



BMJ Open Implementation, efficacy and cost effectiveness of the unified protocol in a blended format for the transdiagnostic treatment of emotional disorders: a study protocol for a multicentre, randomised, superiority controlled trial in the Spanish National Health System

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ABSTRACT

Introduction Emotional disorders (EDs) have become the most prevalent psychological disorders in the general population, which has boosted the economic burden associated with their management. Approximately half of the individuals do not receive adequate treatment. Consequently, finding solutions to deliver cost-effective treatments for EDs has become a key goal of today's clinical psychology. Blended treatments, a combination of face-to-face and online interventions, have emerged as a potential solution to the previous. The Unified Protocol for the Transdiagnostic Treatment of EDs (UP) might serve this purpose, as it can be applied to a variety of disorders simultaneously and its manualised format makes it suitable for blended interventions.

Methods and analysis The study is a multicentre, randomised, superiority, clinical trial. Participants will be 310 individuals with a diagnosis of an ED. They will be randomised to a treatment as usual (individual cognitive behavioural therapy) or a UP condition in a blended format (face-to-face individual UP +online, app-based UP). Primary outcomes will be ED diagnostic criteria and depression and anxiety symptoms. Cost efficiency of the intervention, app usability, as well as opinion and confidence in the treatment will also be evaluated. Assessment points will include baseline and 3 months, 6 months and 12 months after UP treatment.

Ethics and dissemination The study has received approvals by the Ethics Research Committee of Navarra, Castellón, Euskadi, Castilla y León, Extremadura, Lleida and Aragón. The study is currently under an approval process by the Ethics Research Committees of all the remaining collaborating centres. Outcomes will be disseminated through publication in peer-reviewed journals and presentations at international conference meetings.

Trial registration number NCT04304911.

Strengths and limitations of this study

- This study is the first randomised controlled trial to test the efficacy, implementation and cost effectiveness of a transdiagnostic intervention in a blended format for the treatment of emotional disorders (EDs) in public settings in Spain.
- The blended Unified Protocol for the Transdiagnostic Treatment of EDs (UP) may allow clinicians to use the same treatment for the most prevalent psychological disorders, that is, EDs.
- The blended UP can enable clinicians to use technology to motivate, monitor, give support and provide treatment to patients without losing the benefits of individual face-to-face treatments.
- A UP-based treatment programme in a blended format might help reduce dropouts and waiting lists because it allows clients to take advantage of the time between sessions, which might help them progress and engage with their treatments and, therefore, improve earlier and be discharged sooner.
- One limitation could be that some people may be resistant to participate in the blended condition because they perceive it as more impersonal and less effective.

INTRODUCTION

Emotional disorders (EDs; ie, anxiety disorders, unipolar mood disorders and related disorders)¹ are the most prevalent mental disorders in the general population.² In Spain, anxiety disorders and mood disorders affect approximately two million (4.1%) and two and half million (5.2%) individuals, respectively.³ These disorders have a direct cost of €22 000 million (€500 per capita and year) and the total expense of these disorders

entails 2.2% of the gross domestic product in Spain.⁴ Due to the excessive demand for treatment, mental health services of our National Health System (NHS) are overwhelmed with large waiting lists, which results in a great difficulty to dedicate the recommended time to attend patients who require psychological treatment.^{4 5} Therefore, there is an urgent need to find cost-effective solutions for the treatment of EDs in our NHS.

The Unified Protocol (UP)^{6 7} is a structured, manualised transdiagnostic intervention for the treatment of EDs based on cognitive behavioural therapy (CBT). The UP aims to treat emotion regulation deficits, which are argued to be the underlying common factor in all EDs.⁸ By focusing on these common mechanisms, the UP offers numerous advantages. For example, it allows the simultaneous treatment of people with different EDs and comorbid presentations with a single protocol⁹ and reduces the costs associated with training mental health professionals.¹⁰ To date, three systematic reviews, which include two meta-analyses, have been conducted to summarise the efficacy of the UP. Overall, these studies reveal that the UP significantly improves anxious and depressive symptoms with moderate to large effect sizes. Additionally, the improvements appear to be maintained over time (up to 3 months and 6 months of follow-up).^{11–13} In Spain, a previous clinical trial conducted in the NHS showed that the UP in a group format, compared with treatment as usual (TAU), achieved significantly larger improvements in anxious and depressive symptoms, as well as in quality of life at 6-month follow-up.¹⁴

The preferred intervention format by patients with EDs attending the Spanish NHS is individual, face-to-face treatment (85.4%), followed by group (14.2%) and online interventions (0.4%).¹⁵ These results justify that blended treatments, which use online treatments but maintain some form of individual, face-to-face intervention, could be a potential solution to the availability problems of treatments for EDs in our Spanish NHS. The advantage of blended treatments is that they are dynamic and flexible and they allow using technology to motivate, monitor, give support and treat patients. Importantly, this is done without losing face-to-face treatment sessions.^{16 17} Research has shown that blended interventions are more effective than face-to-face treatments in the reduction of depression and anxiety symptoms.¹⁸ For example, one study found that a blended smartphone treatment, which consisted of four face-to-face sessions and a smartphone app to be used between the sessions, can be as effective as a full behavioural activation treatment in the reduction of major depression. Moreover, comparable scores were also obtained between the two conditions for treatment credibility and working alliance, and therapist time was reduced by an average of 47% in the blended condition.¹⁹ Finally, a recent meta-analysis has also revealed optimistic results regarding the power of blended interventions, given that they allow saving time to the clinicians, in addition to decreasing dropouts and enhancing the maintenance of the benefits obtained with treatment over time.²⁰

The present study will compare the efficacy and cost efficiency of the UP in a blended format against traditional, individual, unstructured CBT in a sample of patients with EDs. All the participants will seek treatment at the Spanish NHS. To ensure the generalisability of the results, our outcomes will be evaluated in several public mental health centres in Spain.

METHODS AND ANALYSIS

Study protocol

The current study is a superiority, multicentre, randomised controlled trial (RCT) with two active conditions: the UP in a blended format (individual UP face to face and UP-APP for smartphone) and non-structured CBT in an individual format (TAU). The study is planned to start in January 2022 and end in December 2024.

The expected superiority comes from the fact that the participants in the blended condition will receive additional treatment compared with the TAU condition, which should enhance the benefits of the TAU. In the present investigation, all consecutive patients with EDs attending any of the collaborating centres (see the Sample and recruitment section) will be asked to participate. It is important to note that this is a feasibility study in which the context and usual procedures of ED management will be kept as naturalistic as possible for implementation purposes. This means that there are some study characteristics that should be bared in mind. For example, some variables will not be predetermined and will only be known at the end of the investigation. This includes, for example, the frequency of the psychological appointments in both conditions (which will vary depending on the patient's evolution and clinician appraisals) or the time spent in the UP-APP by participants in the blended condition (ie, amount of progress in the treatment modules and exercises). These variables, which might influence on outcomes, will of course be considered in the statistical analysis when the information is available (at the end of the study).

The study was registered on clinicaltrials.gov. The flow chart of the study design is shown in [figure 1](#). A schedule of the enrolment, interventions and assessments is reported following the Standard Protocol Items: Recommendations for Interventional Trials guidelines ([table 1](#)).

Sample size

To calculate the required sample size, we used the G*Power software.²¹ We obtained a sample size of 129 participants per condition with a 95% power, an α of 0.01 and a conservative effect size of 0.30. Considering a dropout rate of 15% and 5% of candidates who will not meet inclusion criteria, we will recruit at least 155 participants per condition (N=310). The expected effect size and dropout rates come from studies showing that blended interventions lead to lower dropout rates²⁰ and better outcomes in patients with anxiety and adjustment disorder¹⁸ when compared with face-to-face interventions.

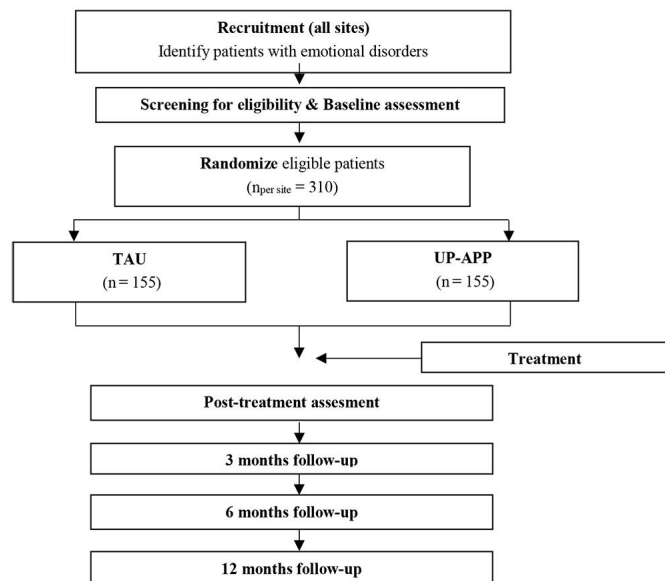


Figure 1 Study flow chart. TAU, treatment as usual; UP, the Unified Protocol for the Transdiagnostic Treatment of Emotional Disorders.

Procedure

UP-APP design (patient and public involvement)

Prior to the design of the UP-APP, our team will conduct two different focus groups, one with patients who already received the UP for their EDs diagnosis and other with therapists trained in the UP intervention. Information about structure, content, format, design, exercises, language, duration, evaluation, feedback, security, adherence, usability and customisation will be collected in the focus groups. Besides, their opinion about the use of apps and technological devices in clinical psychology and advantages and disadvantages of face-to-face therapy and app-based therapy will be also collected. Some researchers of the study and the engineer's team will participate in these focus groups as observers. The focus groups will be recorded on video to be transcribed by two researchers of the study. The qualitative analysis of the data collected will be used to design the UP-APP for smartphone. This analysis will consist of generating a system of codes, grouping the information provided by the participants in the focus groups that referred to the same ideas or highlighting the main ideas.

Sample and recruitment

Participants are individuals over 18 years old, seeking psychological assistance in the Spanish Public Health System. Patients are referred to the study by licensed psychologists, psychiatrists and clinical psychology residents working at the collaborating centres. Mental health professionals (therapists and psychiatrists from the units to which patients are referred to and who want to collaborate in the study) will be responsible for assessing the current Diagnostic and Statistical Manual (DSM) diagnoses (see the Measures section) and the remaining eligibility criteria (see the Eligibility criteria section).

Individuals with comorbid diagnosis of several EDs are also enrolled in the study.

Recruitment is expected to start in January 2022. The study will be conducted in 15 different mental health centres of the Spanish NHS, namely, USM Sagasta (Zaragoza), H. Comarcal de Vinaròs (Castellón), Centro San Francisco Javier (Navarra), USM La Milagrosa (Pamplona), Hospital Universitario Reina Sofía de Córdoba, CSM Eguia-Donostia, H. U. de Alicante, CSM del Segrià en Lleida, USM La Fuente de San Luís (Valencia), USM Montoro de Córdoba, H. U. Río Hortega (Valladolid), CSM Mérida, CSM Zafra, USM Fraga, and USM Tarazona.

Eligibility criteria

Inclusion and exclusion criteria are listed in [table 2](#).

Patients with unspecified anxiety disorders and unspecified depressive disorders will also be included as they are frequent in public settings.

Randomisation

All consecutive patients with a diagnosis of an ED attending any of the collaborating centres will be asked to participate in the present study. Once the inclusion criteria are met, every patient will be randomly assigned to one of the two experimental conditions: TAU or UP in a blended format. Patients who refuse to participate in the study will receive the TAU outside the RCT. The number of people refusing to participate and the reasons for that decision will be recorded and reported due its interest for future studies. Randomisation will be performed by a researcher unrelated to the study using a computer-generated sequence (Randomizer). Randomisation will be stratified according to the severity of the primary measures of depression and anxiety, using the cut-off reported in Spanish clinical samples of ED, which has been 10 (0–20) in both scales.²² This cut-off differentiates patients with moderate–severe symptoms from those with moderate–low symptoms.

Stratification will be made to ensure a comparable proportion of severely depressed and anxious individuals in each group. For each subgroup (ie, severe or less severe depression and/or anxiety), participants will be randomly assigned to the UP in a blended format or to the TAU.

Therapists and interventions

Participants in both conditions will receive the individual therapy in a face-to-face format. Individuals with an ED also frequently receive pharmacological treatment (ie, antidepressants and/or anxiolytics) as treatment of choice in the Spanish NHS. The frequency of the appointment sessions with their clinicians will depend on the characteristics of their centres (eg, existing waiting lists and availability of the clinicians). In addition to these individual face-to-face appointments, participants randomised to the blended condition will be able to use the UP-APP at any time and at whatever pace during the whole duration of the study. Clinicians



Table 1 Study schedule of enrolment, interventions and assessments

Study period							
Time point	Enrolment -t1	Preallocation t ₀ Baseline	Allocation t ₁	Intervention t ₂	Postallocation t ₃ 3 months after the intervention	t ₄ 6 months after the intervention	t ₅ 12 months after the intervention
Enrolment							
Eligibility screen	X						
MINI	X				X	X	X
Informed consent							
Allocation		X					
ODSIS		X		X	X	X	X
OASIS		X		X	X	X	X
Interventions							
TAU				↔			
UP in a blended format							
				↔			
OTHER ASSESSMENTS:							
Demographics		X					
MEDI		X			X	X	X
EuroQoL-5D		X			X	X	X
FFMQ		X			X	X	X
BEAQ		X			X	X	X
DERS		X			X	X	X
ERQ		X			X	X	X
SUS					X	X	X
CEQ					X	X	X
CSRI					X	X	X
TOS					X	X	X
WAI-S				X			
QALYs		X			X	X	X

BEAQ, Brief Experiential Avoidance Questionnaire; CEQ, Credibility/Expectancy Questionnaire; CSRI, Client Service Receipt Inventory; DERS, Difficulties in Emotion Regulation Scale; ERQ, Emotion Regulation Questionnaire; FFMQ, Five Factor Mindfulness Questionnaire; MEDI, Multidimensional Emotional Disorder Inventory; MINI, Mini International Neuropsychiatric Interview; OASIS, Overall Anxiety Severity and Impairment Scale; ODSIS, Overall Depression Severity and Impairment Scale; QALYs, quality-adjusted life years; SUS, System Usability Scale; TAU, treatment as usual; TOS, Treatment Opinion Scale; UP, Unified Protocol for Transdiagnostic Treatment of Emotional Disorders; WAI-S, Working Alliance Inventory-Short.

Table 2 Eligibility criteria

Inclusion criteria	
1	Principal diagnosis of an emotional disorder*
2	The patient is over 18 years of age
3	The patient is fluent in the language in which the therapy is performed (Spanish in the present study)
4	The patient has a smartphone (regardless of the condition, to ensure that the TAU condition does not include more patients that do not have access to a smartphone)
5	Patients taking pharmacological treatment for their ED will be asked to maintain the same dosages and medications for at least 3 months prior to enrolling in the study and during the whole treatment†
6	The patient signs the informed consent form (online supplemental file)
Exclusion criteria	
1	The patient presents a severe condition that would require them to be prioritised for treatment. This includes a severe mental disorder (bipolar disorder, personality disorder, schizophrenia or organic mental disorder), suicide risk at the time of assessment or substance use in the last 3 months
2	The patient has previously received 8 or more sessions of psychological treatment with clear and identifiable CBT principles within the past 5 years

*The following disorders will be included based on diagnostic and statistical manual 5th ed. (DSM-5)² diagnostic criteria: major depression disorder, dysthymic disorder, panic disorder, agoraphobia, obsessive-compulsive disorder, generalised anxiety disorder, posttraumatic stress disorder, social anxiety disorder, hypochondria and adjustment disorders.

†If medication stability is not possible, the participant's data will be treated separately in the analyses.

CBT, cognitive behavioral therapy; TAU, treatment as usual.

will recommend participants in the blended condition to work on modules 1, 2, 5, 6 and 8 during at least 1 week, and modules 3, 4 and 7 during at least 2 weeks (see the Unified Protocol in a blended format section for a detail on the titles of the UP modules).

The relatively naturalistic nature of this study prevents us from defining, prior to the intervention, the exact number of sessions and the time spent in each psychological intervention (TAU vs UP blended). This also applies to the time spent by the participants in the UP-blended condition with the UP-APP. All these variables will be recorded by the UP-APP and the clinicians attending the participants for their inclusion in the statistical analyses.

Previous to start the RCT, we will conduct an open pilot study to analyse the preliminary data of the clinical utility and feasibility of the UP-APP in a small sample of patients with EDs diagnosis. Specifically, after the clinical assessment, from those who met the inclusion and exclusion criteria, we will invite 10 patients (in order of date of receipt) to participate voluntarily in this pilot study. Participants will sign the informed consent and data protection. Then, they will be randomised to one baseline condition: 1 week, 2 weeks and 3 weeks in order of date of receipt (baseline measures will be Overall Depression Severity and Impairment Scale (ODSIS) and Overall Anxiety Severity and Impairment Scale (OASIS)²²). Then patients will receive a face-to-face psychological treatment in a blended format and will receive the instructions to download the UP-APP in their smartphone. They will be asked to complete a special set of questions to assess

the comprehension, appearance, utility, interest, if they would recommend it to other people, usability, intention to use in the future and satisfaction of the content of each module of the UP-APP (ad hoc).

For ethical reasons, if a patient feels uncomfortable with the blended format at any time during the study, they will receive the TAU outside the RCT.

Therapists participating in the study will include licensed psychologists with 8–20 years of experience in delivering CBT.

Unified Protocol in a blended format

For face-to-face interventions, the clinicians in this condition will follow the second edition of the UP therapist manual translated by Osma and Crespo into Spanish.^{23 24}

As described in detail previously,²⁵ therapists in the UP group received a training workshop on UP prior to the start of the intervention. This consisted of two or three group workshop sessions in which the therapists were instructed on the delivery of the different UP treatment modules. The duration of the course was between 10 hours and 20 hours, depending on the availability of the therapists at the centre. In addition to the workshop, all therapists received individual training during 12 therapy sessions through online supervision or participating as a co-therapist with an expert. In both cases, the training was led by the lead author (JO), who has been certified as a UP trainer by the Unified Protocol Institute.

Between sessions, all participants in this condition will have access to the UP-APP. The APP includes the content of the

Table 3 Clinical outcomes

Instrument	Construct	Reliability (α)	Response range
Primary outcomes			
ODSIS ^{22 33}	Severity of depressive symptoms	0.94	5-point Likert scale ranging from 0 (I did not feel depressed) to 4 (constant depression)
OASIS ^{22 34}	Severity of anxiety symptoms	0.87	5-point Likert scale ranging from 0 (I did not feel anxious) to 4 (constant anxiety)
MINI ^{35 36}	Principal diagnosis of ED	NA	Structured diagnostic interview
Secondary outcomes			
Patient outcomes			
MEDI ³⁷	Transdiagnostic dimensions of EDs	NA	9-point Likert response scale ranging from 0 (not characteristic of me/does not apply to me) to 8 (extremely characteristic of me/applies to me very much)
EuroQoL-5D ^{38 39}	Quality of life	NA	5 items ranging from 1 (I do not have problems) to 3 (unable to perform these activities). Thermometer from 0 (worst imaginable health status) to 100 (best imaginable health status)
FFMQ ^{40 41}	Mindfulness dimensions	0.80–0.91	Likert scale ranging from 1 (never or very rarely true) to 5 (very often or always true)
BEAQ ^{42 43}	Experiential avoidance	0.82	6-point Likert scale ranging from 1 (strongly disagree) to 6 (strongly agree)
DERS ^{44 45}	Emotion regulation	.73 to .93	5-point Likert scale ranging from 1 (never or very rarely) to 5 (very often or always)
ERQ ^{46 47}	Cognitive reappraisal and expressive suppression		7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree)
Implementation outcomes			
SUS ^{48 49}	Usability	0.81	5-point Likert scale ranging from 1 (strong disagreement) to 5 (strong agreement)
CEQ ^{50 51}	Confidence in the treatment (credibility and client expectancy)	0.85	9-point scale rated from 1 (not at all confident) to 9 (very confident).
CSRI ^{52 53}	Emergency service (total visits), general medical inpatient hospital admissions (total days) and outpatient healthcare services (total visits)	NA	NA
QALYs ^{54 55}		NA	NA
Patient satisfaction outcomes			
WAI-S ^{56 57}	Working alliance	0.91	7-point Likert scale ranging from 1 (never) to 7 (always)
TOS (ad hoc)	Quality of the intervention and its components, discomfort experienced during treatment and the experience of participating in a blended format	NA	4-point Likert scale ranging from 0 (poor or nothing) to 3 (excellent or very much) and 11-point response scale in some items ranging from 0 (nothing) to 10 (very much)
App Outcomes			
App	Time of use of the App, videos viewed and exercises completed	NA	NA

BEAQ, Brief Experiential Avoidance Questionnaire; CEQ, Credibility/Expectancy Questionnaire; CSRI, Client Service Receipt Inventory; DERS, Difficulties in Emotion Regulation Scale; ED, emotional disorder; ERQ, Emotion Regulation Questionnaire; FFMQ, Five Facet Mindfulness Questionnaire; MEDI, Multidimensional Emotional Disorder Inventory; MINI, Mini-International Neuropsychiatric Interview; NA, Not Applicable; OASIS, Overall Anxiety Severity and Impairment Scale; ODSIS, Overall Depression Severity and Impairment Scale; QALYs, quality-adjusted life years; SUS, System Usability Scale; TOS, Treatment Opinion Scale.

patient's manual, but using more dynamic and attractive digital material (videos and audios). The UP includes eight modules: (1) setting goals and maintaining motivation; (2) understanding your emotions; (3) mindful emotion awareness; (4) cognitive flexibility; (5) countering emotional behaviours; (6) facing physical sensations; (7) emotion exposures and (8) moving UP from here.

In the UP-APP, after completing each module, an assessment of the knowledge acquired will be carried out using true/false questions. The APP will collect the correct/incorrect responses and will provide feedback to the participants. Thus, participants will receive positive reinforcement as they progress through the modules and get correct answers to keep them engaged and motivated in the use of the APP. In

addition, participants will have to complete different exercises throughout the modules, such as records or activities to identify emotion-driven behaviours. They will also be provided with examples of real patients with whom they can identify and which will help them to complete their records. Finally, a weekly assessment will be made to evaluate the evolution of the depression and the anxiety symptoms (ODSIS and OASIS).²² The scores over time will be shown to the participants with a graphic display. This weekly evaluation with the APP will also include the participants' degree of motivation to continue working on the intervention.

Treatment as usual

This treatment condition will include individual, non-structured CBT using the following techniques: psychoeducation, cognitive restructuring, relaxation techniques, mindfulness techniques, exposure techniques, activity scheduling, problem solving and training in communication techniques. This is the treatment of choice by the psychologists at the collaborating Public Mental Health Centres.

Measures

The evaluation protocol is administered by the therapists in a paper and pencil format at the participant's health centre or, when possible, through the internet using the Qualtrics platform. The assessments will occur in four different time points: baseline, 3 months after starting the intervention (t_3), 6 months after starting the intervention (t_4) and 12 months after starting the intervention (t_5). Assessment instruments include demographic characteristics (age, sex, education, marital status and work status), a diagnostic interview and well-established questionnaires for both primary and secondary outcomes.

At the end of the study, the clinicians in the TAU condition will complete a self-report sheet describing the characteristics of their interventions using treatment modules as cues (psychoeducation module, identification of negative thoughts, breathing training, etc), the average duration of sessions, the number of sessions delivered, the end-of-treatment date and the information on the number of appointments with the psychiatrist and pharmacological treatment prescribed during the study.

Information on the number of appointments with the psychiatrist and the pharmacological treatment prescribed during the study is also collected for patients in the blended condition following the same procedure described for the TAU condition. All the participants using the UP-APP will be informed about the data that are going to be registered while using it. Primary and secondary outcomes are listed in [table 3](#).

Analyses

For the efficacy analyses, both completers and non-completers (intention-to-treat) analyses will be conducted separately. Then, a baseline comparison of both conditions in all study outcomes will be conducted to ensure that the randomisation was successful. Next, mixed, multilevel, linear models will be conducted using the restricted maximum likelihood

method to estimate the parameters. All the evaluations from all time points will be used in the models. The models will include covariates if baseline differences are detected. Specifically, the linear mixed model analysis will include the main effects of time (each variable collected at each evaluation time to analyse the evolution over time). The treatment condition and the number of sessions will also be included as interaction effects with time (in order to see differences in the evolution of the variables as a function of the treatment condition and/or as a function of the number of sessions). Finally, the centre where the participants have received the treatment will be included as random effects in the model. These analyses will be computed both for the primary and the secondary outcomes. The effect sizes will be computed and interpreted following the Cohen's proposal. Additionally, we will also calculate the Reliable Change Index and the Reliable Recovery Index (RRI) to evaluate the effectiveness of both interventions, as proposed by Jacobson and Truax.²⁶

Missing data will be handled using mixed models, which can be conducted with missing data.²⁷ For the remaining implementation outcomes (usability, acceptability and satisfaction), we will compute descriptive analyses. Cost effectiveness will be calculated by exploring the relationship between the cost of each intervention (cost of TAU or UP in a blended format, number of sessions, medication and use of health resources carried out by the participants (evaluated through the Client Service Receipt Inventory)) and its consequences in the form of quality-adjusted life years (QALYs) (standardised health units that allow the quantification of individuals' preferences regarding the quality of life that has been produced by a health intervention,²⁸ the information obtained through the EuroQol allows the calculation of QALYs). Other measures of intervention penetration will be used, such as the number of consumers who were eligible or willing to use the app (end users). All analyses will be conducted with SPSS V.24.0²⁹ and Mplus V.8.0.³⁰ The study will follow the Consolidated Standards of Reporting Trials recommendations.³¹

Ethics

This study will be carried out in accordance with the study protocol, the Declaration of Helsinki and good clinical practice. This superiority, multicentre, RCT is currently under an approval process by the ethical and research committees of all the collaborating centres. It has already been approved by Ethics Research Committee of Navarra, Castellón, Euskadi, Castilla y León, Extremadura, Lleida and Aragón.

Data handling will be carried out according to the premises established by Spanish laws.³² The security and confidentiality of the participants' data are guaranteed by using alphanumeric codes (SUP001) instead of names. In addition, the demographic data will be held separately from the rest of the data and will only be available to the researchers responsible for the data. The right to privacy will be a priority. The data obtained with the UP-APP will also comply with the mentioned guidelines. We will follow the necessary technical measures to ensure data safety and confidentiality, such as information encryption, access control and protection, security copies, updating of the operating system, security patches,

centralised management of passwords, roles, users and privileges, patches management and vulnerabilities detection. Outcomes will be disseminated through publication in peer-reviewed journals and presentations at international conference meetings. In addition, we will give visibility to the results through www.researchgate.net, <https://clinicaltrials.gov/> and the website of our research group.

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