants due to session scheduling or participant refusal to participate in a group intervention or do the complete follow-ups (81). However, the possible reasons for attrition and other issues will be registered regarding MAGI framework (38).

Therefore, the creation of a 6-session group program addressing lifestyle modifications (plus testing the monitoring with ICTs by adding a smartwatch to one of the intervention group) appears to be a good choice for depression treatment. The long-term aim of this study is to establish intervention for patients with depression, making it accessible in their PHCs, effective and cost-effective.

Execution dates

Initial recruitment of patients: April 2020.

Finalization of patient recruitment: May 2020.

Finalization of patient monitoring period: June 2021.

Publication of results: July 2021.

Partial Patient and Public Involvement: PPI representatives worked with us to refine the research question; however, it was difficult to involve patients in other areas of the study design due to data protection restrictions and the very technical methods required to do a data linkage analysis. PPI representatives will write a plain language summary and design a leaflet for dissemination to their peers and distributing to patient groups.

Ethics approval: Ethics approval was granted by the Research Ethics Committee of Aragón (CEICA, PI18/286) and the Research Ethics Committee of the Balearic Islands (IB3950/19 PI). The

study has been developed in accordance with the Helsinki Declaration. All of the subjects will sign an informed consent form, their data will be anonymized and will only be used for the purposes of the study. Participants and healthcare professionals will be informed about the results. Patients of the TAU group will be invited to participate in the LMP at the end of the study. The Ethics Committee will be notified of any protocol modifications.

Authors' contributions: BOB, MJSR and MGT led the design and developed the study and had the original idea. RMB, MJSR, CN and BOB coordinated the fieldwork. AAL and CCV undertook the fieldwork. AAL, BOB, EG and SBS wrote the first draft of the article. The rest of the signing authors have read the manuscript critically, offering contributions and approving the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: None.

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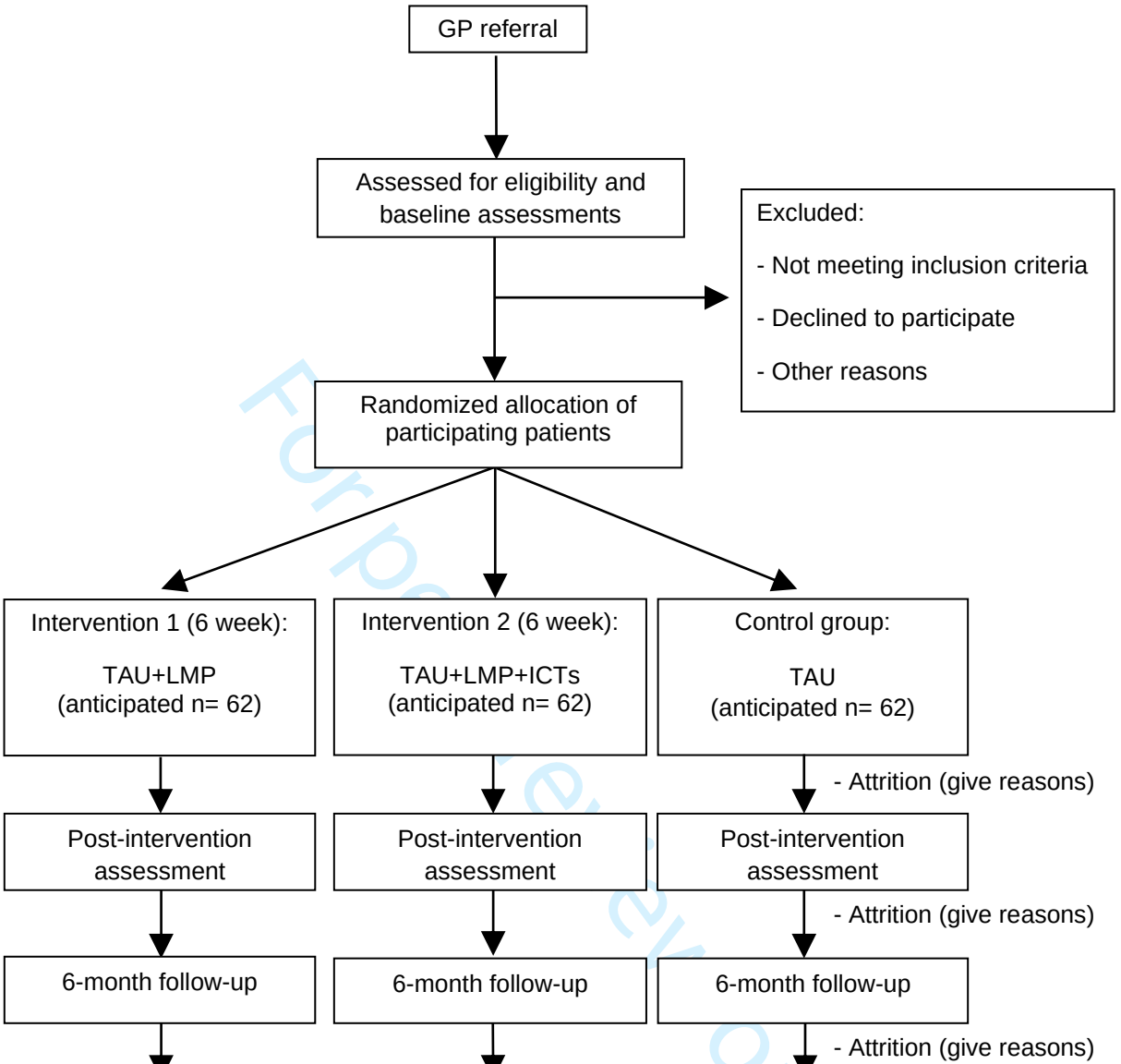
Figure 1: Flowchart of the study: randomization, sampling and monitoring of patients.



GP, General Practitioner; TAU, Treatment as Usual; LMP, Lifestyle Modification Program; ICTs, Information and Communication Technologies; MI, Multiple Imputation.

DOCUMENTO DE INFORMACIÓN PARA EL PARTICIPANTE

Título de la investigación: Efectividad y coste-utilidad de un programa de Estilo de Vida Mediterráneo en la prevención y tratamiento de la depresión subclínica, leve y moderada en Atención Primaria.

Promotor: Instituto de Salud Carlos III (Ministerio de Economía y Competitividad)

Investigador Principal: Bárbara Oliván Tfno: 976 761000 ext4547

Centro: Universidad de Zaragoza

1. Introducción:

Nos dirigimos a usted para invitarle a participar en un proyecto de investigación que estamos realizando en Aragón y Mallorca, específicamente en Zaragoza, en los centros de salud de "Fuentes Norte", "Parque Goya" y "Arrabal", y en Mallorca, en los centros de salud de "Son Cladera", "Son Serra-La Vileta" y "Valldargent". Su participación es importante para obtener el conocimiento que necesitamos, pero antes de tomar una decisión debe:

- Leer este documento entero
- Entender la información que contiene el documento
- Hacer todas las preguntas que considere necesarias
- Consultar con su médico-persona de confianza
- Tomar una decisión meditada
- Firmar el consentimiento informado, si finalmente desea participar.

Si decide participar se le entregará una copia de este documento y del consentimiento firmado. Por favor, consérvelos por si lo necesitara en un futuro.

2. ¿Por qué se le pide participar?

Se le solicita su colaboración porque usted cumple los que criterios de inclusión en el estudio, que son: ser mayor de 18 años, padecer una depresión subclínica, leve o moderada con una duración de al menos dos meses.

En total en el estudio participarán 340 pacientes de estas características.

3. ¿Cuál es el objeto de este estudio?

El objetivo de este estudio es analizar si un tratamiento grupal sobre modificación de estilo de vida, sumando al tratamiento habitual prescrito por su médico de familia es eficaz en el tratamiento de su depresión.

4. ¿Qué tengo que hacer si decido participar?

Recuerde que su participación es voluntaria y si decide no participar esto no afectará a su asistencia o a su relación con el investigador y su equipo.

Si decide entrar en el estudio, su participación consistirá en la cumplimentación de un cuaderno de recogida de datos sobre su depresión, otras enfermedades que padezca (además de recoger talla, peso y tensión arterial), calidad de vida, si realiza la modificación de estilos de vida (realiza ejercicio, dieta que lleva, higiene del sueño, y apoyo social) y variables que influyen en realizar esta modificación de estilos de vida. Cumplimentar este cuestionario le costará aproximadamente entre cuarenta y cincuenta minutos. El primero que cumplimente será un poco más largo, ya que tenemos que comprobar que cumple los criterios para ser incluida en el estudio.

Posteriormente a esta primera evaluación, se le asignará de manera aleatoria, es decir, por azar, como si se lanzara una moneda al aire, a un grupo de tratamiento, que puede ser: un tratamiento grupal de 6 semanas de duración, con una sesión semanal de hora y media sobre modificación de estilos de vida; un tratamiento grupal igual que el anterior pero se le facilitará algún dispositivo para monitorizar su actividad física y horas de sueño; y grupo control, que no se le asignará a ningún tratamiento a parte del prescrito por su médico de familia. Estos tratamientos grupales consistirán en 6 sesiones y se harán una por semana. En estas sesiones se abordará el estilo de vida mediterráneo, es decir, explicaremos temas como la importancia de la dieta mediterránea, y que es recomendable comer, la importancia del ejercicio físico y cómo se debe realizar, de la exposición a la luz, de la higiene del sueño, de la activación conductual y social, para poder vencer la apatía, etc. Estas sesiones se desarrollarán en su centro de salud. Al principio de cada sesión, se tratará la cumplimentación y las dificultades de llevar a cabo el tema tratado en la sesión anterior durante 10-15 minutos. El audio de esta valoración será grabado para su posterior transcripción y análisis. Estas grabaciones serán guardadas por la investigadora principal (en su equipo informático) y no tendrá nadie más acceso a las mismas hasta su transcripción, momento en el cual serán destruidas. En dicha trascripción no se identificará a los/as autores/as de los contenidos y no serán utilizadas exclusivamente para analizar la cumplimentación y las dificultades encontradas en la modificación de estilos de vida.

En caso de que fuera asignado a este último, al finalizar el estudio, en caso de que los resultados lo aconsejaran, se le ofertará la posibilidad de realizar el tratamiento grupal sobre modificación de estilos de vida.

Posteriormente a esta intervención, se le realizará otra evaluación, así como a los 6 meses y al año de haber finalizado. La duración de estas evaluaciones tendrá una duración aproximada de media hora.

Se revisará su historia clínica en caso de que tenga alguna otra enfermedad como diabetes, insuficiencia cardiaca o hipercolesterolemia, para recoger valores de estas enfermedades en el último análisis de sangre que su médico de familia le haya realizado.

5. ¿Qué riesgos o molestias supone?

Tanto por la evaluación como por la intervención que se va a desarrollar en este estudio, usted no tiene ningún riesgo ni debería tener ninguna molestia. Los cuestionarios que se van a utilizar no implican ninguna prueba invasiva ni dolorosa, son cuestionarios ampliamente utilizados en investigación y en la práctica clínica. Tanto la evaluación como la intervención que se va a desarrollar va a estar dirigida por personal cualificado (psicólogos/as).

Si se detecta que usted está empeorando gravemente en su estado de depresión, se contactará con su médico de familia.

6. ¿Obtendré algún beneficio por mi participación?

Al tratarse de un estudio de investigación orientado a generar conocimiento es probable que no obtenga ningún beneficio por su participación si bien usted contribuirá al avance del conocimiento y al beneficio social. Usted no recibirá ninguna compensación económica por su participación.

7. ¿Cómo se van a gestionar mis datos personales?

Toda la información recogida se tratará conforme a lo establecido en la legislación vigente en materia de protección de datos de carácter personal. En la base de datos del estudio no se incluirán datos personales: ni su nombre, ni su nº de historia clínica ni ningún dato que le pueda identificar. Se le identificará por un código que sólo el equipo investigador podrá relacionar con su nombre.

Sólo el equipo investigador tendrá acceso a los datos de su historia clínica y nadie ajeno al centro podrá consultar su historial. En caso de que se necesite este acceso se debe especificar quién, con qué fin, durante qué periodo de tiempo, qué datos se van a revisar y solicitar consentimiento expreso para este acceso.

De acuerdo a lo que establece la legislación de protección de datos, usted puede ejercer los derechos de acceso, modificación, oposición y cancelación de datos. Además puede limitar el tratamiento de datos que sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio. Para ejercitar sus derechos, diríjase al investigador principal del estudio. Así mismo tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho.

Si usted decide retirar el consentimiento para participar en este estudio, ningún dato nuevo será añadido a la base de datos, pero sí se utilizarán los que ya se hayan recogido. En caso de que desee que se destruyan tanto los datos como las muestras ya recogidos debe solicitarlo expresamente y se atenderá a su solicitud.

Los datos codificados pueden ser transmitidos a terceros y a otros países pero en ningún caso contendrán información que le pueda identificar directamente, como nombre y apellidos, iniciales, dirección, nº de la seguridad social, etc. En el caso de que se produzca esta cesión, será para los mismos fines del estudio descrito o para su uso en publicaciones científicas pero siempre manteniendo la confidencialidad de los mismos de acuerdo a la legislación vigente.

El promotor/investigador adoptará las medidas pertinentes para garantizar la protección de su privacidad y no permitirá que sus datos se crucen con otras bases de datos que pudieran permitir su identificación o que se utilicen para fines ajenos a los objetivos de esta investigación.

Las conclusiones del estudio se presentarán en congresos y publicaciones científicas pero se harán siempre con datos agrupados y nunca se divulgará nada que le pueda identificar.

9. ¿Quién financia el estudio?

Este proyecto se financia con fondos procedentes del Instituto de Salud Carlos III, perteneciente al Ministerio de Economía y Competitividad.

El conocimiento derivado de este estudio no es probable que genere en un futuro beneficios comerciales. No obstante, en caso de que generase estos beneficios, pertenecerían al equipo investigador. Los participantes no tendrán derecho a reclamar parte de ese beneficio.

10. ¿Se me informará de los resultados del estudio?

Usted tiene derecho a conocer los resultados del presente estudio, tanto los resultados generales como los derivados de sus datos específicos. También tiene derecho a no conocer dichos resultados si así lo desea. Por este motivo en el documento de consentimiento informado le preguntaremos qué opción prefiere. En caso de que desee conocer los resultados, el investigador le hará llegar los resultados.

¿Puedo cambiar de opinión?

Tal como se ha señalado, su participación es totalmente voluntaria, puede decidir no participar o retirarse del estudio en cualquier momento sin tener que dar explicaciones y sin que esto repercuta en su atención sanitaria. Basta con que le manifieste su intención al investigador principal del estudio.

Si usted desea retirarse del estudio se eliminarán los datos recogidos.

¿Qué pasa si me surge alguna duda durante mi participación?

En caso de duda o para cualquier consulta relacionada con su participación puede ponerse en contacto con el investigador responsable, Dña. Bárbara Oliván, en el teléfono 976 761000 ext 4547 en horario de mañanas o por correo electrónico en la dirección bolivan@unizar.es.

Muchas gracias por su atención, si finalmente desea participar le rogamos que firme el documento de consentimiento que se adjunta.

DOCUMENTO DE CONSENTIMIENTO INFORMADO

Título del PROYECTO: Efectividad y coste-utilidad de un programa de Estilo de Vida Mediterráneo en la prevención y tratamiento de la depresión subclínica, leve y moderada en Atención Primaria.

Yo, ... (nombre y apellidos del participante)

He leído el documento de información que se me ha entregado.

He podido hacer preguntas sobre el estudio y he recibido suficiente información sobre el mismo.

He hablado con: .....(nombre del investigador)

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:

1) cuando quiera
2) sin tener que dar explicaciones
3) sin que esto repercuta en mis cuidados médicos

Presto libremente mi conformidad para participar en el estudio.

Deseo ser informado sobre los resultados del estudio: sí no (marque lo que proceda)

Doy mi conformidad para que mis datos clínicos sean revisados por personal ajeno al centro, para los fines del estudio, y soy consciente de que este consentimiento es revocable.

He recibido una copia firmada de este Consentimiento Informado.

Firma del participante: .....

Fecha: .....

He explicado la naturaleza y el propósito del estudio al paciente mencionado

Firma del Investigador: .....

Fecha:

$$n = \frac{\left(z_\alpha + z_{2\beta}\right)^2 \sigma_d^2}{(\Delta m)^2}$$

$\Delta m = 4.8$

α=0.05

β= 0.20

$z_\alpha = 1.96$

$z_{2\beta} = 1.28$

$\sigma_d^2 = 136$

SLEEP DURATION AND SUNLIGHT

Day	Time to get up and go to bed	Sleep duration (hours)	Sunlight exposure (in minutes)
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

SLEEP DURATION AND SUNLIGHT

Day	Time to get up and go to bed	Sleep duration (hours)	Sunlight exposure (in minutes)
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

PHYSICAL ACTIVITY

Day	Activity	Sport	Duration (min)	Company	How do I feel next?
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

SLEEP DURATION AND SUNLIGHT

Day	Time to get up and go to bed	Sleep duration (hours)	Sunlight exposure (in minutes)
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

PHYSICAL ACTIVITY

Day	Activity	Sport	Duration (min)	Company	How do I feel next?
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

MEDITERRANEAN DIET

Day	Breakfast	Snack	Appetizer	Lunch	Snack	Dinner
Monday						
Tuesday						
Wednesday						
Thursday						
Friday						
Saturday						
Sunday						

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3-14
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page
	5b	Name and contact information for the trial sponsor	14
	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	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7
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	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	4-5

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, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
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
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)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	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)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-11
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)	7-8
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was	6

		determined, including clinical and statistical assumptions supporting any sample size calculations	
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection methods	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	7-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants	7

		who discontinue or deviate from intervention protocols	
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	7
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11-13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7 & 13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility	14

		criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6-7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	7 & 14
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Material 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Effectiveness and cost-effectiveness of a Lifestyle Modification Program in the prevention and treatment of subclinical, mild and moderate depression in primary care. A randomized clinical trial protocol.

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Effectiveness and cost-effectiveness of a Lifestyle Modification Program in the prevention and treatment of subclinical, mild and moderate depression in primary care. A randomized clinical trial protocol

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Abstract

Introduction:

Major depression is a highly prevalent pathology that is currently the second most common cause of disease-induced disability in our society. The onset and continuation of depression may be related to a wide variety of biological and psychosocial factors, many of which are linked to different lifestyle aspects. Therefore, health systems must design and implement health promotion and lifestyle modification programs, taking into account personal factors and facilitators. The main objective of this protocol is to analyze the clinical effectiveness, cost-effectiveness and cost-utility of a Lifestyle Modification Program and a Lifestyle Modification Program with ICTs as adjunctive treatment for depression in primary care patients. The secondary objectives are to analyze the clinical effectiveness in the subgroup that presents comorbidity and to analyze the correlation between personal factors on health behavior and lifestyle patterns.

Methods and analysis:

A randomized, multicenter pragmatic clinical trial with 3 parallel groups consisting of primary healthcare patients suffering from subclinical, mild or moderate depression. The following interventions will be used: 1. Usual antidepressant treatment with psychological advice and/or psychotropic drugs prescribed by the General Practitioner (treatment-as-usual, TAU). 2. TAU + Lifestyle Modification Program (LMP). A program to be imparted in 6 weekly 90-minute group sessions, intended to improve the following aspects: behavioral activation + daily physical activity + adherence to the Mediterranean diet pattern + sleep hygiene + careful exposure to sunlight. 3. TAU + LMP + ICTs: healthy lifestyle recommendations (TAU+LMP) + monitoring using ICTs (a wearable smartwatch). The primary outcome will be the depressive symptomatology and the secondary outcomes will be the quality of life, the use of health and social resources, personal factors on health behavior, social support, lifestyle patterns and chronic comorbid pathology. Data will be collected before and after the intervention, with 6- and 12-month follow-ups.

Ethics and dissemination: This study has been approved by the Research Ethics Committee of Aragón (CEICA) (Approval Number: C.P. - C.I. PI18/286) and the Research Ethics Committee of the Balearic Islands (IB3950/19 PI)**.** Data distribution will be anonymous. Results will be disseminated via conferences and papers published in peer-reviewed, open-access journals.

Trial registration number: ClinicalTrials.gov Identifier: NCT03951350

Strengths and limitations of this study:

- The intervention has the potential to be highly scalable and sustainable for the Spanish National Health Service.
- Increased motivation, upon introducing self-registers for everyone and a group that will be monitored using wearable smartwatches.
- Most healthcare professionals can implement the intervention groups.
- Some individuals may refuse to participate in group intervention or may withdraw from the study during the 12-month trial period.
- Difficulty of entire group's attendance to a session held on one specific date and time.

Keywords: Depression, Lifestyle modifications, Diet, Exercise, Sunlight exposure, Sleep patterns

Introduction:

Depression is considered to be the principle cause of disability worldwide, and it contributes to the overall global burden of morbidity and mortality. By 2030, it is expected to be the main contributor to the burden of morbidity (1–3). Approximately 25-35% of all primary care patients suffer from psychiatric disorders, and over 80% of these patients suffer from depression or anxiety disorders (4,5). In Spanish primary healthcare centers (PHCs) the prevalence of depression ranges from 9.6% to 20.2% (6,7). Furthermore, depression generates great disability and high economic and social costs (8).

The prevalence of depression in Spain is 13% over one's lifetime and 4% per year (9). Indeed, comorbidity with other chronic conditions is also high (64.9% to 71.0%) (diabetes, hypertension, cardiovascular diseases and cancer, among others) (10–12) as well as with other psychiatric diseases such as anxiety disorders (40% to 66%) (13).

Despite the negative impact of depression on people's lives and the existence of numerous treatment interventions (14), these often are not appropriately used in PHC services (6), mainly due to physician time or resource limitations (7). Thus, pharmacological (15) treatment is usually recommended, even though research has shown that in subclinical, mild or moderate depression, non-pharmacological interventions are recommended (15,16).

Since options and outcomes for the care of individuals suffering from depression and their access to treatment remains limited (17), it is important to promote cost-effective treatment options. The onset and continuation of depression has been linked to numerous biological and psychosocial factors, many of which are related to distinct lifestyle aspects (18–21). Therefore, many of the strategies promoting a healthier lifestyle could have antidepressant utility (20,22–24). In addition to multimodal studies, others have focused on one aspect of lifestyle modification: daily physical activity (25), adherence to the Mediterranean diet (26,27), sleep hygiene practices (28,29) and careful exposure to sunlight (30,31).

The present study will be framed around the theory of salutogenesis (32), which establishes that an individual's ability to modify our lifestyle is influenced by Psychosocial Generalized Resistance Resources, which consist of personal, interpersonal or contextual resources (money, knowledge, experience, self-esteem, healthy habits, commitment, social support, cultural capital, intelligence, traditions and vision of life) and the Sense of Coherence (way of making sense of the world, which is a major factor in determining how well an individual manages stress and stays healthy).

Moreover, previous studies show that is quite important the use of facilitators (simplicity of guidelines, tailoring through motivational interviewing, prolonged and intense monitoring throughout the different stages of the disorder, and the provision of adequate feedback and social support) (23) to facilitate adherence to lifestyle modification programs. For example, enhanced motivation can be achieved through the use of Information and Communication Technologies (ICTs) and with the social support resulting from intervention group participation (33). Personal factors and facilitators must be taken into account in lifestyle modification interventions, since they may determine the success of health promotion programs.

The main objective of this protocol is to analyze the clinical effectiveness, cost-effectiveness and cost-utility of a Lifestyle Modification Program and a Lifestyle Modification Program with ICTs as adjunctive treatment for depression in primary care patients. The secondary objectives are to

analyze the clinical effectiveness in the subgroup that presents comorbidity and to analyze the correlation between personal factors on health behavior and lifestyle patterns.

Methods and analysis:

Study design

Multicenter pragmatic randomized controlled trial in 3 parallel groups.

Setting and study sample

We will recruit patients having subclinical, mild or moderate depression (scoring ≥ 10 and ≤ 30 points on the Beck II Self-Applied Depression Inventory (BDI II) (34)) from PHCs of two Spanish areas (Zaragoza and Mallorca). Inclusion criteria: individuals over the age of 18, both sexes, having a duration of depression symptoms of at least 2 months, who understand written and spoken Spanish and who have provided their informed consent (supplementary file 1). Exclusion criteria will be: suffering from another disease that affects the brain (organic brain pathology or having suffered a traumatic brain injury of any severity, dementia); having another psychiatric diagnosis or serious psychiatric illness (substance dependence or abuse, history of schizophrenia or other psychotic disorders, eating disorders) with the exception of anxious pathology or personality disorders (collected through a medical history and from the Mini-International Neuropsychiatric Interview (MINI) (35)); presence of a serious or uncontrolled medical, infectious or degenerative illness that may interfere with the affective symptoms; the presence of delirium or hallucinations, risk of suicide, pregnancy or lactation; patients who have participated in another clinical trial over the past 6 months or who are currently in psychotherapy; or those who practice mindfulness, yoga, meditation or similar practices over the past 6 months, engaging in formal practice at least once a week; and the presence of any medical, psychological or social problem that could seriously interfere with the patient's participation in the study.

Sample size

Scientific evidence suggests that a 17% reduction in the BDI-II (34) is considered clinically relevant (36). In a previous study conducted by our team with psychiatric outpatients, we found that the average BDI score at the beginning of the study was 24.5 points (SD 9.8) (22), so we consider that a reduction of at least 4.8 points would have clinical significance and would benefit the patient. Accepting an α risk of 0.05 and a β risk of 0.20 in a bilateral contrast, 44 subjects will be required for each group. With an estimated withdrawal rate of 20%, the sample size will require approximately 53 patients in each group. The total sample required is 159 subjects. A formula based on the Snedecor's *F* distribution (37) has been used (see supplementary file 2). It is estimated that approximately 50% of these patients will present some physical or mental comorbidity (12).

Recruitment

General practitioners (GPs) from the PHCs of Zaragoza and Mallorca will be invited to refer patients who are suspected of suffering from depression. Most representative PHCs in the area will be invited, based on size, urban or rural area and PHCs with a different socio-demographic profile will be selected. GPs will explain the characteristics of the study to their patients and if they agree to participate, they will be asked to provide a phone number to be contacted by a trained Research Assistant (RA) during the next week. The RA will phone patients, establish an appointment in their PHC, in which he will explain them the study, providing them the Patient Information Sheet and signed the Informed Consent. To ensure that they fulfill the inclusion criteria, the RA will administrate the BDI-II (34) and the MINI (35). If participants meet the criteria, the RA will administer the baseline questionnaires at the same appointment.

Recruitment and baseline assessments will be carried out until the final sample size has been achieved.

Randomization, allocation and masking of study groups

Once baseline data is collected, the participants will be randomized. An independent statistician will perform the individual randomization using a computer-generated random number sequence. The randomization will be carried out using a list of patients from Zaragoza and Mallorca (Figure 1). Given the nature of the interventions, participants will not be blind to their allocation. An RA will phone them to explain their assigned intervention and where they should go and when. The RA will request that participants not inform other researchers of their allocation.

[Figure 1 about here]

Data collection and monitoring

One RA will collect the data and another will perform entry and coding of the identified data. All RA managing the data will be blinded to participant allocation, as well as the RA conducting the outcome assessments and data analysis. All information collected will be treated in accordance with the provisions of current legislation on personal data protection.

The study will not have a formal data monitoring committee since adverse intervention events have not been reported. Any serious unexpected adverse events or outcomes will be discussed by the trial management committee (identical to the authors of this protocol). There are no plans to discontinue or modify interventions, or to improve adherence or promote participant retention. The trial management committee will monitor recruitment, treatment and attrition rates and any concerns related to the study. Reasons for dropping out will be also registered. Concomitant care is permitted and registered as long as it is not one of the exclusion criteria. Group-specific processes will be taken into account and will be evaluated and informed, in accordance with recommendations of the "Mechanisms of Action in Group-based Interventions"(MAGI) framework (38).

Intervention development and evaluation

Patients allocated in the first arm (control group) will follow the usual treatment provided by their GP (treatment-as-usual, TAU).

Patients allocated in the second arm (1st intervention group) will follow the TAU and the Lifestyle Modification Program (LMP). This program will consist of 6 weekly group sessions (lasting 90 minutes each) led by an experienced psychologist and complemented by PowerPoint presentations.

Patients allocated in the third arm (2nd intervention group) will follow TAU and LMP and will be monitored using a wearable smart wristwatch that will track their daily sleep patterns and physical activity (LMP+ICTs).

The group sessions will consist of the following content:

1) Presentation of the project and psychoeducation on depression: Presentation of the project and a review of the study objectives. Definition, symptoms, causes, consequences of depression and, also, how lifestyles and social environment changes influence the symptomatology of depression.

2) Behavior activation: a psychologist will provide information on the importance of establishing, maintaining and monitoring activities. For the LMP+ICTs group, they will also learn how to use the smart wristwatch, ensuring all participants are able to use it.

3) Sleep hygiene habits and careful exposure to sunlight: recommendations on healthy sleep habits, factors influencing sleep quality and possible solutions. The benefits of careful exposure to sunlight and recommendations of when to do so and for how long. Responding to questions regarding the previous session.

4) Physical activity: the benefits of engaging in regular physical activity. Personalized recommendations about what physical exercise may be practiced, how and when to do so. Responding to questions regarding the previous session.

5) Adherence to the Mediterranean diet: explanations about the Mediterranean diet, food groups and their characteristics, as well as the most beneficial foods for physical and mental health, how to cook it and food-related habits. Responding to questions regarding the previous session

6) Summary of previous sessions with practical final suggestions: personalized experiences and doubts of the participants throughout the course. Recommendations for daily healthy lifestyle practices for the future and farewell.

At the end of each session, the participants will receive a paper with self-registration tables (supplementary file 3). They will complete the tables with the information on their daily routines regarding the modification of lifestyles on which they have been instructed. They will be asked about when they wake up and when they go to bed, the duration of their sleep, the time spent exposed to sunlight, the diet pattern, the physical activity and sports practiced, the social support, and the subjective perception of satisfaction after these activities. A qualitative study associated with this study will be included to analyze the participants' difficulties in following the intervention.

Outcomes and measures

We will collect patient data using the questionnaires administered in baseline, immediately after the intervention (in a period of 2 to 7 days after the last intervention session) and at 6 and 12-month follow-up after the last intervention session (with a margin of ± two weeks) (see Table 1). A blinded RA will phone each patient of the three arms and set up an appointment in their PHC for questionnaire administration. Study outcomes and measures are summarized in Table 1.

Table 1
Study variables

Instrument	Assessment area	Measures
BDI-II (34,39)	Severity of depression	Baseline and follow-up sessions[a]
MINI (35)	Psychiatric diagnosis	Baseline
Gender, age, marital status, education, occupation, economical level	Sociodemographic	Baseline and follow-up sessions[a]
Glucose concentration (mg/dL), glycated	Comorbidity with chronic diseases	Baseline and 6 and 12-month follow-up.

hemoglobin (%), creatinine, arterial pressure (mmHg) and cholesterol (mg/dL)		
EQ-5D (40,41)	Health-related quality of life	Baseline and follow-up sessions[a]
MOS-SS (42,43)	Social support	Baseline and follow-up sessions[a]
CSRI (44,45)	Health and social services use	Baseline and follow-up sessions[a]
IPAQ-SF (46,47)	Physical activity	Baseline and follow-up sessions[a]
MEDAS (48,49)	Adherence to the Mediterranean Diet	Baseline and follow-up sessions[a]
PSQI (50,51)	Quality and patterns of sleep	Baseline and follow-up sessions[a]
Self-Efficacy Scale (52,53)	Self-Efficacy	Baseline and follow-up sessions[a]
PAM (54,55)	Patient activation in their own health	Baseline and follow-up sessions[a]
SOC-13 (56,57)	Sense of coherence	Baseline and follow-up sessions[a]
HLS-EUQ16 (58,59)	Health Literacy	Baseline and follow-up sessions[a]
IPS (60,61)	Procrastination	Baseline and follow-up sessions[a]

BDI-II, Beck II Self-Applied Depression Inventory; MINI, Mini-International Neuropsychiatric Interview; EQ-5D, the European Quality of Life-5 Dimensions questionnaire; MOS-SS, Medical Outcomes Study Social Support Survey; CSRI, Client Service Receipt Inventory; IPAQ-SF, Physical Activity Questionnaire-Short Form; MEDAS, 14-item Mediterranean Diet Adherence Screener; PSQI, Pittsburgh Sleep Quality Index; PAM, Patient Activation Questionnaire; SOC-13, Sense of Coherence questionnaire; HLS-EUQ16, Health Literacy Europe Questionnaire; IPS, Irrational Procrastination Scale.

[a]Follow-up sessions: post-intervention (in a period of 2 to 7 days after the last session of the intervention), 6 and 12-month follow-up (6 and 12-month after the last session of the intervention [± two weeks]).

Sociodemographic data

We will collect information on gender, age, marital status, education, occupation, economical level. These data will be collected through an ad hoc questionnaire.

Primary outcome

Severity of depression

The primary outcome will be measured using the BDI-II (34). This is a self-report inventory for measuring the severity of depression, consisting of 21 multiple-choice questions with each answer being scored on a scale ranged from 0 to 3. It was translated and validated into Spanish with a reliability of .89 (39). The standardized cutoffs are: 0–13: minimal depression; 14–19: mild depression; 20–28: moderate depression; 29–63: severe depression.

Secondary outcomes

Health-related quality of life

Health-related quality of life will be measured using the European Quality of Life-5 Dimensions questionnaire (EQ-5D) (40,62). EQ-5D scores will be used to calculate the quality-adjusted life year (QALY) during the monitoring period by adjusting the length of time affected by the health result by the utility value. It contains five health dimensions (mobility, selfcare, usual activities,

pain/discomfort and anxiety/depression) and each of these has three levels (no problems, slight problems or moderate and severe problems). The EQ records the patient's self-rated health on a vertical visual analogue scale of 20 centimeters (VAS), where the endpoints are labeled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgment. Patients mark the point on the vertical line that best reflects their assessment of their current global health status (41). Cronbach's Alpha coefficient has been calculated in research with disease-specific populations. We highlight Seoane et al. (63), in which the overall alpha value was .788. The only study with a general population, it provides an overall mean estimate of the Minimum Important Difference (MID) for the EQ-5D, which is .074 (64).

Comorbidity with chronic diseases

Comorbidity with chronic diseases will be determined according to the International Classification of Diseases (ICD-10) (65): diabetes (glucose concentration (mg/dl), glycated hemoglobin (%), creatinine), arterial hypertension and diseases of lipid metabolism. In patients with chronic heart disease, coagulation variables will be added. They will be collected from the last blood test or control measurements of the clinical history, taken by their GP or nurse (assuming they were taken over the past 3 months). Otherwise, their GP will be asked for a blood control test. It is estimated that approximately 50% of these patients will present some comorbidity (12). Anthropometric measures will also be collected (weight, size and perimeter of the waist).

Social support

It will be measured by the Medical Outcomes Study Social Support Survey (MOS-SS) (66). It is a self-report instrument consisting of four subscales (emotional/informational, tangible, affectionate, and positive social interaction) and an overall functional social support index. It has a good reliability (Cronbach's alpha ≥ .91) and is quite stable over time. It has 19 items, a five-point Likert scale. Higher scores indicate more support. We will use the Spanish validated version (43).

Use of health and social services

It will be measured using the Client Service Receipt Inventory (CSRI) (44). This data may be used for a wide range of applications, including estimates of the costs of service receipt. To collect information on the entire range of services and supports used by study participants. It retrospectively collects data on the use of services over the past 6 months (e.g., rates of use of individual services, mean intensity of service use, rates of accommodation use over time). We will use the validated Spanish version (45).

Assessment of lifestyle

Physical activity

Physical activity will be measured using the International Physical Activity Questionnaire-Short Form (IPAQ-SF) (46). It assesses the levels of habitual physical activity over the last 7 days. It has 7 items and records the activity of four intensity levels: vigorous-intensity activity, moderate-intensity activity (walking and sitting). We will use the validated Spanish version (47). IPAQ-SF has acceptable validity for the measurement of total and vigorous physical activity and poor validity for moderate activity and good reliability (67).

Adherence to the Mediterranean Diet

Measured using the 14-item Mediterranean Diet Adherence Screener (MEDAS), developed within the PREDIMED study group (48). It includes items on food consumption and intake habits: the use of olive oil as the main source of cooking fat, preference for white meat over red meat, servings of vegetables, portions of fruit, red meat or sausages, servings of animal fat, sugar-sweetened beverages, red wine, legumes, fish, commercial pastries and dressing food with a traditional sauce made of tomatoes, garlic, onion, or leeks sautéed in olive oil. The total score ranges from 0 to 14, with a higher score indicating a better accordance with the Mediterranean diet (49).

Quality and patterns of sleep

Measured using the Pittsburgh Sleep Quality Index (PSQI) (50). To measure sleep quality and patterns in adults. It differentiates between "poor" and "good" sleep by measuring seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the past month. It consists of 19 self-applied questions and 5 questions that request the evaluation of the patient's bedmate or roommate (these are not scored). Answers range from 0 (no difficulty) to 3 (severe difficulty). The overall score ranges from 0 to 21 points. In its Spanish version, the Cronbach's alpha coefficient is .81, sensitivity of 88.63% and specificity of 74.99%. We will use the validated Spanish version (51).

Personal factors on health behavior

We will assess: 1) self-efficacy (52); 2) activation (54); 3) sense of coherence (56); 4) health literacy (58); and , 5) procrastination (61).

Self-Efficacy

Measured using by the Self-Efficacy Scale (52). To measure General Self-Efficacy subscale (17 items including individuals' beliefs in their ability to perform well in a variety of situations) and Social Self-Efficacy subscale (6 items). It contains 23 items that are rated on a 14-point scale (ranging from strongly agree to strongly disagree). Higher scores indicate higher levels of self-efficacy. It has a Cronbach coefficient alpha of .86 for General Self-efficacy subscale and .71 for the Social Self-efficacy subscale. The unpublished Spanish version was translated by Godoy in 1990 (53).

Patient activation in their own health

Measured using the Patient Activation Questionnaire (PAM) with regard to the management of their health (54). It evaluates the patient's perceived knowledge, skills, and confidence to engage in self-management activities. It has 13 items, a Likert scale from 1 (strongly disagree) to 4 (strongly agree). The resulting score (between 0 and 100) places the individual at one of four levels of activation, each of which reveals insight into a range of health-related characteristics, including behaviors and outcomes. Higher scores indicate higher levels of activation (54). This scale is only validated in Spanish for chronic patients. It had an item separation index for the parameters of 6.64 and a reliability of .98 (55).

Sense of coherence

Measured using the Sense of Coherence (SOC-13) questionnaire by Antonovsky (56). It values the personal disposition towards the assessment of vital experiences. It measures the sense of

coherence, comprehensibility, manageability and meaningfulness. It has 13 items scoring between 13 and 91 points. It has consistency rates of between .84 and .93. Higher scores (after reversal of the inverted items) indicate a higher sense of coherence. We will use the validated Spanish version (57).

Health Literacy

Measured using the Health Literacy Europe Questionnaire (HLS-EUQ16) (58). It can indicate that the probability of functional literacy in limited health is high, a possibility of functional literacy in limited health, and a functional health literacy in adequate health. It contains 16 items. Higher scores indicate better health literacy. It presents a high consistency (Cronbach's alpha of .982) in the Spanish validation (59).

Procrastination

Measured using the Irrational Procrastination Scale (IPS) (60). To measure general procrastination (dysfunctional delay). It has 9 items, rated on a 5-point Likert scale, with higher scores (after reversal of the three procrastination-inconsistent items) indicating a higher level of procrastination. Its Cronbach's alpha value is 0.90. We will use the validated Spanish version (61).

Data analysis plan

Analysis of the outcomes at baseline

First, descriptive analyses of all the variables (proportions for qualitative variables; means and standard deviation for quantitative variables) will be performed. Then, correlation analysis will be carried out between the questionnaires that evaluate personal factors on health behavior (Self-Efficacy Scale, PAM, SOC-13, HLS-EUQ16 and IPS), social support (MOS-SS) and depression (BDI-II). We will also analyze the correlation between personal factors on health behavior and the questionnaires assessing lifestyle patterns (IPAQ-SF, MEDAS and PSQI). Finally, we will analyze the relation of lifestyle patterns and social support with depression. Inferential statistical analysis will be carried out using the Chi-square test for qualitative variables, and Student's t-test or one-way ANOVA test to assess the potential relationship between qualitative and quantitative variables.

Data collection and statistical analysis will be performed using Excel software, SPSS software (version 25.0) (68) and the R statistical software environment (version 3.6.2) (69).

Clinical effectiveness analysis

The report of the results will follow a pre-specified plan, based on the CONSORT guidelines (70) in order to compare the three groups using an intention-to-treat analysis (ITT) and Multiple Imputation technique (MI) for handling missing data. Initially a descriptive comparison (proportions, means or medians) will be carried out between groups for prognostic variables in order to establish their baseline comparability after randomization. To analyze the clinical effectiveness, a repeated-measure linear regression will be conducted, including all evaluations over time. For this purpose, the main variable, BDI-II score, will be used as a continuous variable. The models will include adjustments for the baseline value of the BDI-II and for any other variable that would have shown differences in the baseline measurement. Possible Group per Time interactions will be examined using linear regression. Similar analyses will be carried out using the secondary outcomes (personal factors on health

behavior and assessment of lifestyle). To counteract the problem of multiple comparisons we will use Bonferroni correction.

Comparisons will also be made between the LMP and LMP + ICTs groups regarding adherence to lifestyle modification requirements. Adherence will be considered as a good or beneficial score on the questionnaires assessing lifestyle patterns (IPAQ-SF, MEDAS and PSQI). In addition, we will compare the LMP and combined LMP+ICTs groups, assuming that they are comparable to each other and the two groups have significant results.

A binary variable regarding comorbidity will be created (comorbidity yes/no). We will determine if the effectiveness of the intervention differs in the subgroup presenting comorbidity and if the pathology improves. Statistical analyses will be selected based on subsample size (parametric or non-parametric tests).

As for the time-point in which we administrate the follow-up questionnaires, we will consider the first follow up assessment (in a period of 2 to 7 days after the last session of the intervention) as the more relevant. We expect to find an immediate effect in the LMP and LMP+ICTs groups after attending group intervention, due to the potential social support received. In the 6 and 12-month follow-up, we expect a beneficial change in the questionnaires assessing lifestyle, reflecting a long-lasting effect.

Cost-effectiveness and cost-utility analysis

The effectiveness of the interventions will be estimated using the difference between the BDI-II baseline score and the score at the 6 and 12-month follow-ups, and utility will be estimated using QALYs at the 6 and 12-month follow-ups. QALYs will be calculated based on these scores using the Spanish EQ-5D tariffs (71). Along with the EQ-5D utility scores, scores recorded on the EQ VAS will also be used as an outcome for the analysis.

Cost effectiveness will be explored through the calculation of incremental cost-effectiveness ratios (ICERs) for the active intervention groups (LMP and LMP+ICTs) using the TAU group as the control. ICER is defined as the ratio between incremental costs and incremental effectiveness. In this way, cost utility will be explored by calculating incremental cost-utility ratios (ICURs), which are defined as the ratio between incremental costs and incremental utilities measured on QALYs. QALYs gained in each evaluation are approximated using the area under-the-curve technique (72).

Total costs will be calculated by adding direct and indirect costs. Direct costs will be calculated by adding the costs derived from the medication and the use of health services and clinical tests. The medication costs will be calculated by determining the price per milligram during the study period according to the Vademecum of the last year of study, including value-added tax (VAT). The total cost of drug treatment will be calculated by multiplying the price per milligram by the daily dose in milligrams and the number of days the treatment is received. Costs derived from the use of health services will be calculated considering the data from the Oblikue database (73). Indirect costs will be calculated based on the sick leave days and multiplying them by the Spanish minimum daily wage during the study period, 2019-2020.

We assume that data will be missing at random (MAR). Only patients with both cost and relevant outcome data at the 6 and 12-month follow-ups will be included in the cost-effectiveness and cost-utility analyses. Notwithstanding this, sensitivity analysis imputing missing 6 and 12-month

data will test the robustness of cost-effectiveness and cost-utility results. The imputations will be performed using the "mice" package (74), freely available in cran-R (69).

Discussion

Depression is a significant cause of morbidity having low detection and treatment rates in primary care (75,76). Only 9% of all depressed primary care patients receive adequate treatment, and only 6% achieve remission, making depression an important management issue in primary care (77). An effective treatment for depression that can be implemented in PHCs is brief psychotherapy (6 to 8 sessions programs), which have the advantage of being performed by either mental health professionals or trained non-mental health providers (78). In this case, the promotion of healthy lifestyles will be used to address depressive symptoms, as it has shown efficacy in a number of studies (20–31). To ensure treatment adherence, facilitators should be used, such as the use of ICTs and the group format. They provide monitoring and social support, respectively (33). Organizing group therapies in PHCs generates a range of organizational benefits, in relation to efficient use of facilities, high therapist-to patient ratios and potential reductions to treatment wait-times (79). Moreover, participants are just as likely to engage in group treatment as individual work and the benefits are also maintained over time (80).

The strengths of this study include the design and the wide range of outcome measures. It will provide a wealth of information on the interplay between depression, personal factors on health behavior and lifestyles. Study limitations include the possible attrition of participants due to session scheduling or participant refusal to participate in a group intervention or do the complete follow-ups (81). However, the possible reasons for attrition and other issues will be registered regarding MAGI framework (38).

Therefore, the creation of a 6-session group program addressing lifestyle modifications (plus testing the monitoring with ICTs by adding a smartwatch to one of the intervention group) appears to be a good choice for depression treatment. The long-term aim of this study is to establish intervention for patients with depression, making it accessible in their PHCs, effective and cost-effective.

Execution dates

Initial recruitment of patients: April 2020.

Finalization of patient recruitment: May 2020.

Finalization of patient monitoring period: June 2021.

Publication of results: July 2021.

Partial Patient and Public Involvement: PPI representatives worked with us to refine the research question; however, it was difficult to involve patients in other areas of the study design due to data protection restrictions and the very technical methods required to do a data linkage analysis. PPI representatives will write a plain language summary and design a leaflet for dissemination to their peers and distributing to patient groups.

Ethics approval: Ethics approval was granted by the Research Ethics Committee of Aragón (CEICA, PI18/286) and the Research Ethics Committee of the Balearic Islands (IB3950/19 PI). The study has been developed in accordance with the Helsinki Declaration. All of the subjects will sign an informed consent form, their data will be anonymized and will only be used for the purposes of the study. Participants and healthcare professionals will be informed about the

results. Patients of the TAU group will be invited to participate in the LMP at the end of the study. The Ethics Committee will be notified of any protocol modifications.

Authors' contributions: BOB, MJSR and MGT led the design and developed the study and had the original idea. RMB, MJSR, CN and BOB coordinated the fieldwork. AAL and CCV undertook the fieldwork. AAL, BOB, EG and SBS wrote the first draft of the article. The rest of the signing authors have read the manuscript critically, offering contributions and approving the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: None.

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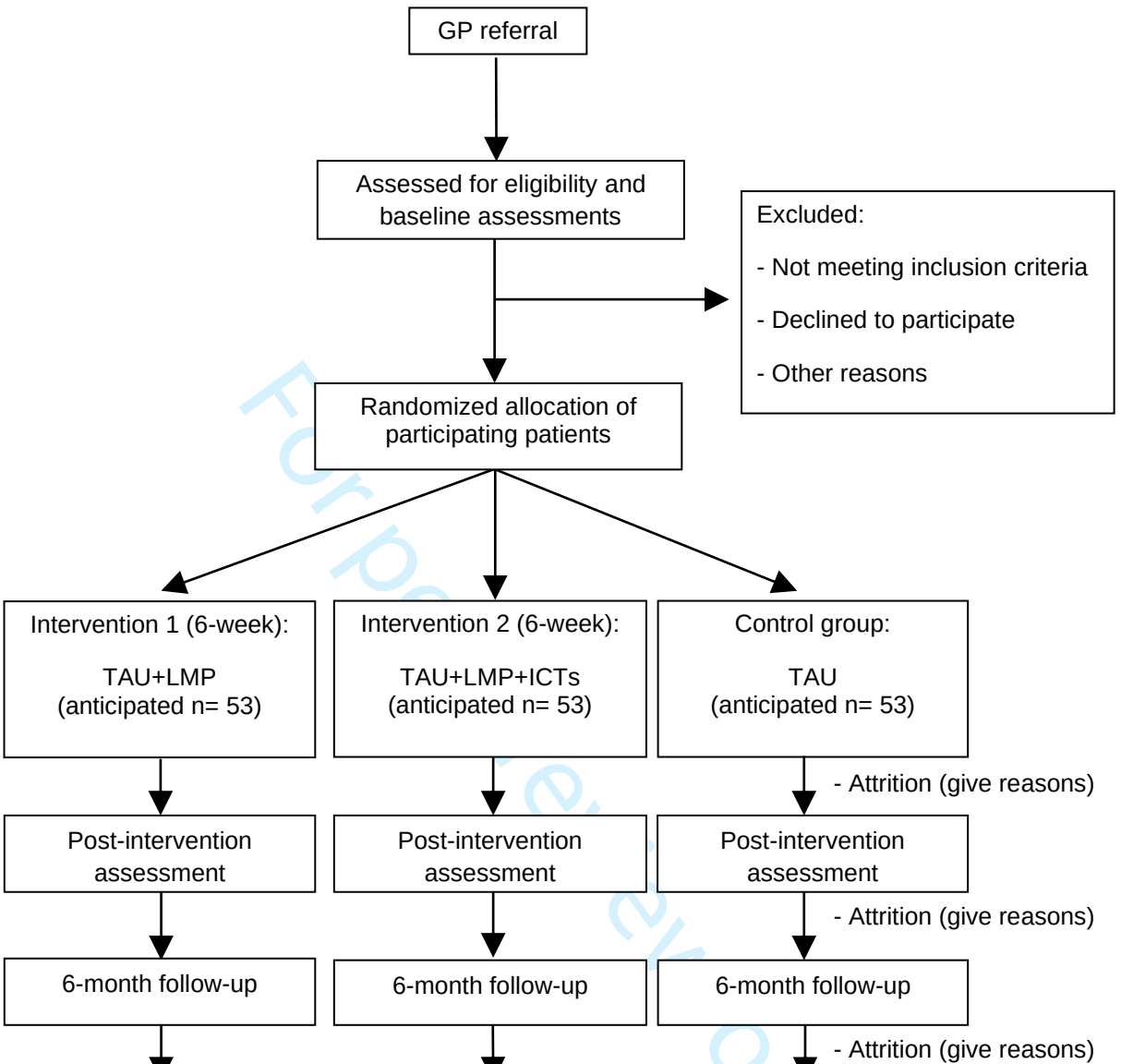
Figure 1: Flowchart of the study: randomization, sampling and monitoring of patients

GP, General Practitioner; TAU, Treatment as Usual; LMP, Lifestyle Modification Program; ICTs, Information and Communication Technologies; MI, Multiple Imputation.

Figure 1: Flowchart of the study: randomization, sampling and monitoring of patients.



GP, General Practitioner; TAU, Treatment as Usual; LMP, Lifestyle Modification Program; ICTs, Information and Communication Technologies; MI, Multiple Imputation.

DOCUMENTO DE INFORMACIÓN PARA EL PARTICIPANTE

Título de la investigación: Efectividad y coste-utilidad de un programa de Estilo de Vida Mediterráneo en la prevención y tratamiento de la depresión subclínica, leve y moderada en Atención Primaria.

Promotor: Instituto de Salud Carlos III (Ministerio de Economía y Competitividad)

Investigador Principal: Bárbara Oliván Tfno: 976 761000 ext4547

Centro: Universidad de Zaragoza

1. Introducción:

Nos dirigimos a usted para invitarle a participar en un proyecto de investigación que estamos realizando en Aragón y Mallorca, específicamente en Zaragoza, en los centros de salud de "Fuentes Norte", "Parque Goya" y "Arrabal", y en Mallorca, en los centros de salud de "Son Cladera", "Son Serra-La Vileta" y "Valldargent". Su participación es importante para obtener el conocimiento que necesitamos, pero antes de tomar una decisión debe:

- Leer este documento entero
- Entender la información que contiene el documento
- Hacer todas las preguntas que considere necesarias
- Consultar con su médico-persona de confianza
- Tomar una decisión meditada
- Firmar el consentimiento informado, si finalmente desea participar.

Si decide participar se le entregará una copia de este documento y del consentimiento firmado. Por favor, consérvelos por si lo necesitara en un futuro.

2. ¿Por qué se le pide participar?

Se le solicita su colaboración porque usted cumple los que criterios de inclusión en el estudio, que son: ser mayor de 18 años, padecer una depresión subclínica, leve o moderada con una duración de al menos dos meses.

En total en el estudio participarán 340 pacientes de estas características.

3. ¿Cuál es el objeto de este estudio?

El objetivo de este estudio es analizar si un tratamiento grupal sobre modificación de estilo de vida, sumando al tratamiento habitual prescrito por su médico de familia es eficaz en el tratamiento de su depresión.

4. ¿Qué tengo que hacer si decido participar?

Recuerde que su participación es voluntaria y si decide no participar esto no afectará a su asistencia o a su relación con el investigador y su equipo.

Si decide entrar en el estudio, su participación consistirá en la cumplimentación de un cuaderno de recogida de datos sobre su depresión, otras enfermedades que padezca (además de recoger talla, peso y tensión arterial), calidad de vida, si realiza la modificación de estilos de vida (realiza ejercicio, dieta que lleva, higiene del sueño, y apoyo social) y variables que influyen en realizar esta modificación de estilos de vida. Cumplimentar este cuestionario le costará aproximadamente entre cuarenta y cincuenta minutos. El primero que cumplimente será un poco más largo, ya que tenemos que comprobar que cumple los criterios para ser incluida en el estudio.

Posteriormente a esta primera evaluación, se le asignará de manera aleatoria, es decir, por azar, como si se lanzara una moneda al aire, a un grupo de tratamiento, que puede ser: un tratamiento grupal de 6 semanas de duración, con una sesión semanal de hora y media sobre modificación de estilos de vida; un tratamiento grupal igual que el anterior pero se le facilitará algún dispositivo para monitorizar su actividad física y horas de sueño; y grupo control, que no se le asignará a ningún tratamiento a parte del prescrito por su médico de familia. Estos tratamientos grupales consistirán en 6 sesiones y se harán una por semana. En estas sesiones se abordará el estilo de vida mediterráneo, es decir, explicaremos temas como la importancia de la dieta mediterránea, y que es recomendable comer, la importancia del ejercicio físico y cómo se debe realizar, de la exposición a la luz, de la higiene del sueño, de la activación conductual y social, para poder vencer la apatía, etc. Estas sesiones se desarrollarán en su centro de salud. Al principio de cada sesión, se tratará la cumplimentación y las dificultades de llevar a cabo el tema tratado en la sesión anterior durante 10-15 minutos. El audio de esta valoración será grabado para su posterior transcripción y análisis. Estas grabaciones serán guardadas por la investigadora principal (en su equipo informático) y no tendrá nadie más acceso a las mismas hasta su transcripción, momento en el cual serán destruidas. En dicha trascripción no se identificará a los/as autores/as de los contenidos y no serán utilizadas exclusivamente para analizar la cumplimentación y las dificultades encontradas en la modificación de estilos de vida.

En caso de que fuera asignado a este último, al finalizar el estudio, en caso de que los resultados lo aconsejaran, se le ofertará la posibilidad de realizar el tratamiento grupal sobre modificación de estilos de vida.

Posteriormente a esta intervención, se le realizará otra evaluación, así como a los 6 meses y al año de haber finalizado. La duración de estas evaluaciones tendrá una duración aproximada de media hora.

Se revisará su historia clínica en caso de que tenga alguna otra enfermedad como diabetes, insuficiencia cardiaca o hipercolesterolemia, para recoger valores de estas enfermedades en el último análisis de sangre que su médico de familia le haya realizado.

5. ¿Qué riesgos o molestias supone?

Tanto por la evaluación como por la intervención que se va a desarrollar en este estudio, usted no tiene ningún riesgo ni debería tener ninguna molestia. Los cuestionarios que se van a utilizar no implican ninguna prueba invasiva ni dolorosa, son cuestionarios ampliamente utilizados en investigación y en la práctica clínica. Tanto la evaluación como la intervención que se va a desarrollar va a estar dirigida por personal cualificado (psicólogos/as).

Si se detecta que usted está empeorando gravemente en su estado de depresión, se contactará con su médico de familia.

6. ¿Obtendré algún beneficio por mi participación?

Al tratarse de un estudio de investigación orientado a generar conocimiento es probable que no obtenga ningún beneficio por su participación si bien usted contribuirá al avance del conocimiento y al beneficio social. Usted no recibirá ninguna compensación económica por su participación.

7. ¿Cómo se van a gestionar mis datos personales?

Toda la información recogida se tratará conforme a lo establecido en la legislación vigente en materia de protección de datos de carácter personal. En la base de datos del estudio no se incluirán datos personales: ni su nombre, ni su nº de historia clínica ni ningún dato que le pueda identificar. Se le identificará por un código que sólo el equipo investigador podrá relacionar con su nombre.

Sólo el equipo investigador tendrá acceso a los datos de su historia clínica y nadie ajeno al centro podrá consultar su historial. En caso de que se necesite este acceso se debe especificar quién, con qué fin, durante qué periodo de tiempo, qué datos se van a revisar y solicitar consentimiento expreso para este acceso.

De acuerdo a lo que establece la legislación de protección de datos, usted puede ejercer los derechos de acceso, modificación, oposición y cancelación de datos. Además puede limitar el tratamiento de datos que sean incorrectos, solicitar una copia o que se trasladen a un tercero (portabilidad) los datos que usted ha facilitado para el estudio. Para ejercitar sus derechos, diríjase al investigador principal del estudio. Así mismo tiene derecho a dirigirse a la Agencia de Protección de Datos si no quedara satisfecho.

Si usted decide retirar el consentimiento para participar en este estudio, ningún dato nuevo será añadido a la base de datos, pero sí se utilizarán los que ya se hayan recogido. En caso de que desee que se destruyan tanto los datos como las muestras ya recogidos debe solicitarlo expresamente y se atenderá a su solicitud.

Los datos codificados pueden ser transmitidos a terceros y a otros países pero en ningún caso contendrán información que le pueda identificar directamente, como nombre y apellidos, iniciales, dirección, nº de la seguridad social, etc. En el caso de que se produzca esta cesión, será para los mismos fines del estudio descrito o para su uso en publicaciones científicas pero siempre manteniendo la confidencialidad de los mismos de acuerdo a la legislación vigente.

El promotor/investigador adoptará las medidas pertinentes para garantizar la protección de su privacidad y no permitirá que sus datos se crucen con otras bases de datos que pudieran permitir su identificación o que se utilicen para fines ajenos a los objetivos de esta investigación.

Las conclusiones del estudio se presentarán en congresos y publicaciones científicas pero se harán siempre con datos agrupados y nunca se divulgará nada que le pueda identificar.

9. ¿Quién financia el estudio?

Este proyecto se financia con fondos procedentes del Instituto de Salud Carlos III, perteneciente al Ministerio de Economía y Competitividad.

El conocimiento derivado de este estudio no es probable que genere en un futuro beneficios comerciales. No obstante, en caso de que generase estos beneficios, pertenecerían al equipo investigador. Los participantes no tendrán derecho a reclamar parte de ese beneficio.

10. ¿Se me informará de los resultados del estudio?

Usted tiene derecho a conocer los resultados del presente estudio, tanto los resultados generales como los derivados de sus datos específicos. También tiene derecho a no conocer dichos resultados si así lo desea. Por este motivo en el documento de consentimiento informado le preguntaremos qué opción prefiere. En caso de que desee conocer los resultados, el investigador le hará llegar los resultados.

¿Puedo cambiar de opinión?

Tal como se ha señalado, su participación es totalmente voluntaria, puede decidir no participar o retirarse del estudio en cualquier momento sin tener que dar explicaciones y sin que esto repercuta en su atención sanitaria. Basta con que le manifieste su intención al investigador principal del estudio.

Si usted desea retirarse del estudio se eliminarán los datos recogidos.

¿Qué pasa si me surge alguna duda durante mi participación?

En caso de duda o para cualquier consulta relacionada con su participación puede ponerse en contacto con el investigador responsable, Dña. Bárbara Oliván, en el teléfono 976 761000 ext 4547 en horario de mañanas o por correo electrónico en la dirección bolivan@unizar.es.

Muchas gracias por su atención, si finalmente desea participar le rogamos que firme el documento de consentimiento que se adjunta.

DOCUMENTO DE CONSENTIMIENTO INFORMADO

Título del PROYECTO: Efectividad y coste-utilidad de un programa de Estilo de Vida Mediterráneo en la prevención y tratamiento de la depresión subclínica, leve y moderada en Atención Primaria.

Yo, ... (nombre y apellidos del participante)

He leído el documento de información que se me ha entregado.

He podido hacer preguntas sobre el estudio y he recibido suficiente información sobre el mismo.

He hablado con: .....(nombre del investigador)

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:

1) cuando quiera
2) sin tener que dar explicaciones
3) sin que esto repercuta en mis cuidados médicos

Presto libremente mi conformidad para participar en el estudio.

Deseo ser informado sobre los resultados del estudio: sí no (marque lo que proceda)

Doy mi conformidad para que mis datos clínicos sean revisados por personal ajeno al centro, para los fines del estudio, y soy consciente de que este consentimiento es revocable.

He recibido una copia firmada de este Consentimiento Informado.

Firma del participante: .....

Fecha: .....

He explicado la naturaleza y el propósito del estudio al paciente mencionado

Firma del Investigador: .....

Fecha:

$$n = \frac{(z_\alpha + z_{2\beta})^2 \sigma_d^2}{(\Delta m)^2}$$

$\Delta m = 4.8$

α=0.05

β= 0.20

$z_\alpha = 1.96$

$z_{2\beta} = 1.28$

$\sigma_d^2 = 96.04$

SLEEP DURATION AND SUNLIGHT

Day	Time to get up and go to bed	Sleep duration (hours)	Sunlight exposure (in minutes)
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

SLEEP DURATION AND SUNLIGHT

Day	Time to get up and go to bed	Sleep duration (hours)	Sunlight exposure (in minutes)
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

PHYSICAL ACTIVITY

Day	Activity	Sport	Duration (min)	Company	How do I feel next?
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

SLEEP DURATION AND SUNLIGHT

Day	Time to get up and go to bed	Sleep duration (hours)	Sunlight exposure (in minutes)
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

PHYSICAL ACTIVITY

Day	Activity	Sport	Duration (min)	Company	How do I feel next?
Monday					
Tuesday					
Wednesday					
Thursday					
Friday					
Saturday					
Sunday					

MEDITERRANEAN DIET

Day	Breakfast	Snack	Appetizer	Lunch	Snack	Dinner
Monday						
Tuesday						
Wednesday						
Thursday						
Friday						
Saturday						
Sunday						

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3-14
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page
	5b	Name and contact information for the trial sponsor	14
	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	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	7
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	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	4-5

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, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
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
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)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	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)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-11
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)	7-8
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was	6

		determined, including clinical and statistical assumptions supporting any sample size calculations	
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6-7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection methods	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	7-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants	7

		who discontinue or deviate from intervention protocols	
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	7
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11-13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7 & 13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility	14

		criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6-7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	7 & 14
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
	31b	Authorship eligibility guidelines and any intended use of professional writers	14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Material 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.