Effectiveness of a mental health stepped-care programme for healthcare workers with psychological distress during the COVID-19 pandemic: a multi-centre randomised controlled trial in Spain

Study protocol

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Effectiveness of a stepped-care programme of internet-based psychological interventions for healthcare workers with psychological distress: Study protocol for the RESPOND healthcare workers randomised controlled trial

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Abstract

Background and aims: The coronavirus disease 2019 pandemic has challenged health services worldwide, with a worsening of healthcare workers' mental health within initial pandemic hotspots. In early 2022, the Omicron variant is spreading rapidly around the world. This study explores the effectiveness and cost-effectiveness of a stepped-care programme of scalable, internet-based psychological interventions for distressed health workers on self-reported anxiety and depression symptoms.

Methods: We present the study protocol for a multicentre (two sites), parallel-group (1:1 allocation ratio), analyst-blinded, superiority, randomised controlled trial. Healthcare workers with psychological distress will be allocated either to care as usual only or to care as usual plus a stepped-care programme that includes two scalable psychological interventions developed by the World Health Organization: A guided self-help stress management guide (Doing What Matters in Times of Stress)

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and a five-session cognitive behavioural intervention (Problem Management Plus). All participants will receive a single-session emotional support intervention, namely psychological first aid. We will include 212 participants. An intention-to-treat analysis using linear mixed models will be conducted to explore the programme's effect on anxiety and depression symptoms, as measured by the Patient Health Questionnaire – Anxiety and Depression Scale summary score at 21 weeks from baseline. Secondary outcomes include post-traumatic stress disorder symptoms, resilience, quality of life, cost impact and cost-effectiveness.

Conclusions: This study is the first randomised trial that combines two World Health Organization psychological interventions tailored for health workers into one stepped-care programme. Results will inform occupational and mental health prevention, treatment, and recovery strategies.

Registration details: ClinicalTrials.gov Identifier: NCT04980326.

Keywords

MeSH terms, coronavirus disease 2019, anxiety, depression, adjustment disorders, psychological distress, resilience, psychological, psychosocial intervention, internet-based intervention, healthcare facilities, workforce and services, analysis, cost

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The coronavirus disease 2019 (COVID-19) pandemic has challenged healthcare systems worldwide. Healthcare workers (HCWs) in some of the early pandemic hotspots, such as Spain, experienced major restructuring at work. For instance, they were deployed from their usual functions, sometimes to COVID-19-specific activities, working long shifts, with limited access to adequate protective equipment, as well as being forced to make decisions on patient prioritisation without proper guidelines (1–3). At the same time, increasing levels of discrimination and violence were being reported (4–6), which resulted in transnational organisations such as the World Health Organization (WHO) or the International Committee of the Red Cross (ICRC) calling for protection for HCWs. Many cross-sectional studies showed that both poor working conditions and self-perceived stigma were associated with poor self-reported anxiety and depression symptoms, sleep problems, post-traumatic stress disorder (PTSD) symptoms or suicidal ideation (7–11) – mental health problems already reported by HCWs before the COVID-19 pandemic (12).

During the first half of 2020, HCWs in Spain were massively exposed to potentially traumatic stressors, while lockdown measures restricted regular social activities and hampered access to existing mental health services, including psychotherapy. By late 2020, the prevalence of major depressive disorder, generalised anxiety disorder (GAD) and PTSD amongst Spanish HCWs was high (24%, 19,4%, and 21%, respectively (13). As the pandemic drags on into 2022, countries worldwide are imposing once again severe restrictive measures – including lockdowns – to contain the spread of the Omicron variant of the virus – Spain shows the highest incidence rates since the pandemic began, and primary care services are completely overburdened. Since poor mental health outcomes seem to persist over time among HCWs (14,15), evidence-based mental health interventions need to be culturally and locally adapted to COVID-19's rapidly changing environment. However, the adaptation process presents several challenges. First, mental health programmes must be feasible. They should consider the economic impact of the COVID-19 pandemic, which requires intervention programmes that are not only efficacious but also cost-effective. In this regard, internet-based psychological interventions can help overcome these issues by reducing costs (16), and increasing access to mental health care services, besides allowing HCWs and mental health service providers to comply with social distancing measures (17). Second, the prevalence of mental health problems and the persistence of the COVID-19 pandemic require that programmes be scaled-up at early stages to rapidly reach as many HCWs in need as possible and at a lower cost. The implementation of stepped-care programmes, which are based on principles such as *doing more with less* (i.e., providing care to more people with less amount of effort devoted to each one) (18) or *what works for whom* (19) has been shown to be cost-effective for common mental health problems. These programmes are becoming increasingly popular in mental health (20–22) and offer help that gains intensity only if the participant does not reach a particular milestone – e.g., if they do not lose weight in a weight-loss intervention (23). Finally, intervention protocols should be standardised to prove their effect across

different settings, such as general hospitals and primary healthcare settings.

Taking these factors into account, we designed a stepped-care programme including two scalable WHO internet-based psychological interventions that were locally adapted and tailored for HCWs in Spain. In the adaptation process, we included HCWs from a wide variety of care facilities and used standardised protocols for training care providers and implementing the interventions to improve transferability across settings. We chose two interventions developed by the WHO for communities affected by adversity (24). These brief, evidence-based interventions include self-help materials and guided self-help programmes that can be easily adapted to different contexts; they are affordable and can be delivered online. The first step consists of access to a guided self-help intervention delivered through a mobile-supported website adapted from a stress management guide called 'Doing What Matters in Times of Stress' (DWM), which is part of WHO's evidence-based self help plus (SH+) stress management course (25). DWM uses a model adapted from another scalable WHO intervention (i.e., Step-by-Step, a guided self-help online intervention) which has shown to be effective in treating depression in communities exposed to adversity in Lebanon (26). The second step is problem management plus (PM+) (27), an intervention based on cognitive behavioural therapy (CBT) techniques delivered individually through video calls and offered only to participants who show no reduction in psychological distress after step 1. Both interventions have proved effective in humanitarian settings (28–30). For instance, SH+ has been implemented as a preventive intervention for asylum seekers and refugees with psychological distress resettled in Europe and Turkey (31,32). It has also been used to reduce psychological distress in South Sudanese female refugees in Uganda (28). Other studies have shown the effectiveness of PM+ in reducing depression and anxiety in communities affected by violence in Kenya (33) and Pakistan (29). In addition, PM+ has been used to help reduce symptoms of anxiety and depression in cancer patients (30).

Although these scalable interventions have been adapted to the COVID-19 pandemic in previous studies for long-term care workers and distressed people (34,35), to our knowledge, this is the first time they have been integrated into an online stepped-care programme for HCWs. This parallel-group clinical trial explores this programme's effect on self-reported anxiety and depression symptoms among HCWs with psychological distress based on the hypothesis that reductions will be larger in the experimental arm than in the control arm (care as usual [CAU]).

Methods and analysis

Study design and participants

This study is a multi-centre (two sites), parallel-group (1:1 allocation ratio), analyst-blinded, superiority, randomised (stratified by centre), controlled (versus CAU) trial that explores the effect of a stepped-care psychological intervention on anxiety and depression symptoms among HCWs with psychological distress at 21 weeks from the baseline assessment. Our main aim is to test the effectiveness of the stepped-care intervention on anxiety and depressive symptoms, based on the hypothesis that the improvement will be larger among participants in the intervention arm compared to CAU. Our secondary aims are to test the effectiveness of the intervention on PTSD symptoms, quality of life, and resilience, based on the hypothesis that the improvement will be larger among the participants in the intervention arm compared to CAU. We prospectively published the trial protocol on ClinicalTrials.gov on 28 July 2021. The record log does not show any significant modification after the first participant entered the study on 1 November 2021. The study is part of an European Union (EU)-funded project named 'Improving the Preparedness of Health Systems to Reduce Mental health and Psychosocial Concerns resulting from the COVID-19 Pandemic' (RESPOND) (www.respond-project.eu), and it is sponsored and coordinated by the Hospital La Paz Institute for Health Research (Instituto de Investigación del Hospital Universitario La Paz).

RESPOND is conducting trials focused on different population groups, including our trial on HCWs. RESPOND-HCWs is done in Spain, where 17 Autonomous Communities are responsible for healthcare provision and policy. Participants will be recruited from the Community of Madrid and Catalonia. In the Community of Madrid, with a registered population of 6,745,591 as of January 2021, eligible participants are HCWs employed by the Department of Health (88,717 workers as of October 2021). In Catalonia, with a registered population of 7,716,760 as of January 2021, eligible participants are HCWs funded by the Department of Health (109,346 workers as of December 2020). On the day the first participant was enrolled in the study (1 November 2021), 364 and 517 confirmed COVID-19 cases were reported by the Community of Madrid and Catalonia, respectively.

The research team will contact all participants interested in the study by phone. After confirming their interest and signing the informed consent form (see Supplemental File 1), the assessor will conduct a brief interview to explore whether they can be enrolled. We interview participants for approximately 15 min and ask a series of pre-specified screening questions (e.g., have you got any acute medical conditions? Have you ever been diagnosed with a mental disorder?) and items (e.g., Does the person understand the questions? Does the person find it hard to follow the interview?) to check whether they meet inclusion and exclusion criteria.

We set the following inclusion criteria:

1. HCW from primary, specialised, or emergency care facilities, including doctors, psychologists, nurses, nursing technicians, orderly, and administrative staff.
2. Psychologically distressed, as measured by the Kessler Psychological Distress Scale (K10) above cut-off score of 15.9 (36).
3. 18 or older.
4. Able to read and speak Spanish, Catalan, or both.

We also set the following exclusion criteria:

1. Acute medical conditions that require immediate hospitalisation.
2. Imminent risk of suicide or self-harm or risk of harming others.
3. Severe mental disorder (e.g., psychotic disorder, delirium).
4. Severe cognitive impairment (e.g., intellectual disability, dementia).
5. Initiated, stopped, or significantly modified pharmacotherapy in the last eight weeks.
6. Initiated or stopped standardised psychological treatment (e.g., CBT, psychoanalytic therapy) in the last eight weeks.

We did not specify any study withdrawal criterion.

The scalable interventions used in this trial can be delivered by non-professional helpers, such as a trained peer, a workplace helper, or a psychosocial worker. These interventions have also been designed to be widely applicable to various mental health problems, such as anxiety and depression, and are easily adaptable to different populations, cultures, and languages. Care providers in RESPOND-HCWs are junior psychiatrists, psychologists, and mental health nurses in training (e.g., residents) who have undergone specific preparation shortly before the trial (6 days of training in Psychological First Aid [PFA] and online delivery of DWM and PM+). Training includes presentations, group activities, active discussion, case studies and role-plays. Care providers will also attend weekly supervision sessions during the trial, consisting of 60-min online group sessions with trained supervisors. In these sessions, care providers can ask for guidance for specific participants or enquire more generally about the intervention protocol. The trainers/supervisors are psychiatrists and clinical psychologists who have received 9 days of master training from senior mental health professionals who were involved in the development of the intervention programmes or were trained directly by intervention developers. Supervisors will also ensure protocol adherence and carry out informal weekly competency and fidelity checks, which will inform individualised feedback for care providers. Supervisors will also conduct a formal fidelity check at the end of the trial, which will consist of structured checklists to be completed based on audios of the intervention and video recordings. Local project managers will supervise trainers/supervisors, providing training in supervision skills.

Interventions

We use intervention programmes developed by the WHO. Following the Programme Design, Implementation, Monitoring, and Evaluation (DIME) protocol (37), we used a two-step qualitative research design to interview frontline HCWs, mental health experts, administrators, and service planners in Spain, and we analysed their responses to locally adapt and tailor the interventions for HCWs in Spain, following similar studies (38,39). Participants in the intervention arm are offered a stepped-care programme consisting of two scalable psychological interventions: DWM in Times of Stress (DWM) – part of the Self-Help Plus (SH+) course, and PM+. All participants are also offered a short counselling session, namely PFA, and can maintain their usual care, which might include non-structured psychological support or stabilised psychopharmacological treatment.

We did not establish any intervention withdrawal criterion, but care providers will report adverse events to the principal investigator, who will decide whether a participant must discontinue the intervention.

PFA. WHO defines PFA as a 'humane, supportive and practical help to fellow human beings suffering serious crisis events' (40). PFA providers are trained in three basic helping skills: *looking*, *listening*, and *linking*. RESPOND participants are HCWs that have not necessarily been exposed to serious adversities but have been exposed to a stressful and potentially traumatic event such as the COVID-19 pandemic. We include PFA in a single 15-min phone session conducted 2–5 days after enrolment. Before starting PFA, the helper tells participants whether they have been allocated to the intervention arm or the control arm (see Figure 1) and answer any questions regarding the intervention process, including the allocation. Next, the helper informs participants about the aim of the call and its duration, explaining that they have 15 min to talk about anything they need. The helper will then support the participant with basic skills and strategies and offer specific resources that might be helpful (e.g., hotlines for people in distress or experiencing loneliness, support for women who might be suffering gender-based violence, etc.). If participants do not answer the phone, helpers will try to contact them twice, after which they will label the intervention as 'not provided'.

Stepped-care programme. We designed a two-step programme for the RESPOND trial comprising two scalable psychological interventions. Firstly, a guided stress-management course based on the SH+booklet called

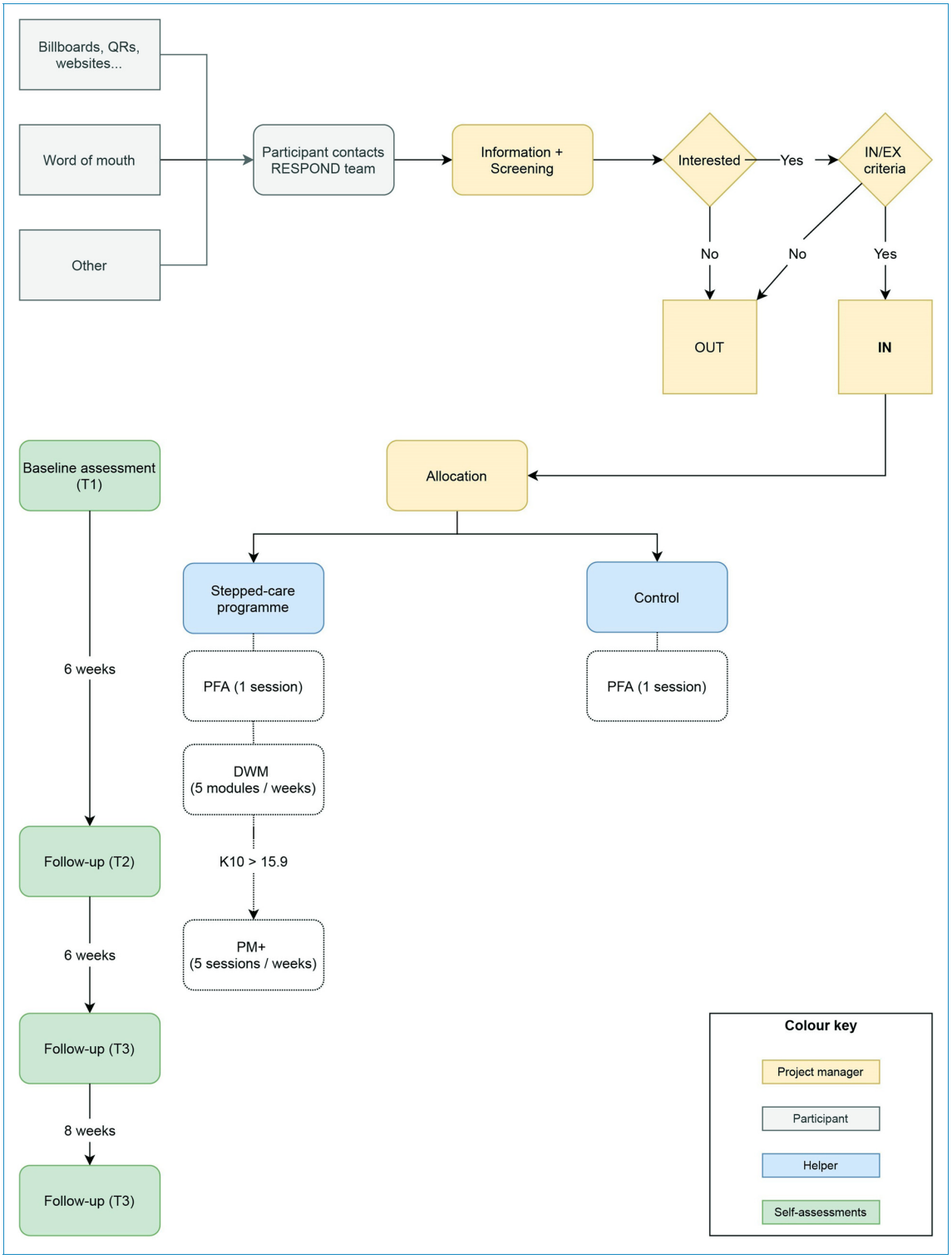

Figure 1. Participants' flow diagram since they show interest in the study until they complete the follow-up assessment. DWM: Doing What Matters; K10: Kessler Psychological Distress Scale; PFA: Psychological First Aid; PM+: Problem Management Plus.

Doing What Matters in Times of Stress (DWM) (25) and, secondly, *PM+*, an individual intervention based on CBT (27). The criterion for stepping up is reporting significant levels of psychological distress after step 1, as measured by a K10 score higher than 15.9. We will offer PM+ to participants who do not reach that milestone.

Step #1 is DWM, a booklet divided into five monographic chapters covering psychoeducation on stress and its causes, as well as five strategies from acceptance and commitment therapy (ACT) for managing stress. It was designed to support learning during SH+, a 5-week group-based course but is available for use as a standalone stress management guide. The chapters contain the same techniques and skills provided in the longer SH+ course. Chapters include information on the ACT techniques, along with audio recordings to support practice. As a result of the local adaptation process undertaken in RESPOND, we transformed DWM into a mobile-friendly website, re-recorded audios and adapted some content to reflect barriers or stress triggers that might affect HCWs in Spain. This included adding additional exercises to help support motivation to use the guide.

DWM is provided as guided self-help. It uses a model adapted from another WHO intervention Step-by-Step, a guided self-help intervention for depression, which was tested in randomised controlled trials in Lebanon (41). After allocation, DWM users are assigned to a helper who offers ongoing support with practices and key concepts over the phone. An initial call is arranged 2–5 days after entering the study. After that call, the participant receives a message with login details. The course is spread over 5 weeks, and new modules are released every week. Helpers also schedule weekly ongoing support calls. Participants who do not want to receive phone calls can also contact their helpers using the messaging system included on the website. We keep track of every helper-participant contact made by phone or DWM website.

Step #2 is PM+, a brief psychological intervention based on CBT techniques. Helpers or facilitators schedule five weekly interventions covering each strategy. As a result of the local adaptation process, we adapted PM+ to be delivered online (videoconference) and shortened sessions from 90 to 60 min. We also tailored case examples to HCWs (e.g., job-related triggers of stress, barriers for practice because of working shifts, etc.). Helpers will record calls for adherence purposes and go through identified barriers during practice over the week.

We present an overview of the stepped-care programme in Figure 2.

Outcomes

Participants self-report all outcomes at baseline (t_1) and the three endpoint assessments (t_2, t_3, and t_4). We selected three relevant mental health outcomes for HCWs from COVID-19 pandemic hotspots, namely anxiety, depression, and PTSD symptoms (7,8,14). We also included quality of life and resilience as secondary outcomes and the cost of implementing the intervention programme to determine cost-effectiveness. We did not include any harm outcomes, although we will report harm indicators, such as an increase in symptoms or suicidal thoughts, as well as adverse events (see Monitoring for a detailed description of adverse event monitoring). The primary outcome is an aggregated measure of anxiety and depression symptoms at t_4, that is, 21 weeks after baseline assessment or 2 months after PM+. We are unaware of any validation studies conducted among HCWs using our instruments. In a previous study, we used the PHQ-9 in a large sample of HCWs, and Cronbach's alpha was 0.88 (95%CI: 0.87, 0.89) (8).

Self-reported anxiety and depression symptoms, as measured by the Patient Health Questionnaire – Anxiety and Depression Scale (PHQ-ADS) summary score at t_4 *(primary outcome).* The PHQ-ADS (42) is a 16-item self-reported instrument that combines the nine-item PHQ depression scale (PHQ-9) (43) and seven-item GAD scale (44) into a composite measure of depression and anxiety. Respondents are asked how much each symptom has bothered them over the past 2 weeks, with response options of 'not at all', 'several days', 'more than half the days', and 'nearly every day', scored as 0, 1, 2, and 3. The scale can range from 0 to 48, with higher scores indicating higher levels of depression and anxiety symptoms. Spanish versions of both the PHQ-9 (45) and the GAD-7 (46) are validated and will be combined into the PHQ-ADS.

Self-reported anxiety and depression symptoms, as measured by the PHQ-ADS summary score at t_2 *and* t_3 *(secondary outcome).* The PHQ-ADS summary score will also be collected as a secondary outcome at 7 and 13 weeks from the baseline assessment.

Self-reported anxiety and depression symptoms, as measured by the PHQ-ADS anxiety and depression domain scores, at t_2, t_3, *and* t_4 *(secondary outcome).* PHQ-ADS domain scores can range from 0 to 27 and from 0 to 21 for the depression (i.e., PHQ-9) and anxiety (i.e., GAD-7) domains, respectively, with higher scores indicating higher levels of anxiety and depression. The Spanish version of both instruments includes a cut-off score of $\geq$ 10 to detect people with probable depression (47,48) and anxiety (46), and these cut-offs have been used in large samples of Spanish HCWs after the COVID-19 outbreak (7,8).

Self-reported symptoms of PTSD, as measured by the 8-item version of the PTSD Checklist for DSM-5 (PCL-5) summary score, at t_2, t_3, *and* t_4 *(secondary outcome).* The 8-item PCL-5 (49) is a self-reported instrument that measures PTSD symptoms according to DSM-5 criteria. Respondents are asked how much each symptom has bothered them over the past 4 weeks, with response options of 'not at all', 'a little bit', 'moderately', 'quite a bit', and

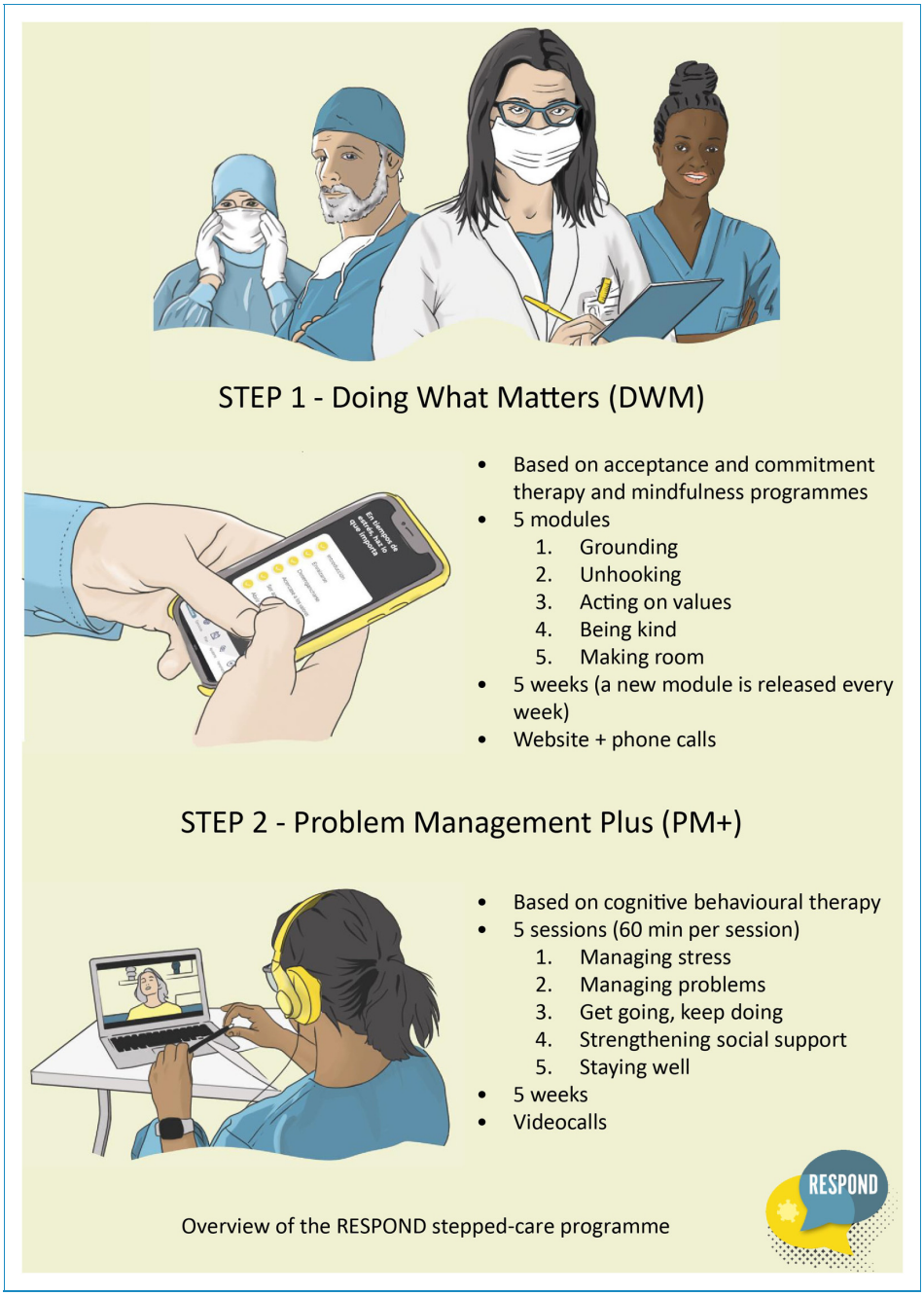

Figure 2. Overview of the RESPOND stepped-care programme.

'extremely'. Items are rated on a 0–4 scale. The scale can range from 0 to 32 for the 8-item version, with higher scores indicating higher levels of PTSD symptoms. The instrument is based on the PCL-C, a DSM-IV-based checklist validated in the Spanish language (50).

Self-reported health-related quality of life, as measured by the EuroQol 5-dimensional descriptive system – 5-level version (EQ-5D-5L) domains at t_2, t_3, *and* t_4 *(secondary outcome).* The EQ-5D-5L (51) consists of the EQ-5D and the EQ-VAS. Part 1, the EQ-5D, rates the level of impairment

across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels: none, slight, moderate, severe, and extreme problems. The labels for the 5L followed the format 'no problems', 'slight problems', 'moderate problems', 'severe problems', and 'unable to'/'extreme problems' for all dimensions. Part 2, the EQ-VAS, is a visual analogue scale. The endpoints of the scale are called 'The best health you can imagine' and 'The worst health you can imagine', and the current health status of that day needs to be indicated, after which the number checked on the scale also needs to be written down. Higher scores indicate poor quality of life. A Spanish version with population-based reference norms is available (52).

Cost of programme implementation, as measured by the domain scores of the Client Service Receipt Inventory (CSRI) – RESPOND adaptation, at t_2, t_3, *and* t_4 *(secondary outcome).* A bespoke version of the CSRI (53) has been developed to collate information on changes in health care service utilisation and changes in usual activities that will inform cost-effectiveness analysis. The RESPOND-bespoke version consists of a 13-item self-reported instrument that asks about the number and duration of contacts with healthcare professionals (physicians, mental health specialists, and nurses) in the past 2 months. It collects data on service utilisation (e.g., use of health system, other services, time out of employment and other usual activities, need for informal care) and related characteristics of people with mental disorders. In addition to collecting data using the CSRI, the trial separately collates information on the resources and costs of implementing the intervention, including resources required for initial and ongoing training/supervision.

Resilience, as measured by the PHQ-ADS summary score in relation to stressor exposure, at t_2, t_3, *and* t_4 *(secondary outcome).* Resilience can be defined as having good mental health when facing adversity, which requires collecting information on mental health status and exposure to stressors (54). The PHQ-ADS measures mental health status, while the RESPOND adapted version of the Mainz Inventory of Microstressors (MIMIS) measures the exposure to objective microstressors or daily hassles (55). After the COVID-19 outbreak, a shorter version, including pandemic-related stressors, was developed (56). In RESPOND, we use an 18-item adaptation that includes: three general life events (e.g., recent break-up); six everyday stressors (e.g., excessive workload, financial problems); five COVID-19-specific stressors (e.g., being forced to quarantine); and four HCW-specific stressors (e.g., COVID-19 patients died under your care). The first three items (general life events) are rated on a 5-point Likert scale, ranging from 0 (never happened) to 4 (it had a major impact on me). The remaining 15 items are rated on a 4-point Likert scale, ranging from 0 (did not happen/almost never) to 3 (every day or nearly every day). All items ask about the last 14 days.

Other measures. We will conduct in-depth interviews with key informants to assess the feasibility of programme implementation (e.g., adherence, penetration, acceptability) and to conduct a process evaluation following widely accepted procedures (57,58). We will select informants among completers and non-completers of DWM and PM+ interventions. We will also use the Positive Appraisal Style Scale, content-focused (PASSc; in preparation), a 12-item self-report measure, to assess typical appraisal of stressors. Respondents are asked to rate the frequency of each item with the options 'never', 'sometimes', 'often', 'almost always', scored as 1, 2, 3, 4.

Participant timeline. After being included in the study, participants will complete baseline assessment within the subsequent 5 days (i.e., before treatment allocation so this will not bias self-reported baseline outcomes). Follow-up assessments are scheduled at weeks 7 (t_2), 13 (t_3), and 21 (t_4), from baseline assessment, with a 14-day window period (e.g., endpoint t_1 may take place 7 or even 8 weeks after baseline). Questionnaires are always presented in the same order, namely (a) sociodemographic characteristics (baseline only), (b) PHQ-ADS (PHQ-9 and GAD-7), (c) stressor exposure (RESPOND-adapted MIMIS), (d) PCL-5, (e) RESPOND-bespoke CSRI, and (f) EQ-5D-5L (7) PASSc. Figure 3 shows an overview of the participants' timeline.

Sample size

We estimated sample size to detect a small-to-moderate effect size (defined as the square root of the ratio of the variance of the tested effect to the comparison error variance, Cohen's $d = 0.3$) on the PHQ-ADS summary score at t_4 based on previous studies using PM+ (33,59) and on recent studies using similar online mental health interventions during the COVID-19 pandemic (34,35). A power calculation for an analysis of variance (ANOVA) repeated measurement design with two time periods to identify the effect of treatment at the last endpoint with a two-sided 5% significance level, a power of 95%, and an estimated attrition of 30%, a sample size of 106 participants per group is required ($n = 212$), for which we anticipate a 12-month inclusion period.

Recruitment

The trial target population includes HCWs from the Community of Madrid and Catalonia. We will recruit participants using word-of-mouth strategies, primarily via social media (e.g., WhatsApp groups, Facebook, LinkedIn posts, etc.). We will contact key stakeholders, including hospital managers and communication departments, scientific societies, labour unions, and other associations. They will be asked to announce the research project through formal (i.e., emails, interviews on press and radio) and informal

		STUDY PERIOD			
	Enrolment	Allocation	Post-allocation		
TIMEPOINT	$-t_1$	0	7 weeks (t_2)	13 weeks (t_3)	21 weeks (t_4)
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
PFA		X			
DWM		←	→		
PM+			←	→	
ASSESSMENTS:					
Sociodemographic variables	X				
Mental health outcomes (PHQ-ADS and PCL-5)	X		X	X	X
Resilience	X		X	X	X
Quality of life (EQ-5D-5L)	X		X	X	X
Costs of programme implementation (CSRI)	X		X	X	X
Positive Appraisal Style Scale (PASSc)	X	X	X	X	X
Feasibility and acceptability of programme implementation					X

Figure 3. Participants' timeline. PFA: Psychological First Aid; DWM: Doing What Matters; PM+: Problem Management Plus; PHQ-ADS: Patient Health Questionnaire – Anxiety and Depression Scale; PCL-5: PTSD Checklist for DSM-5 (PCL-5) ; EQ-5D-5L: the EuroQol 5-dimensional descriptive system – 5-level version; CSRI: Client Service Receipt Inventory; PASSc: Positive Appraisal Style Scale – content focused.

methods (i.e., Whatsapp messages, SMSs). We expect potential participants to enter the study in 'waves', e.g., the days following a certain event in which the trial is advertised. We will enrol new participants as they approach us, taking into account helpers' availability.

Assignment of interventions

A research assistant generated the allocation sequence using the electronic data capture (EDC) software Castor (www.castoredc.com). We stratified randomisation by 'centre' with a 1:1 allocation ratio using random blocks of

unequal sizes. Local project managers will enrol participants (i.e., discuss the trial, assess eligibility, and obtain informed consent) and assign them to each arm based on the allocation sequence. However, they will not be aware of the randomisation sequence nor administer any intervention. The Principal Investigator will restrict the access of the data analyst (i.e., the statistician) to the electronic dataset to ensure blindness after the intervention assignment. The study does not include any outcome assessor who could be kept blinded because there are no observer-reported outcomes. As it often happens with behavioural interventions, neither participants nor care providers (helpers) are blinded to allocation.

Data collection

We collect baseline and outcome data exclusively through electronic case report forms (eCRFs) using Castor EDC and Qualtrics. Participants receive an email with a link to the baseline assessment right after enrolling in the study. We schedule the remaining follow-up assessments at that moment, and they are automatically sent on due time. Participants can complete the assessments using any electronic device. We placed the primary outcome (PHQ-ADS) at the beginning of the form, except for baseline assessments, where we collect sociodemographic variables first. The PHQ-ADS is the only mandatory outcome at all time points, meaning that participants are not allowed to go further on the questionnaire until they have filled in all the items. Results from a pilot testing conducted in both study locations estimate the average completion time of the assessments in 10–15 min. Data collection forms are available from the corresponding author upon request.

We use reminders to maximise responsiveness even among non-adherent participants who discontinue or deviate from the assigned intervention protocol. Three reminders are sent 2, 5 and 10 days after each assessment to those participants without a complete primary outcome assessment. These messages acknowledge the effort made by the participants and emphasise the importance of data collection in clinical trials to increase retention rates. Reminders were locally adapted and translated into Catalan. Participants will not be reimbursed for participating in the trial or performing the assessments.

The same eCRF was used in both study locations.

Data management

Four types of data are generated in this study: participants' outcomes, participants' contact details, DWM metadata, and PM+ recordings. Local teams can only access data generated on their sites at both study locations. All servers comply with the General Data Protection Regulation of the European Union (EU).

Outcomes. Participants enter their outcome data in the eCRF. Data is stored on Castor EDC and Qualtrics servers and is accessible only for local project managers. All variables have a restricted range of valid values, and field-text variables are only used for specifying the option 'Other' to minimise errors.

Contact details. Local project managers note down the contact details of all study participants during the screening call. These details include name and surname, phone number, postal address, and email address. These data are stored in local servers at the Universidad Autónoma de Madrid (Madrid) or the Parc Sanitari Sant Joan de Déu (Barcelona). Local helpers access these data to retrieve participants' phone numbers and manage risks of harm when needed (e.g., knowing the postal address is important if a serious adverse event occurs during a phone call).

Metadata. The DWM website automatically generates and stores metadata on EU servers. These metadata include dates and times of logins and logouts, whether the participants have clicked on a specific audio recording, or whether they have completed a module. This information is available both for helpers (to inform DWM of ongoing support calls) and local project managers (to monitor the app's functioning). We will report some of this data as indicators of feasibility (i.e., adherence) to the DWM intervention.

Recordings. In Madrid, PM+ sessions are video recorded if the participant gives verbal consent at the beginning of the session. Only helpers and trainers/supervisors have access to these recordings. Helpers use corporate accounts of the Department of Health, where recordings are securely stored. In Barcelona, only the audio of the helper (not the participant) is recorded with an external recorder. These recordings are securely stored in servers at Parc Sanitari Sant Joan de Déu, which only helpers/supervisors can access.

Data analysis

We will answer the main research question based on the intention-to-treat (ITT) analysis of the primary endpoint: self-reported anxiety and depression symptoms as measured by the PHQ-ADS summary score measured at t_4. Firstly, we will look for baseline differences between the two groups of participants, using appropriate statistical tests based on variables' types and distributions. Secondly, we will estimate the treatment effect at t_2, t_3, and t_4. We will use a linear mixed model, where treatment (i.e., group) will be entered as a fixed effect and participant (i.e., subject) as a random effect while controlling for the PHQ-ADS summary score measured at baseline (t_1). The model will constrain the treatment fixed effect to be null and look for the time by treatment interaction at all endpoints, although t_4 will be our primary

time point of interest. We will analyse the stepped-care programme as a single intervention (regardless of whether the participant steps up to PM+ or finishes the intervention after DWM), and we will report the proportion of participants at each step, following previous studies (23). Finally, we will report the treatment effect estimators, i.e., the model parameters and the mean difference between treatment arms at each time point plus 95% confidence intervals obtained from robust standard errors. Additional ITT analyses will use the same model on secondary outcomes, namely PHQ-ADS domain scores (PHQ-9 and GAD-7 summary scores, respectively), PCL-5 summary score, and EQ-5D-5L summary and domain scores, as well as on outcome-based resilience scores, as measured by the PHQ-ADS summary score against a stressor reactivity score. These resilience scores will be calculated based on the stressor exposure and the PHQ-ADS to assess individual deviation from the normative stressor reactivity (see (60,61)). Stressor reactivity will be computed based relationship between stressor exposure and mental health problems within the sample.

We will also conduct per-protocol analyses on all outcomes as confirmatory robustness analyses. We will include participants with at least 3 DWM contacts (phone calls or messages) and, if applicable, 5 PM+ sessions. Other additional analyses include exploratory sensitivity analyses clustering participants based on relevant variables (e.g., gender, symptom severity, involvement in the treatment of COVID-19 patients) to explore the effect of the intervention across strata of interest and mediation analyses using appraisal style as measured by the PASSc or treatment adherence proxies as potential mediators.

We will also conduct health economic analyses to determine the cost-effectiveness of stepped care. The total costs of delivering interventions will be estimated and described and combined with data on changes in health service utilisation and time out of usual activity over 21 weeks (from t_1 to t_4) obtained using our bespoke CSRI. The economic analysis will focus on incremental cost per quality adjusted life year gained (using data from the EQ-5D-5L) as well as the incremental cost per change in PHQ-ADS summary score, both at 20 weeks follow up. The analysis will be conducted from both the health care system and societal perspectives. Between-group comparison of mean costs will be completed using appropriate statistical tests depending on the type and distribution of data. Univariate sensitivity analyses and non-parametric bootstrapping will be used to account for uncertainty in trial parameters; cost-effectiveness planes and cost-effectiveness acceptability curves will be constructed.

We will not impute missing data because linear mixed models use all available information to calculate effect estimators. We will report significant deviations from the assumption that data are missing at random or completely at random (e.g., sensitivity analysis including strong predictors of missingness as covariates). To deal with problems associated with multiple testing, at each time point, the global statistical significance of the secondary outcomes will be assessed through the seemingly unrelated regressions equations model, controlling for baseline values. All analyses will be done using R Studio (62) and Stata (63).

Monitoring

Local project managers independent from the study sponsor will act as data monitors. They will access data forms every day and oversee that data is being collected and that no adverse events are reported. Participants who register any serious death thoughts or plans to end their lives as part of follow-up assessments (see 'Outcomes' section) will receive an automatic warning message. That alert reminds them that the research team cannot monitor real-time responses and that they should seek help if they are at imminent risk. One of the trainers/supervisors will reach out to them over the next 48 h to follow up and offer support if necessary. Helpers can also detect adverse events while delivering the interventions. Suppose there is an immediate risk of harm. In that case, helpers will contact one of the trainers/supervisors to evaluate the situation and make rapid decisions (e.g., ask the person to go to the nearest emergency department or send an ambulance if required). If there is no imminent risk, helpers will handle the situation and report to the trainers/supervisors after finishing the intervention. The helpers on Castor EDC will record adverse events. Local project teams will report to the RESPOND Ethics and Data Advisory Board, chaired by Dr Sonja Rutten, which will act as Data Monitoring Committee. We do not plan any interim analyses or any external trial audit.

Ethics and dissemination

The study was approved by institutional review boards (IRBs) at Hospital La Paz in Madrid (ID: PI-4857) and Parc Sanitari San Joan de Deu in Barcelona (ID: PIC-129–21). All participants enrolled in the trial must sign the informed consent form through Docusign (Madrid) or via Qualtrics' digital signature functionality (participants sign using their mouse or their finger on a mobile device). The harm management protocol described above will be implemented if any participant experiences harm due to trial participation. We will not offer any ancillary or post-trial care or compensation. Any necessary protocol modification will be updated on the clinical trial public register and reported to the local IRBs and to the RESPOND Ethics Advisory Board.

Participants' data will be kept confidential unless there is an ethical or legal reason for disclosing it. We need contact details to provide the interventions and monitor harms but they will be stored separately from endpoints data.

Endpoints will only include anonymised data linked to a unique record identifier automatically generated by the EDC software. The key linking contact details and record identifier will be securely stored in Castor EDC and Qualtrics servers and will only be accessible to local project managers.

The final trial dataset will be accessible to local project managers and the data analyst. We will use it to write scientific publications and disseminate outstanding findings to the general audience. All publications, including the trial protocol, will be open access and include the statistical code. The Authors will consist of members of the RESPOND consortium who make significant contributions to the study design, data collection and analysis, and manuscript writing.

RESPOND partners will sign data-sharing agreements. If possible, pooled analyses will be done remotely so that primary custodians can keep complete control of it. We do not plan to share participant-level data outside the RESPOND consortium.

Conclusions

This study is the first randomised trial that combines two scalable psychological interventions developed by the WHO into one stepped-care, internet-based programme tailored for HCWs. Participants will be enrolled amidst a global spread of the highly contagious Omicron variant of severe acute respiratory syndrome coronavirus 2, which puts a lot of pressure on healthcare systems. HCWs shall face this new challenge while dealing with the mid-and long-term psychological impact of early pandemic outbreaks, which were particularly virulent in Spain. Importantly, the pandemic has revealed that most HCWs, and not only those in direct acute care of COVID-19 patients, are exposed to highly distressing working conditions, such as having to work long shifts or experiencing burnout syndromes, that may easily affect not only their working environment but also their personal lives. Therefore, exploring the effectiveness and cost-effectiveness of this programme among such a vulnerable and essential population is undoubtedly pertinent, and it could rapidly inform occupational and mental health prevention, treatment, and recovery strategies that shall persist beyond the COVID-19 pandemic.

Authors' contribution: Conceptualisation, methodology, data curation and writing – review and editing were handled by all authors. Investigation was carried out by RM, KRM, MF-N, AM-M, MFB-O, CB, BR-V, JMH, JLA-M. . Writing – original draft was done by RM, KRM.Supervision was done by JLA-M. Project administration was done by RM, KRM, MF-N, AM-M, MFB-O, CB, BR-V, JMH, JLA-M. Funding acquisition was handled by PN, MS, MP, MM, DM, RK, RB, JMH, JLA-M.

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Research protocol - MADRID

RESPOND PROJECT. PHASE 2 and 3 CLINICAL TRIAL

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Date	3.12.2021
Funding	Horizon 2020 (European Commission). This project has received funding from the European Union's Horizon 2020 research and innovation programme Societal Challenges under Grant Agreement No 101016127
Original title	Improving the P**RE**paredness of Health Systems to Reduce Mental Health and **P**sychosocial Concerns resulting from the C**O**VID-19 Pa**ND**emic
Acronym	RESPOND
Title of the project	RESPOND PROJECT. PHASE 2 AND 3 CLINICAL TRIAL
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Table of contents

1. List of abbreviations and relevant definitions

CAU	**Care As Usual**
COVID-19	**Coronavirus Disease 2019**
CSRI	**Client Service Receipt Inventory**
DWM	**Doing What Matters**
EQ-5D-5L	**EuroQol five dimension five level checklist for quality of life EU European Union**
EDAB	**Ethics and Data Advisory Board**
GAD-7	**Generalized Anxiety Disorder checklist (consisting of 7 items)**
HCWs	**Healthcare workers**
K10	**Kessler Psychological Distress Scale (ten item version)**
MIMIS	**Mainz Inventory of MIcrostressorS**
PASSc	**Positive Appraisal Style Scale – content focused**
PCL-5	**PTSD Checklist for DSM-5 (consisting of 20 items)**
PFA	**Psychological First Aid**
PM+	**Problem Management Plus**
PHQ-9	**Patient Health Questionnaire for depression scoring each of the 9 DSM-5 criteria**
PHQ-ADS	**Patient Health Questionnaire – Anxiety and Depression (sum score of PHQ-9 and GAD-7)**
PSYCHLOPS	**Psychological Outcomes Profiles**
PTSD	**Posttraumatic Stress Disorder**
RESPOND	**pREparednesS of health systems to reduce mental health and Psychosocial concerns resulting from the COVID-19 paNDemic**
RCT	**Randomized Controlled Trial**
WHO	**World Health Organization**

2. Introduction and rationale

RESPOND Project
This study is embedded in the larger, EU H2020 CORONAVIRUS-funded RESPOND (PREparednesS of health systems to reduce mental health and Psychosocial concerns resulting from the COVID-19 paNDemic) project. This study protocol presents the second and third phase of the previously approved protocol: **PI-4498** (*"ANÁLISIS DE LAS NECESIDADES DE LOS TRABAJADORES SANITARIOS EN PRIMERA LÍNEA PARA INTEGRAR LOS PROGRAMAS DE APOYO PSICOSOCIAL COVID-19 DE LA OMS EN LOS SISTEMAS DE SALUD MENTAL EN ESPAÑA")*

Healthcare workers are vulnerable to adverse mental health impacts of the COVID-19 pandemic.

Health care workers (HCWs) represent a particularly vulnerable group during pandemics, due the high risk of infection, fear of contagion and spread to family members and increased work-related stressors. These circumstances place health care workers at risk for poorer mental health (i.e., anxiety, depression, burnout, insomnia, moral distress, and post-traumatic stress disorder). For instance, studies conducted in 18 healthcare institutions across six autonomous regions of Spain found that almost half of Spanish health care workers have a high risk of suffering a mental disorder, and a 3.5% experienced suicidal thoughts after the first wave of the Coronavirus Disease 2019 (COVID-19) pandemic (Alonso et al., 2021; Mortier et al., 2021).

Given that professionals who care for COVID-19 patients are highly susceptible to psychological burden, it is crucial to develop strategies to support these professionals by designing and implementing specific MH interventions (Almeda et al., 2021).

Scalable psychological interventions to improve resilience, mental health and wellbeing

The World Health Organization (WHO) has developed a number of scalable psychological interventions for populations affected by adversity (WHO, 2017). They include -amongst others- Doing What Matters (DWM) and Problem Management Plus (PM+). A core feature of all WHO scalable interventions is that they can be trained to and delivered by non-highly specialized professional helpers (WHO, 2017; Epping-Jordan et al., 2016). They have also been designed to be easily adaptable to different populations, cultures and languages. The interventions and their implementation materials are freely available on the WHO website.

DWM has a strong focus on mindfulness practices and includes exercises which aim to enhance stress reduction and build social support, adaptive coping and resilience (Epping-Jordan et al., 2016). It has been implemented with different populations of refugees in Europe, Turkey (Purgato et al., 2019) and Northern Uganda (Tol et al., 2020).

PM+ is a transdiagnostic intervention (Banbury et al., 2018) that reduces symptoms of depression, anxiety, Posttraumatic Stress Disorder (PTSD), and related conditions. PM+ comprises 5 weekly sessions using evidence-based techniques: (a) problem solving, (b) stress management, (c) behavioral activation, and (d) accessing social support. PM+ has been successfully implemented in Kenya (Bryant et al., 2017) and Pakistan (Rahman et al., 2016b). Both DWM and PM+ have been implemented through two large EU H2020 funded projects, STRENGTHS (733337) and RE-DEFINE (779255).

The first phase of the Respond study (already approved by the CEIC, PI-4498) allowed to culturally adapt both interventions (DWM and PM+) to the context of COVID-19 and to health care workers' needs. In particular, DWM has been culturally adapted including inputs from qualitative interviews and the original manual (illustrated guide, WHO, 2020a) has been digitalized using a mobile application tool. Using this format, people can use the self-help app in their own time. The five weekly sessions in the app will follow the 5 chapters of the illustrated guide (grounding, unhooking, acting on your values, being kind and making room). The PM+ manual has also been culturally adapted using the input from the qualitative work (phase 1, already approved). More information about the process of adaptation for the materials (DWM and PM+) can be found in **Annex I**.

People participating in DWM will have access to the DWM-app and also receive support from a trained helper. Helpers will be non-highly specialized professionals (e.g., residents of psychiatry, clinical psychology, and mental health nursing). The so-called helper will support participants in using the app via short weekly calls or text messages. Participants will decide how contacts with the helpers will be stablished (phone or message). PM+ will be delivered individually, remotely (e.g., videoconferencing tools such as Teams or Zoom), and delivered by the same helper. Both programs (DWM and PM+) are low-intensity interventions. The intervention manuals are included in **Annex II**.

3. Objectives

3.1. PRIMARY OBJECTIVE

To evaluate the (cost-)effectiveness, feasibility, and acceptability of the culturally and contextually adapted DWM/PM+ stepped-care program among health care workers during the COVID-19 pandemic in terms of mental distress, resilience, wellbeing, health inequalities, and costs to health systems.

3.2. SECONDARY OBJECTIVE

To identify barriers and facilitators to treatment engagement and adherence and opportunities for scaling up among the target population in Spain.

4. Study design

Study phase 2: Randomized controlled trial (RCT) (stepped-care DWM/PM+ intervention with Psychological First Aid (PFA) and care-as-usual (CAU) vs. PFA and CAU alone)
Study phase 3: Process evaluation with qualitative interviews and focus groups to assess barriers and facilitators of engagement and adherence to the stepped-care intervention and opportunities for scaling up the implementation of the intervention.

Study phase 2

We will conduct a **single-blind RCT in HCWs** with increased psychological distress to determine whether the stepped care intervention (i.e. DWM/PM+) leads to stronger decreases in mental health outcomes, and increase in wellbeing among compared to care-as-usual. The RCT will be implemented, and field work will be carried out in two sites Barcelona (Parc Sanitari Sant Joan de Deu, PSSJD) and Madrid (Servicio Madrileño de Salud, SERMAS). The current study protocol has already been sent for approval to the ethics committee of PSSJD.

The trial is designed as a multi-center, randomized, single-blind parallel-group trial with one treatment arm and one comparison arm. All participants in both the treatment and the comparison group will receive PFA and CAU. In addition to PFA and CAU, participants randomized into the treatment group will receive the DWM/PM+ stepped-care intervention, while participants randomized in the comparison group will receive PFA and CAU only. We expect to enroll 105 participants per arm (N = 210).

All participants in the treatment group (i.e. those who receive DWM and PM+ and those who only receive DWM because symptoms subside) will be followed for a period of 2 months after the end of the PM+ session (see Figure 1 for assessment points).

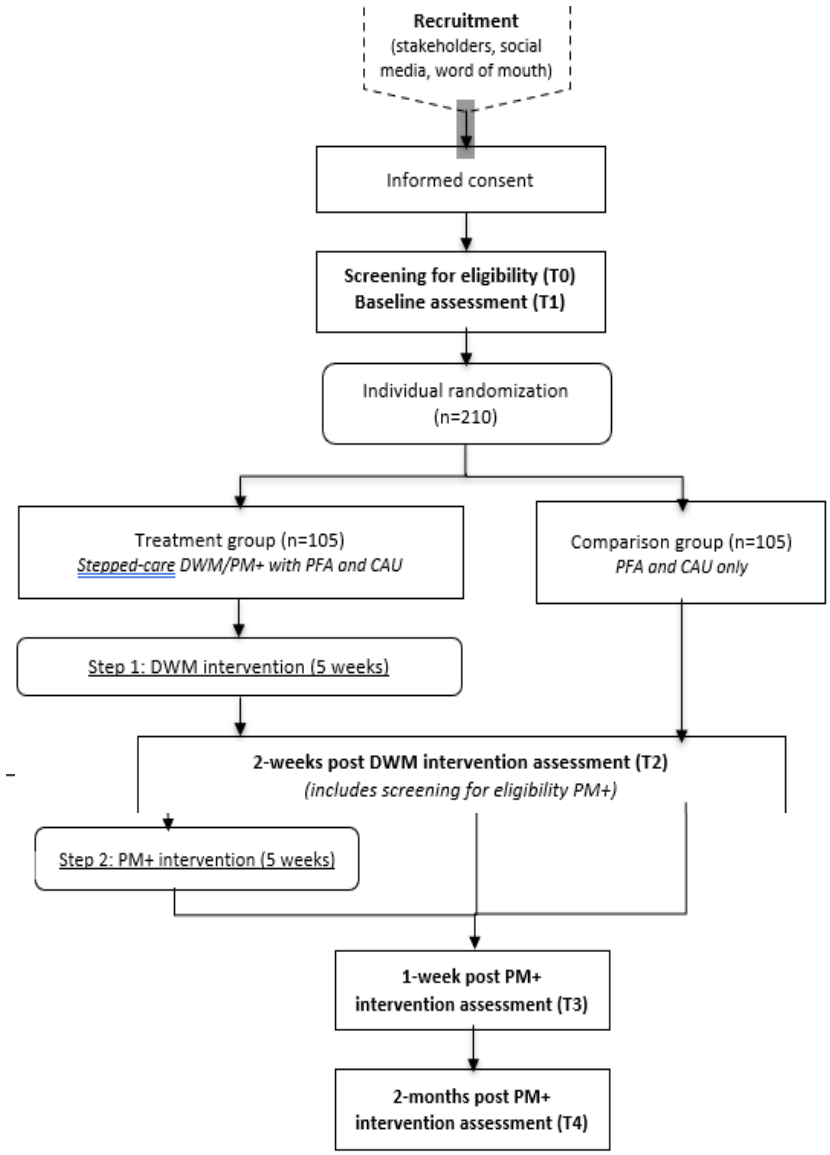


Figure 1. Flowchart of randomized controlled trial

Study phase 3

Study phase 3 is a qualitative study, consisting of interviews and/or focus group discussions among key stakeholders to evaluate barriers and facilitators to treatment engagement and adherence to the DWM/PM+ stepped-care intervention, as well as opportunities for scaling up the implementation of the intervention within the existing healthcare system. This

will inform partners in RESPOND of the synthesis and dissemination of the DWM/PM+ stepped-care intervention for vulnerable groups during a pandemic.

Key stakeholders include (a) participants in the RCT in study phase 2 who completed DWM (n=6; improved and not improved), who completed PM+ (n=6; improved and not improved), who dropped-out during DWM (n=6), and who dropped-out during PM+ (n=6)); (b) their family members/close persons of participants in study phase 2 who completed the intervention (n=6) and who dropped-out during the intervention (n=6); (c) professionals (n=20-25) (e.g. mental health practitioners and local stakeholders of participating centers, clinical staff in primary and secondary care, local & national policy makers); (d) facilitators of the DWM and PM+ intervention (both helpers and trainers/supervisors).

5. Study population

5.1. POPULATION

Study phase 2
Participants for the RCT will be HCWs hired by SERMAS (including physicians, nurses, technicians, and administrative staff). Participants will be recruited via official channels of the institutions, social networks, and stakeholders that took part in the recruitment study phase 1 (PI 4498). These official channels include (1) Madrilenian general hospitals' heads of Departments of Psychiatry and (2) the Oficina Regional de Salud Mental. They will disseminate the study, if they wish, by forwarding a pre-specified information sheet to potential elegible participants. The final decision on whether to read the information and contact the research team will rely on the potential participants only. The enrolment and recruitment phase is planned to start in September-October 2021 (after obtaining CEIC approvals for each of the sites), and will extend 18 months. The documents that will be created for recruiting and disseminating the study will be send to this Committee.

Study phase 3
Participants for the qualitative process evaluation will be key informants, such as participants who took part in the RCT; family members/close friends of participants who took part in the RCT; DWM/PM+ facilitators (helpers and supervisors); mental health professionals and decision makers (recruited through participating centers in study phase 2). For participants who took part in the RCT, we aim to include both those who took part only in DWM and those who took part in PM+ as well. Also drop-outs from both the DWM and PM+ intervention will be asked to participate in the qualitative process evaluation.

5.2. INCLUSION CRITERIA

Participants will be eligible to participate in the study (phase 2 (and 3)) if they meet all of the following criteria:

- Being 18 years or older
- Being a HCW currently employed by SERMAS
- Having elevated levels of psychological distress, as measured by the Kessler Psychological Distress Scale (K10) (score > 15.9)

- Having signed the informed consent form before entering the study[1]

5.3. EXCLUSION CRITERIA

Potential participants who meet the inclusion criteria will be excluded from participation in this study (phase 2 (and 3)) if they meet any of the following criteria:

- Having acute medical conditions (requiring hospitalization)
- Imminent suicide risk, or expressed acute needs, or protection risks that require immediate follow-up
- Having a severe mental disorder (e.g., psychotic disorders, substance-dependence)
- Having severe cognitive impairment (e.g., severe intellectual disability or dementia)
- Currently specialized psychological treatment (e.g., Eye movement desensitization and reprocessing, Cognitive behavioral therapy)
- In case of current psychotropic medication use, not being on a stable dose during the past 2 months being on an unstable dose for at least 2 months.

5.4. SAMPLE SIZE CALCULATION FOR THE CLINICAL TRIAL

A total number of 210 participants will be included (105 in Madrid and 105 in Barcelona). Based on prior studies on a PM+ intervention (Bryant et al., 2017; Rahman et al., 2016b), we aim to detect a small to medium Cohen's *d* effect size of 0.4 in the PM+ group at 2 months post-treatment based on the primary composite outcome Patient Health Questionnaire – Anxiety and Depression (PHQ-ADS) (Kroenke et al., 2016; 2019). The PHQ-ADS is the combined sum score of depression and anxiety symptoms of the Patient Health Questionnaire (PHQ-9) and General Anxiety Disorder-7 (GAD-7), respectively and has shown good internal consistency (α = .88 to .92) (Kroenke et al., 2016; 2019). A power calculation for a repeated measurement design suggests a minimum sample size of N=73 per group (power=0.80, alpha=0.05, two-sided, rho=0.9). Considering 30% attrition, we aim to include a total number of 210 participants (105 in the stepped-care DWM/PM+ treatment group (with PFA and CAU) and 105 in the PFA and CAU comparison group).

6. Treatment of participants in the clinical trial

6.1. CONTROL- AND TREATMENT CONDITION

Psychological First Aid (PFA)

All participants, both in the treatment and the comparison group, will be offered individual PFA through teleconferencing or phone calls. PFA is a WHO developed support strategy that involves humane, supportive, and practical help for individuals suffering from serious humanitarian crises. PFA does not necessarily involve a discussion of the event(s) that cause the distress but aims particularly at five basic elements that are crucial to promote in the aftermath of crises, i.e., a sense of safety, calm, self- and community efficacy, connectedness, and hope (Hobfoll et al., 2007). PFA consists of a conversation (approximately 30-45 minutes) that a helper has with a participant. The helper

[1] Due to COVID-19 restrictions, informed consent form will be signed remotely. A signable, pdf file will be created, and the participant will be able to either sign it electronically, or print it, sign it, and send it back to the research team.

provides non-intruding practical care and support, assesses needs and concerns, helps people to address basic needs (e.g., information), listens to people without pressuring them to talk, comforts people and helps them to feel calm, helps people to connect to information, services, and social support, and protects people from further harm (WHO, 2011). PFA will be adapted to HCWs' needs based on the outcomes of the first phase of the study (**Annex I**)

Care-as-usual (CAU)
In addition to PFA, both the treatment and the comparison group will receive CAU. Of note, CAU will not include specialized psychological treatment, as it is an exclusion criterion in the study. However, if someone fulfills inclusion criteria but at some points starts specialized psychological treatment, he or she will not be withdrawn from the study.

6.2. TREATMETN CONDITION

Treatment group: Stepped-care Doing What Matters/Problem Management Plus (DWM/PM+)
Stepped-care models assume to provide health care in the most efficient and cost-effective way: the first step of care is readily available for all those in need and more expensive treatments are reserved only for those not responding. Evidence suggest that stepped-care models are modestly effective (van Straten, Hill, Richards & Cuijpers, 2014; Ho, Yeung, Ng & Chan, 2016) although there is a high heterogeneity of such models (number of steps, duration of steps, rules about stepping up) and their effects. Interestingly, research in clinical practice has shown that results improve when care providers switch from a matched care to a stepped-care approach (Boyd, Baker & Reilly, 2019). The treatment group will receive the stepped-care program consisting of DWM (step 1) and PM+ (step 2) in addition to PFA and CAU (for details of CAU, see: '*Care-as-usual (CAU)'* above). Step 2 will only be provided if the participant still has elevated levels of psychological distress (K10 > 15.9) at 2 weeks after DWM, i.e., during the second quantitative assessment at 2 weeks after DWM.

Step 1: Doing What Matters (DWM)

The DWM program has been developed by WHO and collaborators working in the humanitarian field. DWM was designed to be relevant for large segments of adversity-affected populations: it is intended to be transdiagnostic, easily adaptable to different cultures and languages, and it is a low-intensity intervention. DWM is based on acceptance and commitment therapy, a form of cognitive-behavioral therapy, with distinct features (Hayes, Levin, Plumb-Vilardaga, Villatte & Pistorello, 2013). The acceptance and commitment therapy is based on the concept that ongoing attempts to suppress unwanted thoughts and feelings can make these problems worse, so instead it emphasizes on learning new ways to accommodate these thoughts and feelings without letting them dominate. The acceptance and commitment therapy has been shown to be useful for a range of mental health issues (Tjak et al., 2015) and has been used successfully in a guided self-help format (Hayes et al., 2013).

The original DWM program consists of a self-help guide called *'Doing What Matters in Times of Stress'* that is complemented with pre-recorded audio exercises. The audio material imparts key information about stress management and guides participants through individual exercises. Additionally, participants are guided by a briefly trained helper.

DWM includes five sections (or modules), each of which focuses on a specific skill:

- **Section 1:** *Grounding:* Bringing attention back to the present moment when caught up in distressing emotions.
- **Section 2:** *Unhooking:* Noticing difficult thoughts and feelings, naming difficult thoughts and feelings, and refocusing on what you are doing.
- **Section 3:** *Acting on your values:* Identifying personal values and then taking small or big actions to live in line with these values.
- **Section 4:** *Being kind:* Enhancing and encouraging kindness towards oneself and towards others.
- **Section 5:** *Making room:* Learning how to tolerate stress while still acting consistently with values.

In this study, the DWM program will be delivered as an online intervention. The DWM intervention, i.e. both the audios and the self-help guide, will be adapted for use on a smartphone or other device with internet access during Phase 1 of RESPOND. The format of DWM is innovative in that it seeks to ensure that key intervention components are delivered as intended using pre-recorded audio, without the burden of extensive training and supervision. In the online application tool, a new module (i.e., section) is released every week so participants will be asked to go through the entire DWM intervention within 5 weeks with weekly guidance from a helper. Due to its format, the DWM program does not require much time from experts for implementation. The delivery mode for the support from the helper will be flexible and in line with COVID-19 regulations. Additionally, research has found that guided self-help programs produce much better results than "pure" (unguided) self-help, and the effects produced by guided self-help are similar to face-to-face interventions (Fledderus, Bohlmeijer, Pieterse & Schreurs, 2012). When delivering the intervention, helpers will contact participants periodically, either via text message or phone call, depending on participants' preferences. These contacts will focus on identifying barriers and facilitators for the practice, in order to provide a more personalized attention.

Protocol adherence

We will assess DWM protocol adherence at post-intervention based on metadata collected during the intervention. Metadata do not include information typed into the app by the participant (e.g., the content of a text box where the participant is asked to provide an example of a stressful event). Rather, it refers to participants' usage of the DWM app such as who accesses what page, how often, how much time participants spend on the app etc. We will only use this meta-data during the intervention to remind each participant (e.g., through e-mail) after finishing each module to let them know that they should start a new module. Additionally, participants receive a weekly phone call from a helper to see how they are doing and to check on their progress.

Step 2: Problem Management Plus (PM+)

PM+ is a new, brief, psychological intervention program based on CBT techniques that are empirically supported and formally recommended by the WHO (Dua et al., 2011). The full protocol was developed by WHO and University of New South Wales, Australia. The manual involves the following empirically supported elements: problem solving plus stress management, behavioral activation, facing fears, and accessing social support. Figure 2 shows a brief outline of the five sessions. In these 60-minute sessions participants may talk to trained non-professional helpers (who are supervised by registered (clinical) psychologists). We will follow this outline, except that we excluded all assessment instruments from the manual, since they are administered at the assessments instead of at the intervention sessions. PM+ has four core features, and it is brief (five sessions).
In this study, the delivery mode of the PM+ intervention will be flexible, with remote delivery in phases of the pandemic when physical distancing rules apply (SERMAS's Microsoft Teams accounts will be used). This is a future-oriented attempt towards a more holistic mental health care system that can flexibly switch between modes of delivery (e.g. remotely (e.g. Zoom) or face-to), depending on the needs and the specific containment measures that apply, and the specific preferences and needs of the participant.

Protocol adherence

Helpers' adherence to treatment protocols will be ensured by weekly supervisions provided by the PM+ trainers/supervisors as well as the fidelity checklist (Dawson et al., 2016). In addition to these, audio records of the sessions will be used for fidelity checks. The sessions will be audio recorded with professional equipment only if the participant gives consent to be recorded.

Helpers in PFA, DWM and PM+ interventions

Helpers selected to provide support to users will be residents of psychiatry, clinical psychology, or mental health nursing, hired by SERMAS. They will be trained in the stepped-care intervention (DWM and PM+) and in PFA by experienced psychologists and psychiatrists. Helpers and trainers will sign a confidentiality agreement.

Training PFA helpers

Before providing PFA, helpers need training to enhance knowledge and gain better understanding of appropriate psychosocial responses and skills in providing support to individuals exposed to adversity (Sijbrandij et al., 2020). This half- or one-day training (WHO, 2013) includes explanations of the basic concepts and PFA principles, how to support (very) distressed people, and how not to cause further harm by using participatory learning (i.e. role-play).

Training DWM helpers

Similar to PFA-helpers, the role of the coach in DWM is to provide brief motivational support to the participants; not provide specialized mental health services. Helpers should be empathetic and motivated to do this. Before working as a helper, helpers will receive a short training (2 or 3 days depending on whether they are already trained in PFA) by academics and/or mental health-care professionals. Helpers will be trained in providing support using the stress management guide (i.e., practice using the stress management in role-plays with other helpers) and practice to deliver support remotely (i.e. practice providing support in role-play settings). Helpers will receive a written manual as a guide for the brief support sessions.

Training PM+ helpers

PM+ helpers will receive roughly 5 days of training, followed by three practice cases, on-the-job training, and close supervision during the whole trial by the PM+ trainers/supervisors. Audio records of PM+ sessions will also be used for supervision. The training program comprises of education about common mental disorders, basic counseling skills, delivery of intervention strategies and self-care (Rahman et al., 2016a).

Trainers/supervisors

All DWM/PM+ helpers will be actively trained and supervised by more senior psychologist and psychiatrists and will be continued to be monitored throughout the process. These clinicians will also independently assess and monitor treatment sessions at-random to ensure treatment adherence and fidelity. Furthermore, these expert clinicians will supervise the entire assessment and therapeutic process to reduce the burden on and risks for participants. DWM/PM+ trainers/supervisors will be approximately five licensed mental health care professionals such as health-care psychologists or psychiatrists. They will be trained by a Master Trainer via a training-of-trainers program, consisting of the same elements as the training for helpers, but also of training and supervision skills (Rahman et al., 2016a). The PM+ trainers/supervisors will be responsible for close supervision of the PM+ helpers. Therefore, as a next step, they will train DWM/PM+ helpers. Figure 3 shows how the training-of-trainers of PM+ is planned.

Supervision of the helpers by the trainers/supervisors will take place on a weekly basis (Dawson et al., 2016). This will be done remotely or face-to-face, depending on the preference of the trainers/supervisors and accounting for COVID-19 regulations. The trainers/supervisors will also receive supervision by the Master trainer when necessary.

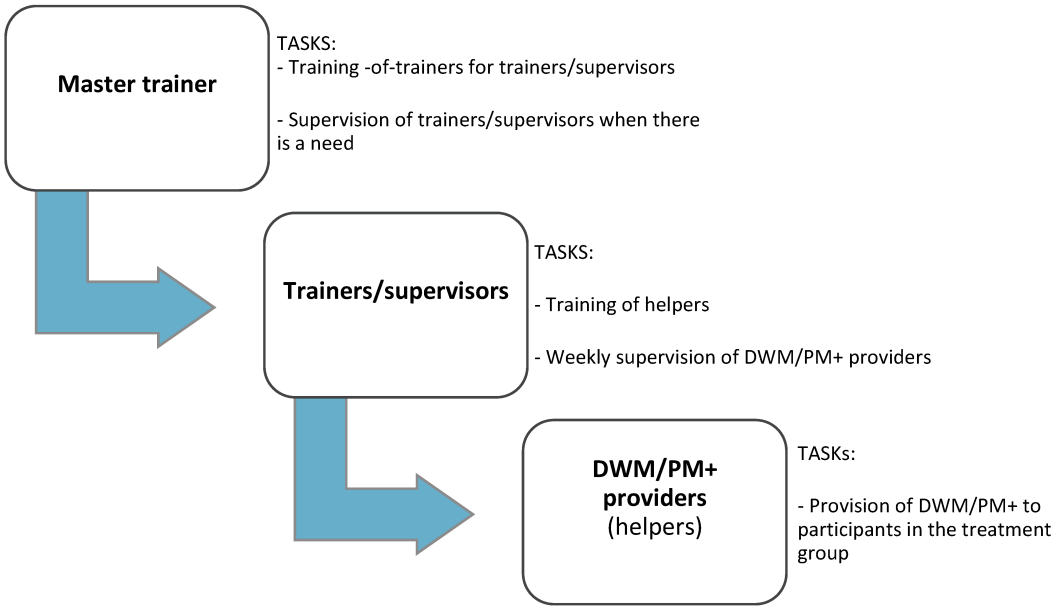


Figure 3. Training of Trainers/Supervisors and DWM/PM+ Helpers.

7. Methods

7.1. STUDY PARAMETERS/ENDPOINTS

All participants will have five assessments (T0-T4), consisting of online questionnaires mostly. The five assessments will take place at the following time-points (see also Figure 1):

T0: Screening for eligibility, including psychological distress

T1: Baseline assessment

T2: within 2 weeks post DWM intervention assessment

T3: 1-week post PM+ intervention assessment

T4: 2-months post PM+ intervention assessment

The hypothesis to be tested is that the stepped-care program consisting of DWM (step 1) and PM+ (step 2) plus PFA and CAU will be more effective in decreasing psychological distress compared to PFA and CAU alone.

7.1.1. Main study parameter/endpoint

The main study parameter will be the decrease in symptoms of anxiety and depression, from baseline to two-month follow-up, after the PM+ intervention ended, as measured by the combined sum score of the PHQ-9 and GAD-7 -

previously validated as the PHQ-ADS (Kroenke et al., 2016; 2019). A description of the measure(s) can be found under 'Study Procedures'. Based on prior studies on PM+ in Pakistan and Kenya (Rahman et al., 2016b; Bryant et al., 2017) where PM+ was administered as a standard treatment, we expect to detect a Cohen's *d* effect size of 0.4 in the PM+ group at 2 months post-treatment.

7.1.2. Secondary study parameters/endpoints

1. Depression scores (PHQ-9)
2. Anxiety scores (GAD-7)
3. Posttraumatic stress scores (PCL-5)
4. Self-identified problems (*Psychological Outcomes Profiles*, PSYCHLOPS)
5. Quality of life (EQ-5D-5L)
6. Cost of care: impact on use of health system, other services, time out of employment and other usual activities and need for informal care (*Client Service Receipt Inventory*, CSRI schedule)

The measurement instruments are described under 'Study procedures'.

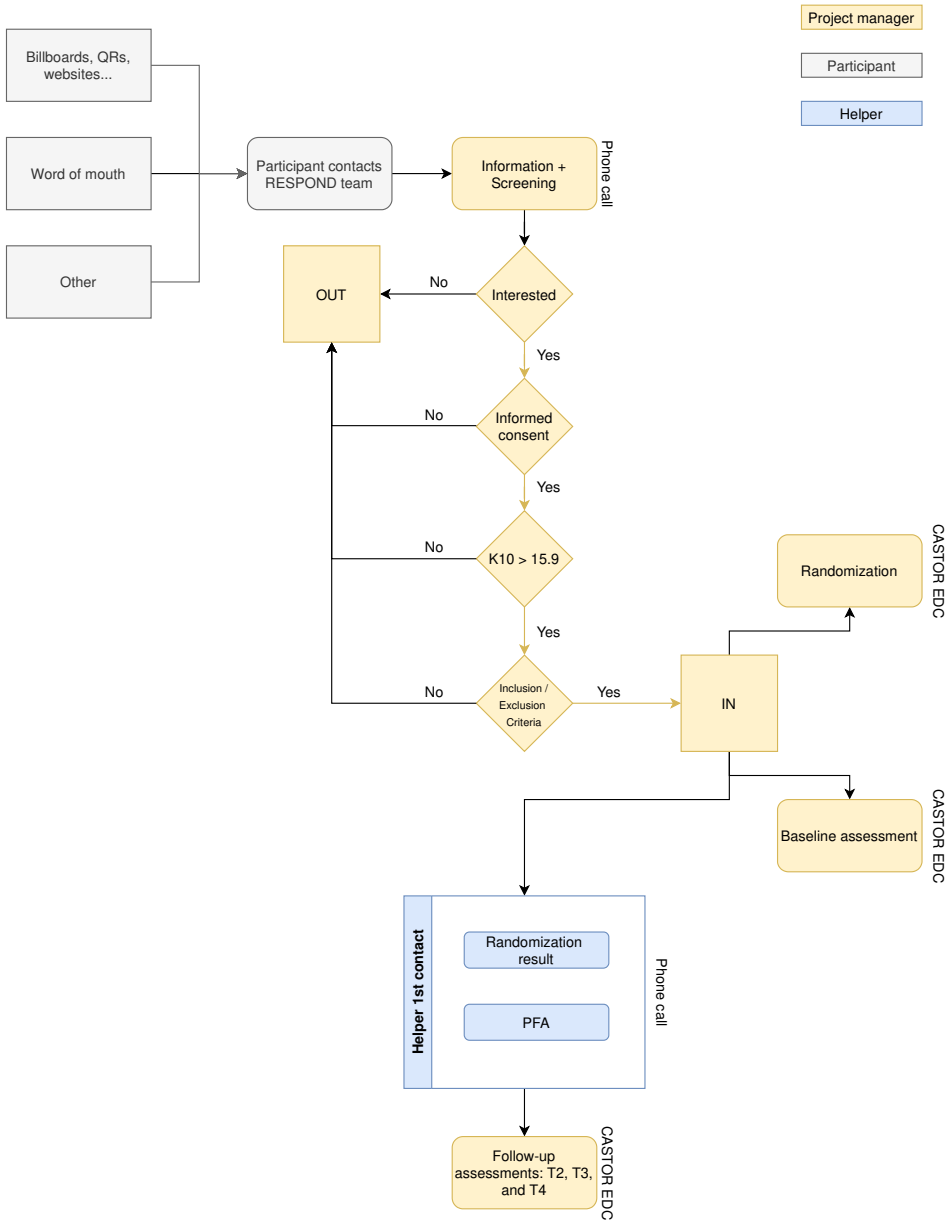
7.1.3. Other study parameters

1. Demographic data
2. Stressors' list designed ad hoc, based on the *Mainz Inventory of MIcrostressorS*(MIMIS)
3. Treatment fidelity (DWM: tracking app usage based on meta-data, PM+: audio records, checklists)
4. Level of self-identified complaints during PM+ (PSYCHLOPS)
5. Satisfaction (qualitative assessment in study phase 3)
6. Acceptability of the program (qualitative assessment in study phase 3)
7. Implementation indicators: reach, dose, resource use, costs of recruiting, training, and retaining staff delivering the stepped-care program, program costs, adaptation, etc.

7.2. RANDOMIZATION, BLINDING AND TREATMENT ALLOCATION

Participants will send their contact details (first name, phone number, and contact preferences) to the project office if they are interested in enrolling in the study. The project manager will call the participant to provide more information. If the participant is still interested, the project manager will send an email with the information sheet and the informed consent form, and the K-10 screening scale. During the call, the participant will be able to ask any questions related to the study and technical issues regarding electronic signature will be solved. Then, the project manager will check that the informed consent form is correctly signed and will rapidly correct the K-10. If the person scores above 15.9, the project manager will continue with the screening. If the participant screens out, at any stage, the project manager will provide feedback about the reasons for screening out, and will provide information for alternative mental health interventions if the participant asks for it. The participant will also be able to contact the project office if he or she has any further questions regarding the study. If the participant screens in, the project manager will inform about next steps. After hanging up, an electronic software (CASTOR) will randomly allocate the participant to either the experimental or the control arm. Once this is done, the software will send a link with the baseline assessment. The

participant needs to complete in the next 3-5 days. After that time, another person (a helper) will contact the participant and inform him/her about the outcome of the randomization process. Regardless of the intervention arm, the helper will then deliver the PFA intervention, which can be done easily and quickly on the phone. If the participant is allocated to the experimental arm, the helper will also talk with the participant about next step, which include an introductory call to the DWM intervention. If the participant is allocated to the control arm, the helper will remind him or her to contact the project office any further questions.



7.3. STUDY PROCEDURES

Recruitment

We will put up different non-probabilistic, sampling strategies. We will contact SERMAS representatives to circulate the information among their employees. We will also use snowball sampling techniques to forward flyers and informative sheets among potential participants via text messages, WhatsApp messages, and email. For this, we will identify local stakeholders (many of them already involved in the first step of this study), contact them, and ask them to share the information. These messages will include (1) an email address and (2) a link to the RESPOND website. If they are interested in participating, they could email the project manager and provide basic contact information.

The project manager will then contact the potential participant, send the information sheet approved by this Ethics Committee. The project manager will go through any question that the person might have, highlighting that (a) the person might not be eligible based on inclusion and exclusion criteria and (b) the person is as likely to receive an intervention as not to receive it. The informed consent will be signed remotely.

Screening (T0)

Following informed consent, participants will be invited to complete step 1 of the first assessment: screening. It comprises a self-administered scale (K-10), and a series of questions performed by the researcher to check inclusion and exclusion criteria. More detailed explanations of all measures are described under *'Measurement Instruments'.*

When participants are not selected for the trial because they score below the cut-off scores for the K10 or when they meet the exclusion criteria, they will immediately be provided feedback e.g., on the screening outcomes (including K10 score) and an explanation why they are not eligible for the study. When participants are excluded because of an imminent suicide risk, expressed acute needs/protection risks (for example, a young woman who expresses that she is at acute risk of being assaulted or killed), observed (suspicion of) severe mental disorders, or observed (suspicion of) severe cognitive impairment, they will be referred for appropriate treatment and support (e.g., general practitioner, mental health specialized support, emergency department, etc.).

Baseline assessment (T1)
If participants meet the eligibility criteria and score above the cut-off of the K10, they will continue with the baseline assessment. This step includes administration of contact information, preferences for remote contact (e.g. video-conferencing, e-mail/telephone) questionnaires about socio-demographic characteristics; the PCL-5; the PSYCHLOPS, the PHQ-9, the GAD-7, the MIMIS, the EQ-5D-5L, and the CSRI. All instruments are self-reported.

Post-intervention and follow-up assessment (T2, T3, T4)
Quantitative assessments will take place four times for all participants: at screening (T0) and baseline (T1: before the intervention), at 2 weeks after DWM (T2) and at 1 week (T3) and at 2 months after the PM+ program has finished (T4). All instruments used in the baseline assessment (T1) will be used for each of the post-intervention and follow-up assessments, see Table 1. The screening instrument K10 (T0) will be re-assessed at T2 only. In case participants do not respond to a scheduled assessment, they are called a maximum of five times (on different days) for scheduling a new appointment.

Assessors
Assessments T1 to T4 will be conducted online (collective program CASTOR EDC). Additionally, assessment of suicide risk, mental, neurological or substance use disorders, and the CSRI will be conducted by an assessor, in person or through video/telephone calls.

Assessment of treatment fidelity
DWM: Participants' usage of the DWM app will be tracked, such as who accesses what page, how often, how much time participants spend on the app, etc. This way, we can track protocol adherence to the DWM app afterwards, once they finished the intervention. During the intervention, we will only use meta-data to track participants' progress in the sense

that participants will receive an e-mail that the next module has been unlocked and is accessible for them to use one week after they finished the previous module. Additionally, participants receive a weekly phone call from a helper to see how they are doing and check on their progress.
PM+: Audio tapes of the treatment sessions will be recorded to monitor treatment fidelity. The audio tapes can be used for supervision by the trainers/supervisors and will be used to rate treatment fidelity.

Measurement instruments
The measurement instruments that will be used for the four quantitative assessments, i.e. at screening (T0) and baseline (T1), post-intervention 1 (T2), and post-intervention 2 (T3), and follow-up (T4), as well as during the DWM/PM+ intervention are depicted in Table 1. In case there is no translation of a measurement instrument in Spanish, the instrument will be translated and back-translated by the research team.

[PLEASE FIND TABLE 1 below with Overview of the concepts, their measures, the type of study parameter in the study, and the moment of measuring during study phase 2]

Concept	Measures	Type of study parameter	Moment of measuring						
			Screening (T0)	Baseline (T1)	DWM	Post-assessment 1 (T2)	PM+	Post-assessment 2 (T3)	Follow-up assessment (T4)
Psychological distress	K10	Screener	x			x			
Suicide risk:									
- Face-to-face *or*	PM+ tool	Screener	x			x	x		
- Self-administered	Step-by-step question	Screener	x			x		x	x
Mental, neurological or substance use disorders	PM+ tool	Screener	x						
Depression and Anxiety:	PHQ-ADS	Primary							
Subscale depression	PHQ-9	Secondary		x		x		x	x
Subscale anxiety	GAD-7	Secondary		x		x		x	x
Posttraumatic stress reactions	PCL-5	Secondary		x		x		x	x
Stressors	MIMIS	Secondary		x		x		x	x
Resilience factors	PASSc	Secondary		x		x		x	x
Quality of life	EQ-5D-5L	Secondary		x		x		x	x
Impact on resource use/costs	CSRI	Secondary		x		x		x	x
Socio-demographics		Other		x					
Treatment fidelity:	Metadata	Other			x				
- DWM									
- PM+	Audio records	Other					x		
Satisfaction DWM	Interview	Other				x			
Satisfaction PM+	Interview	Other						x	

Screeners

Screening instruments

K10: psychological distress

Psychological distress will be measures using the Kessler-10 Psychological Distress Scale (Kessler et al., 2002). The K10 is a ten-item self-report questionnaire to screen broadly for psychological distress (e.g. anxiety and depression related distress) experienced in the past 30 days. Items are rated on a five-point Likert scale ranging from *none of the time* to *all of the time*. The sum of the ten items gives a total score ranging from 10 to 50. Higher scores represent higher levels of distress. The K10 has strong psychometric properties and has strong discriminatory power to distinguish Diagnostic and Statistical Manual of Mental Disorders-IV cases from non-cases (Kessler et al., 2002). The K10 has been validated in various population samples and is a useful instrument in both primary care (Kessler et al., 2002) and general population samples (Furukawa, Kessler, Slade & Andrews, 2003; Kessler et al., 2005). Moreover, the K10 has been found to not have any substantial bias in regards to education level and gender, thus making it useful for research (Baillie, 2005).

There is no standard cut-off score for the K10 present. In addition to a cut-off score of 20, also lower cut-off scores have been found, e.g. a cut-off score of 12 (Lace et al., 2019) or a cut-off score of 14 (Baggaley et al., 2007). When determining the appropriate cut-off point, it is important to take into account the context in which the measurement instrument is used. In order to not miss potential participants, in research a low cut-off score with a low rate of false negatives and a high sensitivity is favored (Smits, Smit, Cuijpers & De Graaf, 2007). In STRENGHTS, a similar study to the RESPOND project, among Syrian refugees in the Netherlands, a cut-off point of 15 was used to indicate moderate to high levels of psychological distress (de Graaff et al., 2020). This was based on a study among Afghan and Kurdish refugees asylum seekers in New Zealand and Australia where they used the following cut-off scores: 10–15.9 (low risk of psychological distress), 16–21.9 (moderate levels of distress consistent with a diagnosis of moderate depression and/or anxiety disorder), 22–29.9 (high level of distress) and 30 or more (possibility of very high or severe levels of distress) (Sulaiman-Hill & Thompson, 2010). A cut-off score of 15.9 which we believe is appropriate for this varying target population.

Screening instruments for exclusion criteria

Suicidal ideation

Suicidality will be explored at several time-points (at T0, at T1, during PM+ and at follow-up assessments) with either the 'assessment of thoughts of suicide' risk tool (from PM+; WHO, 2016, pp. 86) when assessed in face-to-face contact (e.g., in person or remotely through teleconferencing or telephone) or with the self-administered step-by-step suicidality question (Van 't Hof et al., 2021) when assessed with an online questionnaire. People who have plans to end their life (as indicated by an answer of "yes" on the screening question - "In the past week/month, have you had serious thoughts or a plan to end your life?") will be excluded from the study. Participants who answer "yes" to this additional screening question will be considered at imminent risk of suicide (Van 't Hof et al., 2021). In case of imminent suicidal risk, people are excluded from participation. They will be explained (on-screen or by telephone/teleconferencing or in person) that they cannot participate but that they may need additional mental health support with advice to go to an emergency room. They will also be presented suggestions for steps to follow in order to receive mental health care (e.g., contact general practitioner), encouraged to seek help, and provided with additional self-care tips.

Severe mental disorder

(Suspicion of) a severe mental disorder will be assessed during the screening phase before starting the PM+ intervention 'Impairments possibly due to severe mental, neurological or substance use disorders. This is a tool which is to be filled in by the assessor based on their observations and judgment of the participants' behaviors. No questions are asked to the participant. The tool asks 4 questions related to the participant's behavior: 1) does the participant understand you (even though they speak the same language or dialect)?; 2) Is the participant able to follow what is happening in the assessment to a reasonable extent?; 3) Are the participants' responses bizarre and/or highly unusual?; 4) From the participants' responses and behaviors, does it appear that they are not in touch with reality or what is happening in the assessment? If the answer is no to question 1 or 2, or yes to question 3 or 4, the participant will be excluded.

Primary outcome measure

The PHQ-ADS is the sum of the PHQ-9 and GAD-7 scores (details of both instruments summarized below) and thus can range from 0 to 48, with higher scores indicating higher levels of depression and anxiety symptomatology. Two validation studies of the PHQ-ADS in trial datasets of patients with chronic (musculoskeletal) pain and oncologic diseases have been

published (Kroenke et al., 2016; Kroenke et al., 2019). Evidence shows high internal reliability (Cronbach's alpha of 0.8 to 0.9), strong convergent and construct validity, sufficient unidimensionality and evidence for sensitivity to change (i.e., differentiating between individuals classified as worse, stable, or improved by a reference measure at three months post-intervention).

Secondary outcome measures

PHQ-9: depression (PHQ-9; subscale of PHQ-ADS)
Depressive symptoms during the past two weeks will be measured using the Patient Health Questionnaire depressive module. It asks how often someone was bothered by each of the nine DSM-5 criteria and scores answers on a four-point Likert scale ranging from 0 (not at all) to 3 (nearly every day) (Kroenke, Spitzer, & Williams, 2001). In addition to the nine items, the PHQ-9 asks: "If you checked off *any* problems, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?", which is to be answered with "Not difficult at all", "Somewhat difficult", "Very difficult", or "Extremely difficult". For the current study, we will examine changes in caseness in depression. We will use a cut-off score of 10, which has been found to be a valid cut-off point for diagnosis (Manea, Gilbody & McMillan, 2021).
The PHQ-9 has been translated to and is available in many languages (see https://www.phqscreeners.com/). The PHQ-9 has been found to be a reliable and valid instrument to measure depressive severity. Furthermore, due to its brevity, PHQ-9 is a useful instrument for usage in a clinical or research setting (Kroenke et al., 2001).

GAD-7: anxiety symptoms (GAD-7; subscale of PHQ-ADS)
The GAD-7 questionnaire is a seven-item, self-report anxiety questionnaire which assesses the degree to which the patient has been bothered by feeling nervous, anxious or on edge over the last two weeks. Items also include other generalized anxiety symptoms such as being unable to stop worrying about multiple things, having trouble relaxing or sitting still, feeling irritable and being afraid of something bad happening at all times (Spitzer et al., 2006). Items are scored from 0 to 3, respectively for experiencing symptoms 'not at all', for 'several days', for 'more than half the days' and for 'nearly every day'. The total score ranges from 0 to 21. Cut-off points for mild, moderate and severe anxiety, are scores of 5, 10 and 15, respectively (Spitzer et al., 2006). A score of 10 has been identified as the optimal cut-off score to balance specificity and sensitivity (Spitzer et al., 2006).
The GAD-7 has been translated to and is available in many languages (see https://www.phqscreeners.com/).

PCL-5: PTSD Symptoms
PTSD symptoms during the past week according to the DSM-5 PTSD diagnosis will be measured using the PCL-5 (Weathers et al., 2013). A shortened 8-item version of the original PCL-5 (a 20-item checklist which correspond with the 20 DSM-5 PTSD symptoms) will be used. Items are rated on a 0-4 scale. Added up, the maximum severity score is 32. Higher scores indicate higher symptomatology.

Stressors' list
We will include a checklist of stressors experienced in the past weeks, based on the MIMIS. The MIMIS was recently developed to measure objective microstressors of modern life in the past 7 days (Chmitorz et al., 2020). In the Dynacore-C study (Veer et al., 2021) this was changed into a period of 2 weeks and a shorter general and COVID-19 specific stressor list. The MIMIS uses a definition of resilience as a trade-off between the outcome of mental health and exposure to adversity. Outcome-based resilience will be assessed by relating self-reported changes in mental health problems (i.e. anxiety and depression) over the past 2 weeks (assessed with the PHQ-ADS) to the self-reported exposure to 11 categories of general stressors (life events and daily stressors such as physical health problems, family conflicts or separation form a loved one) and 29 COVID-19 crisis related stressors (such as COVID-19 symptoms, belonging to a risk group for serious COVID-19 symptoms, loss of social contact, or problems arranging childcare (Veer et al., 2021). Items are rated on a five-point Likert scale in which participants can indicate to what extent the situation caused them mental strain, ranging from 0 (not at all straining) to 4 (very straining). e.g., family, friends, work, finances, environmental and

living conditions). If participants did not experience the situation in the past 7 days (or two weeks similar to Dynacore-C study), they can choose 'did not occur'. A high correlation has been found between the ecological momentary assessment, end-of-day, and end-of-week versions of the MIMIS regarding the occurrence and severity of microstressors, thereby indicating ecological validity of the MIMIS questionnaire (Chmitorz et al., 2020).

Resilience related constructs (Dynacore-C study; Veer et al., 2021)

Resilience factors (i.e. underlying factors that lead to resilience) may also be measured by assessing factors like optimism, positive appraisal style, perceived social support (in general and related to COVID-19), perceived self-efficacy and behavioral coping style. In RESPOND, we will assess positive appraisal style with the Positive Appraisal Style Scale – content focused (PASSc). The PASSc is based on positive appraisal style theory of resilience (PASTOR; Kalisch et al, 2015; Kalisch et al, 2021). The PASTOR theory conceptualizes resilience as an outcome: the maintenance of mental health after stressor exposure. Positive appraisal style would therefore not be a measure of resilience, but a resilience factor. It intends to capture the underlying mechanism which leads to resilience. The PASSc is currently used in a number of longitudinal studies (Mainz Resilience Study; Longitudinal Resilience Assessment study, and several studies of the DynaMORE project). The PASSc was originally developed as a 29 items questionnaire featuring generalized positive appraisals of and attitudes towards difficulties, covering specifically the 3 main dimensions of stressor/threat appraisal - appraisal of threat magnitude/cost (relating to catastrophizing vs. trivialization), of threat probability (relating to pessimism vs. optimism), and of one's coping potential (relating to helplessness vs. overconfidence). Internal validity testing and a factor analysis resulted in a reduced list of 12 items, which is the PASSc. A paper (R. Kalish and P. Petri-Ramao) currently being prepared shows internal consistency $\alpha = .87$ and reliability Cronbach's $\alpha = .84$. The PASSc shows convergent validity with other underlying resilience factors as it correlates with optimism .52 (SOP-2), with stress recovery (BRS): .50, with well-being (WHO-5): .42, with trait anxiety (STAI-Y2): -.51 , with neuroticism (from BFI-10): -.49. Discriminant validity is shown in low correlation with I-8 impulsivity subscales urgency, intention <=.13; with openness (from BFI-10): .17, with conscientiousness (from BFI-10): .19.

EQ-5D-5L: quality of life

The EQ-5D-5L measures quality of life and consists of two parts, the EQ-5D and the EQ VAS. Part 1, the EQ-5D, rates the level of impairment across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The EQ-5D-5L is an adapted version of the EQ-5D(-3L), which only had three response options for each dimension and was therefore thought to not sufficiently capture milder health issues and small changes between different states of health (Herdman et al., 2011). The EQ-5D-5L has been used widely and is available in over 150 languages, also for laptop, tablet or Castor EDC (https://euroqol.org/eq-5d-instruments/eq-5d-5l-available-modes-of-administration/self-complete-for-use-in-castor-edc/). Country specific utility weights will be attached to data from the EQ-5D-5L and changes in participant quality of life years gained between intervention and control groups will be determined. Part 2, the EQ VAS, is a visual, vertical, analogue scale. The endpoints of the scale are called 'The best health you can imagine' and 'The worst health you can imagine' and the current health status of that day needs to be indicated, after which the number checked on the scale also needs to be written down.

CSRI schedule: cost of care

The CSRI was developed for the collection of data on service utilization (e.g., use of health system, other services, time out of employment and other usual activities, need for informal care) and related characteristics of people with mental disorders, as the basis for calculating the costs of care for mental health cost-effectiveness research. It has been used cross-culturally and is available for Spain.

Other measures

Socio-demographic information

Socio-demographic information will be collected with predefined items based on the REDEFINE and STRENGTHS studies (i.e. age, gender, nationality, years of education, relationship status, and main work-status and additional questions

regarding country of birth, household population (incl. children < 18 and elderly people), household income on average, occupational area working, mental health condition and overall current health status and housing (square meters of the house, outdoor space available).

Treatment fidelity

To monitor treatment fidelity of DWM, participants' usage of the DWM app will be tracked (more information is provided below). To monitor treatment fidelity of PM+, treatment sessions will be audio-recorded. If participants are randomized into the treatment group, they will be asked for a separate consent to record the sessions (see informed consent). Giving consent to the recording is no requirement to receive the PM+ program. They will be coded by the local research team and used for treatment fidelity analysis. To determine whether the intervention-as-implemented does not differ from the intervention-as-designed, fidelity checklists filled out by the research team for a random sample, stratified on helpers, of sessions / participants. The data will be collected throughout the intervention delivery and reviewed as it is collected, leading to an iterative process of intervention monitoring informing intervention delivery. Treatment fidelity will be analyzed as manipulation check.

Satisfaction and acceptability

Satisfaction and acceptability of the stepped-care DWM/PM+ intervention is measured through qualitative process evaluation (see Study Phase 3).

Implementation indicators

After the intervention has finished, various implementation indicators will be assessed, such as reach, dose, resource use, costs of recruiting and retaining staff delivering the stepped-care program, program costs, adaptation, the process and quality of the stepped-care DWM/PM+ intervention.

Additionally, we will estimate the incremental cost per change in the primary outcome and and in quality of life, as part of the cost-effectiveness analysis. To do this, estimates of the resource use and costs of implementation are needed, making use of data from implementation indicators. This will involve analysis of records on resources and costs for initial training, as well as use of process and fidelity data on resources used for receipt of interventions, such as the number of PM+ sessions attended and input and support from supervisors.

Study phase 3

Study phase 3 consists of a qualitative study. The aim of this study is to explore the feasibility, i.e. identifying barriers and facilitators specific to the target population, of scaling-up the implementation on the stepped-care DWM/PM+ intervention. This will be done by conducting in-depth semi-structured interviews and focus group discussions with key informants. In these interviews, participants' satisfaction and acceptability of the program will also be explored. The interviewer will first ask an open question to the participant (e.g., "how was your experience during the trial?", "could you tell me how being in the trial was for you?"). If the person stops providing information, the interviewer will ask him or her to tell a bit more about it. If the person stops again, the interviewer will ask specifically about satisfaction (e.g., "would you say you were satisfied with the intervention that you received? Why?") and about acceptability (e.g., "was there anything you found difficult during the intervention? What was it and why was it difficult?", "was there anything you found easy during the intervention? What was it and why was it easy?").

Key informants will include participants in the treatment group who completed the DWM intervention (n=6; improved and not improved) or the PM+ intervention (n=6; improved and not improved), who dropped-out during DWM (n=6) or during PM+ (n=6), and family members (or close persons) of participants in the treatment group who completed the DWM or PM+ intervention (n=6) or dropped out during DWM or PM+ (n=6). Participants and their family members will be asked questions concerning the satisfaction and acceptability of the intervention, barriers and facilitators to adherence, and to what extent they think that the stepped-care program has actually contributed to improving participants' functioning. Recruitment for participants of the treatment group and their family members will start at 3 months post-PM+.

Additionally, we will interview (a) mental health practitioners of the participating centers, (b) local stakeholders of the participating centers, e.g. mental health specialists and supervisors, with a role in policy development or implementation, (c) clinical staff in primary (e.g. GPs, social workers) and secondary (e.g. psychologists) care, and (d) local and national policy makers with knowledge on mental health care (20-25 participants in total). Policy decision makers will be interviewed to obtain their perceptions of the benefits and challenges of integrating the stepped-care DWM/PM+ intervention into routine service provision. Health care professionals will be interviewed to explore their views on the potential for scaling-up the stepped-care DWM/PM+ intervention and integrating the program into the health system in Spain. Furthermore, we will conduct focus group discussions with facilitators (n=4-8) of the DWM/PM+ intervention. Facilitators will include both helpers and trainers/supervisors and we will balance for power of various stakeholders. Facilitators will be interviewed on their experience in providing the DWM/PM+ intervention and to obtain their ideas in implementing this intervention in Spain.

Interviews and focal group discussions will be conducted online or in person, depending on the preferences of the participant and will in accordance with COVID-19 regulations. Key informant interviews and focal group discussions will be audio-recorded and transcribed. The transcribed data will be coded and analyzed using the qualitative data analysis software program NVIVO.

7.4. WITHDRAWAL OF INDIVIDUAL PARTICIPANTS

Participants can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a participant from the study for urgent medical reasons, e.g. imminent suicide risk. Since only individuals with imminent suicide risk will be excluded, those with suicidal thoughts at inclusion/screening will be followed up by the helpers. When during calls with DWM/PM+ helpers, participants show deterioration with imminent suicidal plans than the helper will discuss this immediately with one of the DWM/PM+ supervising mental health specialists. Also, when there is clear suspicion of worsening of (severe) mental health problems, participants will be asked to withdraw from the study and contact their general practitioner for a referral to specialized mental health treatment.

7.5. REPLACEMENT OF INDIVIDUAL PARTICIPANTS AFTER WITHDRAWAL

No new PARTICIPANTS will be included for each withdrawn subject. In our power calculation for the sample size, we have taken into account 30% attrition.

7.6. FOLLOW-UP OF PARTICIPANTS WITHDRAWN FROM TREATMENT

If a subject decides to withdraw from the study, the investigator will ask for the reason. It will be enquired whether the subject wishes to withdraw from the study or from a specific time point only and so whether the subject can be re-contacted at a later time. Withdrawal from the study will have no effect on the regular treatment. Participants who leave the study for medical reasons will be followed until the interfering condition has resolved or reached a stable state.

7.7. TEMPORARY HALT FOR REASONS OF SUBJECT SAFETY

We will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited medical research ethics committee without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited medical research ethics committee. The investigator will take care that all participants are kept informed.

7.8. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, FOLLOW-UP OF ADVERSE EVENTS.

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the trial procedure or the stepped care DWM and PM+ intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

A serious adverse event is any untoward medical occurrence or effect that:

- results in death
- is life threatening (at the time of the event)
- requires hospitalisation or prolongation of existing inpatients' hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all serious adverse events to the sponsor without undue delay after obtaining knowledge of the events, except for the following serious adverse events: Not applicable.

The sponsor will report the serious adverse events through the web portal ToetsingOnline to the accredited medical research ethics committee that approved the protocol, within seven days of first knowledge for serious adverse events that result in death or are life threatening followed by a period of maximum of eight days to complete the initial preliminary report. All other serious adverse events will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

8. Ethical considerations

8.1. ANONYMISATION AND PSEUDONYMISATION

Anonymization will be applied to personal data to achieve irreversible de-identification and optimal solution will be decided on a case-by-case basis by using a combination of different techniques:

1. Pseudonymization: personal data (i.e., names and surnames, contact information, department) will be removed from the dataset and kept separately and securely stored in SERMAS's (HULP) secure servers. Organization and departments will be also assigned with a unique ID code. Original values will be securely kept in SERMAS and will be able to be retrieved and linked back to the pseudonym, should the need arise. The ID number will be unique, and shall not have relationship with the original values. Security controls (including administrative and technical ones) will be used to protect the identity database.
2. Generalization: a deliberate reduction in the precision of data, such as converting a person's age into an age range. This technique will be used for values that can be generalized and still be useful for the intended purpose.
3. Synthetic Data: mainly used to generate synthetic datasets directly and separately from the original data, instead of modifying the original dataset.

Since pseudo-anonymised data might still be attributed to a natural person by using additional information such as a decryption key, the General Data Protection Regulation will remain applicable in this particular case.

8.2. DATA ACCESS AND MANAGEMENT

Data access and management

All personal data from the Madrid site will be securely stored in SERMAS's secure servers.

1) Data collection platform (assessments). Data collection for the assessments will be managed using Castor EDC. This platform complies with all the relevant General Data Protection Regulation obligations and HIPAA regulations (more specific information can be found here: https://www.castoredc.com/wp-content/uploads/2021/04/Castor-Assessment-of-GDPR-and-HIPAA-Compliance.pdf).
2) Qualitative study (phase 3). The material recorded in audio, as well as the field notes will be stored on a server within the information systems of SERMAS. This information will be accessible to the research team only. The transcripts will be stored in the SERMAS server and a proprietary license will be used for the data analysis software to which only researchers will have access to.

Metadata (DWM-app). DWM app will collect metadata, such as the time spent in certain sections, the frequency of logins, the time elapsed between one login and the next one, number of sections complete, etc. No personal data will be stored within the app apart from the email address / phone number used for setting reminders or retrieving passwords. Each participant (user) will have a unique identifier that will allow him or her to access the app. That identifier will be linked to the main participant's ID, so that we can evaluate treatment adherence individually.

The platform is hosted on a VPS-server provided by ' VIP internet '. VIP is a certified (ISO 9001, ISO 27001 en NEN 7510) hosting provider. The VPS is located in a datacenter in the Netherlands, runs on Linux with Plesk as a hosting control panel on top of it. Apache is used as a web server with NGINX on top of it as load balancer. MySQL is used as a database server. All data of the system are stored in the MySql database. All directly and indirectly identifiable personal information included given answers in lessons and questionnaires are stored encrypted by the AES algorithm. Furthermore, the data is pseudonymized : the directly and indirectly identifiable personal information is not directly

linked to each other with a referring key but by a hash.The database is automatically backed up each day and is kept for seven days. The data transfers between clients (browsers) and the webserver are encrypted and secured by a Let's Encrypt SSL certificate that is automatically renewed every three months.

Management, communication and transfer of personal data of all participants will be in compliance with Regulation EU 2016/679 of the European Parliament and of the Council of April 27, 2016 on the protection of natural persons as regards to the treatment of personal data and the free circulation of data, being mandatory from May 25, 2018 and to Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights. The legal basis that justifies the treatment of the data is the consent signed by the patient, in accordance with the provisions of article 9 of the EU Regulation 2016/679.

The data collected will be only identifiable by a code, thus no information will be included to identify participants. Only researchers and their collaborators with the right of access to the source data will be able to link the data collected in the study to the participants' personal data. The identity of the participants will not be available to any other person except for a medical emergency or legal requirement.

Those who might have access to the identified personal information are: health authorities, the Research Ethics Committee and personnel authorized by the study promoter, when necessary to check study data and procedures, but always maintaining confidentiality in accordance with current legislation.

Only the encrypted data will be transferred to third parties and other countries, which in no case will contain information that can directly identify the participant (such as name and surname, initials, address, social security number, etc.). In the event that this transfer occurs, it would be for the same purpose of the study described and guaranteeing confidentiality.

In the event that encrypted data transfer is conducted outside the European Union, either in entities related to the hospital center where the patient participates, to service providers or researchers who collaborate with us, the data of the participants will be protected by safeguards such as contracts or other mechanisms established by the data protection authorities.

In addition to the rights that the previous legislation already contemplates (access, modification, opposition and cancellation of data, deletion in the new Regulation), the participants can also limit the management of data collected for the project that is incorrect, request a copy or limit moving data to a third party (portability). To exercise these rights, they shall contact the principal investigator of the study or the Data Protection Officer of the SERMAS through . Likewise, they have the right to contact the Data Protection Agency if they are not satisfied.

Data cannot be deleted even if a participant leaves the study, to ensure the validity of the research and to comply with legal duties and medication authorization requirements.

The Investigator and the Sponsor are obliged to keep the data collected for the study for at least 10 years after its completion. Subsequently, personal information will only be kept by the health care center and by the sponsor for other scientific research purposes if the participant has given his/her consent, and if permitted by applicable law and ethical requirements.

8.3. ETHICS AND DATA ADVISORY BOARD (EDAB)

The RESPOND' Ethics and Data Advisory Board (EDAB) will monitor and provide expert advice on data management and all ethical, legal and societal issues that arise within the project, promoting integrity and a better alignment of RESPOND with social needs and expectations that may arise within or as a result of RESPOND. This includes monitoring the safety, rights, and wellbeing of study participants, and providing input for ethics reports. In addition, the EDAB will provide advice on FAIR data management, including data privacy and adherence to the General Data Protection Regulation. The EDAB

will ensure that the trial and data collection in RESPOND are conducted in accordance with the International Conference on Harmonisation, the WHO Good Clinical Practice standards, Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013), and (inter)national laws (e.g, Medical Research Involving Human Subjects Act (WMO)). In addition, the ethical, legal of the participants and research staff members will be reviewed and interim analyses will be considered in case safety issues are (suspected to be) violated. Incidental findings within RESPOND refer to an extreme score on study instruments (questionnaires or interviews) that need additional follow-up. Other issues that will be considered include privacy and intellectual property rights. Relevant issues will be discussed in an annual meeting, but if issues arise between these meetings, the EDAB will be requested to plan an additional meeting. Additional meetings will be held before submission of ethics documents for formal approval as well as before submission of ethics reports. The EDAB compromises of independent members having no conflict of interest with the sponsor of the study, i.e. dr. Christopher Dowrick, dr. Victor Perez, and dr. Sonja Rutten, member of the Ethics Review Committee Board member (VUA). For RESPOND principal investigator Prof. dr. Marit Sijbrandij will join the EDAB meetings together with assistant professor Dr. Anke Witteveen. Tom Paffen LL.M (VU) will join for matters of data protection and privacy.

The management team and EDAB will ensure that all necessary actions will be undertaken to minimize risks and suggest necessary measures to counter these risks. Through efficient communication between the EDAB, overall management (Work Package 1), and leader of individual Work Packages, the consortium will ensure that mitigation measures will be undertaken in a timely and effective manner.

The advice(s) of the EDAB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the EDAB, the sponsor will send the advice to the reviewing medical research ethics comitees, including a note to substantiate why (part of) the advice of the EDAB will not be followed. The EDAB should conclude each review with their recommendations to RESPOND as to whether the study should continue without change, be modified, or be terminated. Recommendations regarding modification of the design and conduct of the study could include: modifications of the study protocol based upon the review of the safety data; suspension or early termination of the study or of one or more study arms because of serious concerns about participants' safety, inadequate performance, or rate of enrolment; suspension or early termination of the study or of one or more study arms because study objectives have been obtained according to pre-established statistical guidelines.

8.4. PUBLIC DISCLOSURE AND PUBLICATION POLICY

The trial will be registered in a public trial registry (e.g., www.clinicaltrials.gov) before the first patient is recruited. The results of the study will be submitted for publication in international, peer-reviewed journals. Moreover, findings may will be presented in scientific conferences and be disseminated to stakeholders working in the field. In addition to all, the results of the study will be disseminated through the WHO website and other dissemination channels of WHO. A preliminary version of the RESPOND Communication and Dissemination Plan has been delivered to the EU in February 2021.

9. STATISTICAL ANALYSYS

9.1. PRIMARY STUDY PARAMETERS

The statistical analysis of the RCT will estimate effectiveness of the stepped-care DWM/PM+ intervention with PFA and CAU compared to PFA and CAU alone, with PHQ-ADS score as the primary study parameter.

The primary outcome will be summarized using number of participants (*n*), minimum and maximum; and means, standard

deviations (*SD*) for normally distributed data, or medians and inter-quartile ranges for non-normally distributed data. To measure comparisons at baseline between the two treatment arms, either independent-sample *t* or Mann-Whitney tests will be performed on continuous variables, and Fisher's or chi-squared tests on categorical variables.

Both intention-to-treat (ITT) and per-protocol (PP) analyses will be conducted. ITT will include all randomized participants (n ~ 210) while PP will include only those who completed the intervention program. The main conclusion of the trial will be based on the ITT analysis of the primary outcome. A secondary analysis of the primary outcome will also be presented using the PP population.

The statistical analysis will be masked, i.e. the trial statistician will be blinded to the treatment groups until the analysis has been completed. Moreover, the trial statistician will not be involved in determining participants' eligibility, in administering the intervention, in measuring the outcomes or in entering data.

To estimate the treatment effect, either linear or generalized mixed models will be employed for the primary endpoint analysis, which will have treatment as fixed effects, baseline measurement of primary endpoint as covariate, and subject as random effects. The mean difference between two treatment arms at each visit/time together with its 95% confidence interval will be derived from the mixed model. Covariate-adjusted mixed model of primary endpoint will also be performed by adding pre-specified covariates at baseline (gender, age, education, adverse (traumatic) events, COVID-19 related events, and severity of symptoms) into the above model. Post-hoc sensitivity (i.e., moderation) analyses will also be conducted based on baseline characteristics (e.g., different treatment effects for men and women).

Missing data

Missing data will be treated as missing at random. No imputations of missing values will be made, as multilevel models can deal with missing data (Singer, Willett & Willett, 2003).

9.2. SECONDARY STUDY PARAMETERS

Economic outcomes

Health economic analysis will be conducted to determine the difference in costs and outcomes in the intervention arm as compared to the care as usual group. Primary analysis will be the total costs over the 2-month follow-up treatment period. Between-group comparison of mean costs will be completed using standard *t*-test with ordinary least squares regression used for adjusted analysis, with the validity of results confirmed using bootstrapping. Pseudonymized data will be sent to the London School of Economics and Political Science, partner in RESPOND under Work Package 3, for the health economics analysis of the CSRI.

Analysis of secondary outcomes with repeated measurements

Additionally, linear or generalized mixed models as mentioned for the primary outcome analysis (PHQ-ADS) will be carried out for analyzing the following clinical outcomes measured at baseline, at 2 weeks after DWM, at 1 week and at 2 months after finishing PM+: posttraumatic stress reactions (PCL-5), depressive symptoms (PHQ-9), generalized anxiety (GAD-7), resilience (MIMIS) and quality of life (EQ-5D-5L).

Analysis of other secondary outcomes

Changes in caseness of the composite measure anxiety and depression will be calculated for the PP sample using the recommended cut-off of >20 for moderate severity on the PHQ-ADS questionnaire (Kroenke et al., 2016; Kroenke et al., 2019) and will be analyzed using a hierarchical logistic model with the same fixed and random effects as the hierarchical linear models above, from which odds ratio of having a depression together with 95% CI at each time point will be derived.

Corrections for multiple testing

Models will be tested on $\alpha = .05$; we will not apply a post-hoc correction to deal with problems associated with multiple testing, but instead report the number of tests that are carried out.

9.3. OTHER STUDY PARAMETERS

Phase 3 will consist of qualitative interviews and/or focus group discussions among participants and key stakeholders to evaluate possible barriers and facilitators to treatment engagement and adherence to the PM+/DWMS program. The outcomes of these assessments will be used to make informed-decisions for potential mediators or moderators of PM+/DWMS treatment effectiveness.

Treatment fidelity (PM+):

To determine whether the intervention-as-implemented does not differ from the intervention-as-designed, we will select a random sample of participants. PM+ supervisors and trainers will listen to the recordings while they fill out a checklist. These checklists will not disclose anything about the participant, and it will only include an identifier of the helper/provider.

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Research protocol - CATALONIA

RESPOND. Improving mental healthcare of health care working during the COVID-19 pandemic: implementation of a stepped care program. Phase 2 and 3, randomized controlled trial

Version of the protocol	3 (PIC-129-21)
Date	28.02.2022
Funding	Horizon 2020 (European Commission). This project has received funding from the European Union's Horizon 2020 research and innovation programme Societal Challenges under Grant Agreement No 101016127
Original title	Improving the P**RE**paredness of Health Systems to Reduce Mental Health and **P**sychosocial Concerns resulting from the C**O**VID-19 Pa**ND**emic
Acronym	RESPOND
Title of the project	RESPOND. Improving mental healthcare of health care working during the COVID-19 pandemic: implementation of a stepped care program. Phase 2 and 3, randomized controlled trial
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Table of contents

11. List of abbreviations and relevant definitions

BTQ	**Brief Trauma Questionnaire**
CAU	**Care As Usual**
COVID-19	**Coronavirus Disease 2019**
CSRI	**Client Service Receipt Inventory**
DWM	**Doing What Matters**
EQ-5D-5L	**EuroQol five dimension five level checklist for quality of life EU European Union**
EDAB	**Ethics and Data Advisory Board**
GAD-7	**Generalized Anxiety Disorder checklist (consisting of 7 items)**
K10	**Kessler Psychological Distress Scale (ten item version)**
LIRs stressors	**LIRs stressors list**
PASSc	**Positive Appraisal Style Scale – content focused**
PCL-5	**PTSD Checklist for DSM-5 (consisting of 20 items)**
PFA	**Psychological First Aid**
PM+	**Problem Management Plus**
PHQ-9	**Patient Health Questionnaire for depression scoring each of the 9 DSM-5 criteria**
PHQ-ADS	**Patient Health Questionnaire – Anxiety and Depression (sum score of PHQ-9 and GAD-7)**
PTSD	**Posttraumatic Stress Disorder**
RESPOND	**pREparednesS of health systems to reduce mental health and Psychosocial concerns resulting from the COVID-19 paNDemic**
RCT	**Randomized Controlled Trial**
WHO	**World Health Organization**

12. Resum (català)

Introducció. L'actual pandèmia de COVID-19 està tenint un efecte important i potencialment durador sobre la salut mental i el benestar de la població mundial. L'efecte de la pandèmia de la COVID-19 és desproporcionadament més sever en diversos grups vulnerables, com per exemple els professionals sanitaris. Es necessiten intervencions psicològiques dirigides específicament als principals problemes de salut mental resultants de la pandèmia de la COVID-19. Per tal de maximitzar l'ús de recursos, es necessiten intervencions que atenguin a les necessitats particulars d'aquest grup vulnerable però alhora que puguin ser aplicables a d'altres col·lectius. L'Organització Mundial de la Salut ha desenvolupat dues intervencions de baixa intensitat escalables anomenades *Doing What Matters* (DWM; una intervenció d'autoajuda) i *Problem Management Plus* (PM+; una intervenció presencial). Les dues intervencions, tant la DWM com la PM+, poden ser conduïdes per professionals no altament especialitzats, i es poden adaptar a diferents poblacions, cultures i llengües. A més, ambdues intervencions han demostrat ser efectives individualment. En aquest estudi, es combinaran les intervencions DWM i PM+ en forma d'intervenció esglaonada. L'estudi forma part del projecte europeu EU H2020-RESPOND, que té l'objectiu de millorar la preparació del sistema europeu de salut mental de cara a futures pandèmies. La fase 1 d'aquest l'estudi va ser aprovada, PIC277-20, I l'actual protocol presenta les fases 2 i 3.

Objectiu. L'objectiu principal és avaluar la implementació, l'efectivitat i el cost-efectivitat de les versions de DWM/PM+ culturalment i contextualment adaptades per al personal sanitari. Aquestes intervencions van adreçades a millorar el malestar psicològic, la resiliència, les desigualtats sanitàries i costos als sistemes de salut. La principal hipòtesi és que l'administració de les intervencions d'atenció esglaonada DWM/PM+ juntament amb primers auxilis psicològics (PFA, *Psychological First Aid*) i la cura o tractament habitual (CAU, *Care As Usual*) és més efectiva que solament els PFA i la CAU per disminuir el malestar psicològic i els símptomes de problemes de salut mental.

Disseny de l'estudi. Fase 2 de l'estudi (estudi d'intervenció): Assaig d'implementació pragmàtic amb un disseny paral·lel, aleatoritzat i simple cec. Fase 3 de l'estudi: procés d'avaluació qualitativa consistent en entrevistes individuals i grups de discussió focals.

Població d'estudi. Fase 2 de l'estudi: Professionals sanitaris amb nivells de malestar elevats (auto-reportat) (*Kessler Psychological Distress Scale,* K10 >15.9) (n=205). Fase 3 de l'estudi: diversos participants: (a) participants de la fase 2 de l'estudi que han completat la intervenció DWM (n=6; que hagin millorat i que no hagin millorat), que han completat la intervenció PM+ (n=6; que hagin millorat i que no hagin millorat), que han abandonat la intervenció DWM (n=6), i que han abandonat la intervenció PM+ (n=6); (b) familiars o persones properes dels participants de la fase 2 de l'estudi que hagin completat la intervenció (n=6) i que hagin abandonat la intervenció (n=6); (c) professionals (n=20-25) (per exemple professionals de la salut mental i parts interessades dels centres participants, personal clínic d'atenció primària i hospitalària, legisladors locals i nacionals); (d) facilitadors de les intervencions DWM i PM+ (tant els ajudants com els entrenadors/supervisors).

Intervenció – Fase 2 de l'estudi. Tots els participants (tant els del grup de tractament com els del grup control) rebran PFA i CAU. A part dels PFA i la CAU, el grup de tractament també rebrà la intervenció d'atenció esglaonada (DWM amb o sense PM+). La intervenció d'atenció esglaonada consisteix en la DWM (pas 1), i, condicionalment, la PM+ (pas 2) en cas que els participants encara reportin malestar psicològic (K10>15.9) 1 mes després d'haver rebut la DWM. La DWM, que consisteix en un manual d'autoajuda amb àudios pre-gravats, s'adaptarà al format digital en forma d'aplicació mòbil. PM+ consisteix en 5 sessions que seran conduïdes per professionals de la salut mental entrenats per a proporcionar el recolzament requerit de manera virtual i en format individual. A banda dels primers auxilis psicològics, el grup control només rebrà el CAU, que engloba des de l'atenció comunitària fins a tractaments psicològics especialitzats.

Paràmetres i resultats principals de l'estudi. Fase 2 de l'estudi: El cribratge segons els criteris d'inclusió i exclusió el farà l'entrevistador, en persona o bé mitjançant videotrucada (en funció de l'evolució de la pandèmia COVID-19). Les avaluacions online es realitzaran a l'entrar a l'assaig clínic, 1 setmana després d'haver rebut la DWM, i 1 setmana i 2 mesos després d'haver rebut la PM+. El principal paràmetre de l'estudi serà la reducció de símptomes d'ansietat i depressió durant els dos mesos de seguiment des de l'entrada a l'estudi, que es mesurarà segons la suma de les puntuacions obtingudes en els qüestionaris PHQ-9 (*Patient Health Questionnaire*) i GAD-7 (*General Anxiety Disorder-7*), és a dir, en el qüestionari PHQ-ADS (*PHQ-Anxiety and Depression Score*). S'espera una mida de l'efecte de Cohen *d* de 0.4 al grup PM+ 2 mesos després d'haver finalitzat el tractament. Altres resultats d'interès inclouen els nivells d'ansietat

(GAD-7) i depressió (PHQ-9), símptomes d'estrès post-traumàtic (PTSD) (PCL-5, *PTSD Checklist for DSM-5*), esdeveniments traumàtics (BTQ, *Brief Trauma* Questionnaire), LIR's stressors list, factors de resiliència (PASSc), la qualitat de vida (EQ-5D-5L, *EuroQol five dimension five level checklist for quality of life*) i el cost de l'assistència (CSRI, *Client Service Receipt Inventory*). També s'inclouran com a paràmetres de l'estudi les dades demogràfiques, variables d'exposició a la COVID-19, adherència al tractament, i indicadors d'implementació (com per exemple abast, dosis, ús de recursos, i costos associats a la intervenció). Fase 3 de l'estudi: viabilitat d'escalar la implementació de les intervencions de cura esglaonada DWM/PM+ a través d'entrevistes i grups focals al final de l'estudi.

3. Introduction and rationale

RESPOND Project
This study is embedded in the larger, EU H2020 CORONAVIRUS-funded RESPOND (PREparednesS of health systems to reduce mental health and Psychosocial concerns resulting from the COVID-19 paNDemic) project. This study protocol presents the second and third phase of the previously approved protocol: PIC-277-20 (*RESPOND. Mejora de la preparación de los sistemas de salud para reducir las preocupaciones de salud mental y psicosociales resultantes de la pandemia COVID-19: FASE 1, evaluación de las necesidades de los trabajadores sanitarios de primera línea y adaptación de los programas de apoyo SM+ y PM+)*

Healthcare workers are vulnerable to adverse mental health impacts of the COVID-19 pandemic.

Health care workers represent a particularly vulnerable group during pandemics, due the high risk of infection, fear of contagion and spread to family members and increased work-related stressors. These circumstances place health care workers at risk for poorer mental health (i.e., anxiety, depression, burnout, insomnia, moral distress, and post-traumatic stress disorder). For instance, studies conducted in 18 healthcare institutions across six autonomous regions of Spain found that almost half of Spanish health care workers have a high risk of suffering a mental disorder, and a 3.5% experienced suicidal thoughts after the first wave of the Coronavirus Disease 2019 (COVID-19) pandemic (Alonso et al., 2021; Mortier et al., 2021).

Given that professionals who care for COVID-19 patients are highly susceptible to psychological burden, it is crucial to develop strategies to support these professionals by designing and implementing specific MH interventions (Almeda et al., 2021).

Scalable psychological interventions to improve resilience, mental health and wellbeing

The World Health Organization (WHO) has developed a number of scalable psychological interventions for populations affected by adversity (WHO, 2017). They include -amongst others- Doing What Matters (DWM) and Problem Management Plus (PM+). A core feature of all WHO scalable interventions is that they can be trained to and delivered by non-highly specialized professional helpers (WHO, 2017; Epping-Jordan et al., 2016). They have also been designed to be easily adaptable to different populations, cultures and languages. The interventions and their implementation materials are freely available on the WHO website https://www.who.int/publications/i/item/9789240003927; https://www.who.int/mental_health/emergencies/problem_management_plus/en/.

DWM has a strong focus on mindfulness practices and includes exercises which aim to enhance stress reduction and build social support, adaptive coping and resilience (Epping-Jordan et al., 2016). It has been implemented with different populations of refugees in Europe, Turkey (Purgato et al., 2019) and Northern Uganda (Tol et al., 2020).

PM+ is a transdiagnostic intervention (Banbury et al., 2018) that reduces symptoms of depression, anxiety, Posttraumatic Stress Disorder (PTSD), and related conditions. PM+ comprises 5 weekly sessions using evidence-based techniques: (a) problem solving, (b) stress management, (c) behavioral activation, and (d) accessing social support. PM+ has been successfully implemented in Kenya (Bryant et al., 2017) and Pakistan (Rahman et al., 2016b). Both DWM and PM+ have been implemented through two large EU H2020 funded projects, STRENGTHS (733337) and RE-DEFINE (779255).

The first phase of the Respond study (already approved by the CEIC, PIC-277-20) allowed to culturally adapt both interventions (DWM and PM+) to the context of COVID-19 and to health care workers needs. In particular, DWM has been culturally adapted including inputs from qualitative interviews and the original manual (illustrated guide, WHO, 2020a) has been digitalized using a mobile application tool. Using this format, people can use the self-help app in their

own time. The five weekly sessions in the app will follow the 5 chapters of the illustrated guide (grounding, unhooking, acting on your values, being kind and making room). The PM+ manual has also been culturally adapted using the input from the qualitative work.

People participating in DWM will have access to the DWM-app and also receive support from a trained helper. Helpers will be non-highly specialized professionals (e.g., resident physician, clinical psychologist). The so-called helper will support participants in using the app via short weekly calls or text messages. Participants will decide how contacts with the helpers will be stablished (phone or message). PM+ It will be delivered individually, remotely (e.g., videoconferencing tools, but not via app), and delivered by the same or another helper. Both programs (DWM and PM+) are low-intensity interventions.

13. Objectives

13.1. PRIMARY OBJECTIVE

To evaluate the (cost-)effectiveness, feasibility, and acceptability of the culturally and contextually adapted DWM/PM+ stepped-care program among health care workers during the COVID-19 pandemic in terms of mental distress, resilience, wellbeing, health inequalities, and costs to health systems.

13.2. SECONDARY OBJECTIVE

To identify barriers and facilitators to treatment engagement and adherence and opportunities for scaling up among the target population in Spain.

14. Study design

Study phase 2: Randomized controlled trial (RCT) (stepped-care DWM/PM+ intervention with Psychological First Aid (PFA) and care-as-usual (CAU) vs. PFA and CAU alone)
Study phase 3: Process evaluation with qualitative interviews and focus groups to assess barriers and facilitators of engagement and adherence to the stepped-care intervention and opportunities for scaling up the implementation of the intervention.

Study phase 2

We will conduct a **single-blind RCT in health care workers** with increased psychological distress to determine whether the stepped care intervention (i.e. DWM/PM+) leads to stronger decreases in mental health outcomes, and increase in wellbeing among compared to care-as-usual. The RCT will be implemented, and field work will be carried out in two

sites Barcelona and Madrid (Servicio Madrileño de Salud, SERMAS). The current study protocol will be also sent for approval to the ethics committee of Madrid.

The trial is designed as a multi-center, randomized, single-blind parallel-group trial with one treatment arm (n=105 Barcelona and Madrid sites) and one comparison arm (n=105 Barcelona and Madrid sites). All participants in both the treatment and the comparison group will receive PFA and CAU. In addition to PFA and CAU, participants randomized into the treatment group will receive the DWM/PM+ stepped-care intervention, while participants randomized in the comparison group will receive PFA and CAU only.

All participants in the treatment group (i.e. those who receive DWM and PM+ and those who only receive DWM because symptoms subside) will be followed for a period of 2 months after the end of the PM+ session (see Figure 1 for assessment points).

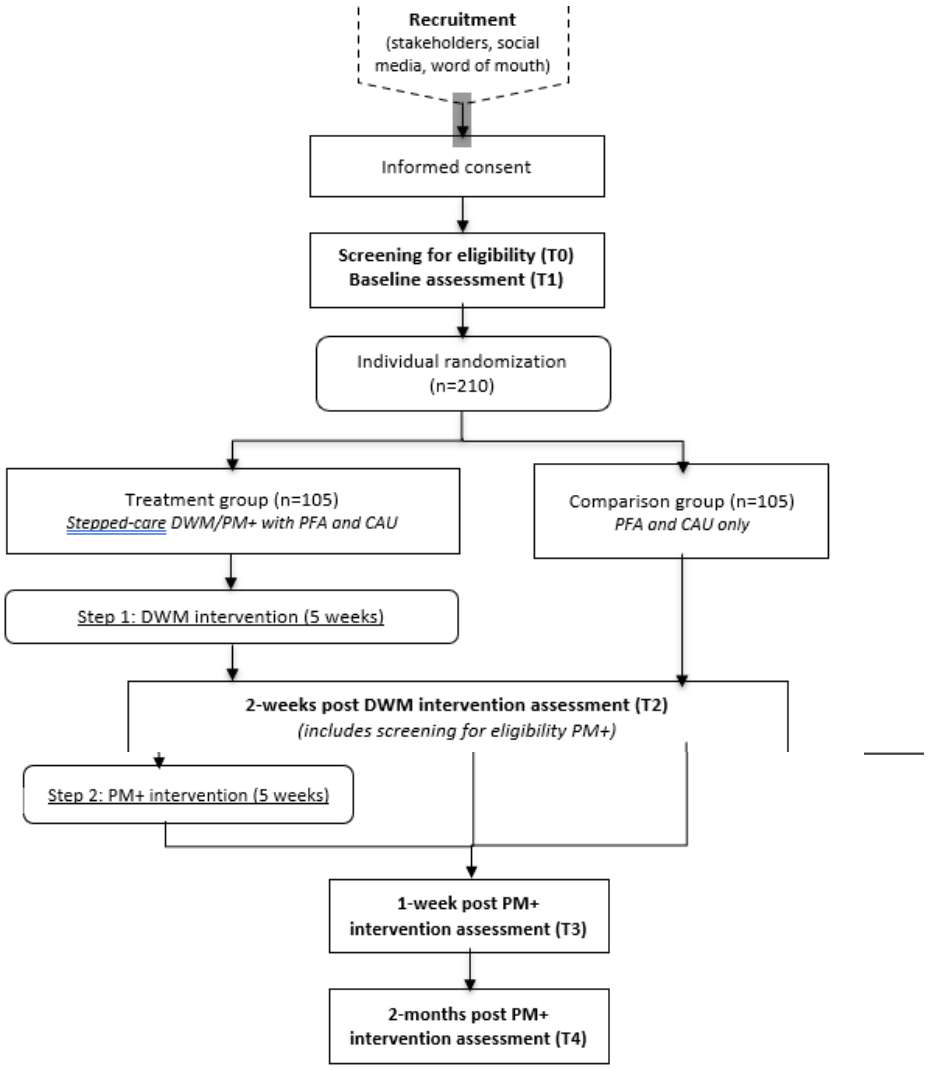

Figure 1. Flowchart of randomized controlled trial

Study phase 3

Study phase 3 is a qualitative study, consisting of interviews and/or focus group discussions among key stakeholders to evaluate barriers and facilitators to treatment engagement and adherence to the DWM/PM+ stepped-care intervention, as well as opportunities for scaling up the implementation of the intervention within the existing healthcare system. This will inform partners in RESPOND of the synthesis and dissemination of the DWM/PM+ stepped-care intervention for vulnerable groups during a pandemic.

Key stakeholders include (a) participants in the RCT in study phase 2 who completed DWM (n=6; improved and not improved), who completed PM+ (n=6; improved and not improved), who dropped-out during DWM (n=6), and who dropped-out during PM+ (n=6)); (b) their family members/close persons of participants in study phase 2 who completed the intervention (n=6) and who dropped-out during the intervention (n=6); (c) professionals (n=20-25) (e.g. mental health practitioners and local stakeholders of participating centers, clinical staff in primary and secondary care, local & national policy makers); (d) facilitators of the DWM and PM+ intervention (both helpers and trainers/supervisors).

15. Study population

15.1. POPULATION

Study phase 2
Participants for the RCT will be health care workers (including physicians, nurses, technicians, and administrative staff) from public and concerted health system. Participants will be recruited via official channels of the institutions, social networks, and stakeholders that took part in the recruitment study phase 1 (PIC 277-20). Stakeholders include those participants from the first phase of the study in which qualitative interviews were conducted (n= 47 interviews in Barcelona) to evaluate the mental healthcare worker's needs. These participants include mental health professionals and frontline workers (nurses, physicians, nurse assistants)." The enrolment and recruitment phase is planned to start in September-October 2021 (after obtaining CEIC approvals for each of the sites), and will last 18 months.

Study phase 3
Participants for the qualitative process evaluation will be key informants, such as participants who took part in the RCT; family members/close friends of participants who took part in the RCT; DWM/PM+ facilitators (helpers and supervisors); mental health professionals and decision makers (recruited through participating centers in study phase 2). For participants who took part in the RCT, we aim to include both those who took part only in DWM and those who took part in PM+ as well. Also drop-outs from both the DWM and PM+ intervention will be asked to participate in the qualitative process evaluation.

15.2. INCLUSION CRITERIA

Participants will be eligible to participate in the study (phase 2 (and 3)) if they meet all of the following criteria:

- 18 years or older
- Living in Catalonia
- Having elevated levels of psychological distress (Kessler Psychological Distress Scale (K10) >15.9).
- Having signed the digital informed consent before entering the study.

- Being a health care worker from public and concerted health system, including those that are not directly involved in patient care but potentially exposed to infectious agents that can be transmitted among from HCW and patients (emergency medical service personnel, physicians, nurses, nursing assistants, technicians, ancillary and administrative staff)

15.3. EXCLUSION CRITERIA

Potential participants who meet the inclusion criteria will be excluded from participation in this study (phase 2 (and 3)) if they meet any of the following criteria:

- Having acute medical conditions (requiring hospitalization);
- Imminent suicide risk, or expressed acute needs or protection risks that require immediate follow-up
- Having a severe mental disorder (e.g. psychotic disorders, substance dependence);
- Having severe cognitive impairment (e.g. severe intellectual disability or dementia);
- Currently specialized psychological treatment (e.g. Eye movement desensitization and reprocessing, Cognitive behavioral therapy);
- In case of current psychotropic medication use: being on an unstable dose for at least 2 months.

15.4. SAMPLE SIZE CALCULATION FOR THE CLINICAL TRIAL

A total number of 210 participants will be included (total of participants from Madrid and Barcelona sites). Based on prior studies on a PM+ intervention (Bryant et al., 2017; Rahman et al., 2016b), we aim to detect a small to medium Cohen's *d* effect size of 0.4 in the PM+ group at 2 months post-treatment based on the primary composite outcome Patient Health Questionnaire – Anxiety and Depression (PHQ-ADS) (Kroenke et al., 2016; 2019). The PHQ-ADS is the combined sum score of depression and anxiety symptoms of the Patient Health Questionnaire (PHQ-9) and General Anxiety Disorder-7 (GAD-7), respectively and has shown good internal consistency (α = .88 to .92) (Kroenke et al., 2016; 2019). A power calculation for a repeated measurement design suggests a minimum sample size of N=73 per group (power=0.80, alpha=0.05, two-sided, rho=0.9). Taking into account 30% attrition, we aim to include a total number of 210 participants (105 in the stepped-care DWM/PM+ treatment group (with PFA and CAU) and 105 in the PFA and CAU comparison group).

15.5. CONTROL- AND TREATMENT CONDITION

Psychological First Aid (PFA)
All participants, both in the treatment and the comparison group, will be offered individual PFA through teleconferencing or phone calls. PFA is a WHO developed support strategy that involves humane, supportive and practical help for individuals suffering from serious humanitarian crises. PFA does not necessarily involve a discussion of the event(s) that cause the distress but aims particularly at five basic elements that are crucial to promote in the aftermath of crises, i.e. a sense of safety, calm, self- and community efficacy, connectedness, and hope (Hobfoll et al., 2007). PFA consists of a (telephone) conversation (approximately 15-30 minutes) that a helper has with a participant. PFA has various themes; in PFA, the helper provides non-intruding practical care and support, assesses needs and concerns, helps people to address basic needs (e.g. information), listens to people without pressuring them to talk, comforts people and helps them to feel calm, helps people to connect to information, services, and social support, and protects people from further harm (WHO, 2011).

Care-as-usual (CAU)

In addition to PFA, both the treatment and the comparison group will receive CAU; they will be allowed to receive any usual care. CAU does not include specialized psychological treatment, since it is an exclusion criteria for the current study.

15.6. TREATMENT CONDITION

Treatment group: Stepped-care Doing What Matters/Problem Management Plus (DWM/PM+)
Stepped-care models assume to provide health care in the most efficient and cost-effective way: the first step of care is readily available for all those in need and more costly treatments are reserved only for those not responding. Evidence suggest that stepped-care models are modestly effective (van Straten, Hill, Richards & Cuijpers, 2014; Ho, Yeung, Ng & Chan, 2016) although there is a high heterogeneity of such models (number of steps, duration of steps, rules about stepping up) and their effects. Interestingly, research in clinical practice has shown that results improve when care providers switch from a matched care to a stepped-care approach (Boyd, Baker & Reilly, 2019).
The treatment group will receive the stepped-care program consisting of DWM (step 1) and PM+ (step 2) in addition to PFA and CAU (for details of CAU, see: '*Care-as-usual (CAU)'* above). Step 2 will only be provided if the participant still has elevated levels of psychological distress (K10 > 15.9) at 1 week after DWM, i.e. during the second quantitative assessment at 1 week after DWM.

Step 1: Doing What Matters (DWM)
The DWM program has been developed by WHO and collaborators working in the humanitarian field. DWM was designed to be relevant for large segments of adversity-affected populations: it is intended to be transdiagnostic, easily adaptable to different cultures and languages, and it is a low-intensity intervention. DWM is based on acceptance and commitment therapy, a form of cognitive-behavioral therapy, with distinct features (Hayes, Levin, Plumb-Vilardaga, Villatte & Pistorello, 2013). The acceptance and commitment therapy is based on the concept that ongoing attempts to suppress unwanted thoughts and feelings can make these problems worse, so instead it emphasizes on learning new ways to accommodate these thoughts and feelings without letting them dominate. The acceptance and commitment therapy has been shown to be useful for a range of mental health issues (Tjak et al., 2015) and has been used successfully in a guided self-help format (Hayes et al., 2013).

The original DWM program consists of a self-help guide called *'Doing What Matters in Times of Stress'* that is complemented with pre-recorded audio exercises. The audio material imparts key information about stress management and guides participants through individual exercises. Additionally, participants are guided by a briefly trained helper.

DWM includes five sections (or modules), each of which focuses on a specific skill:

- **Section 1:** *Grounding:* Bringing attention back to the present moment when caught up in distressing emotions.
- **Section 2:** *Unhooking:* Noticing difficult thoughts and feelings, naming difficult thoughts and feelings, and refocusing on what you are doing.
- **Section 3:** *Acting on your values:* Identifying personal values and then taking small or big actions to live in line with these values.
- **Section 4:** *Being kind:* Enhancing and encouraging kindness towards oneself and towards others.
- **Section 5:** *Making room:* Learning how to tolerate stress while still acting consistently with values.

In this study, the DWM program will be delivered as an online intervention. The DWM intervention, i.e. both the audios and the self-help guide, will be adapted for use on a smartphone or other device with internet access during Phase 1 of RESPOND. The format of DWM is innovative in that it seeks to ensure that key intervention components are delivered as intended through the use of pre-recorded audio, without the burden of extensive training and supervision. In the online application tool, a new module (i.e. section) is released every week so participants will be asked to go through the entire DWM intervention within 5 weeks with weekly guidance from a helper. Due to its format, the DWM program does not require much time from experts for implementation. The delivery mode for the support from the helper will be flexible and in line with COVID-19 regulations. Additionally, research has found that guided self-help programs produce much

better results th an “pure” (unguided) self-help, and the effects produced by guided self-help are surprisingly similar to face-to-face interventions (Fledderus, Bohlmeijer, Pieterse & Schreurs, 2012).

Protocol adherence

We will assess DWM protocol adherence at post-intervention based on meta-data collected during the intervention (i.e. by tracking participants usage of the DWM app such as who accesses what page, how often, how much time participants spend on the app etc.). We will only use this meta-data during the intervention to remind each participant (e.g. through e-mail) after finishing each module to let them know that they should start a new module. Additionally, participants receive a weekly phone call from a helper to see how they are doing and to check on their progress.

Step 2: Problem Management Plus (PM+)

PM+ is a new, brief, psychological intervention program based on CBT techniques that are empirically supported and formally recommended by the WHO (Dua et al., 2011). The full protocol was developed by WHO and University of New South Wales, Australia. The manual involves the following empirically supported elements: problem solving plus stress management, behavioral activation, facing fears, and accessing social support. Figure 2 shows a brief outline of the five sessions. Originally, the sessions lasted 90 minutes, but it has been adapted to 60 minutes, since the original intervention is structured to be done face to face and we will deliver it remotely (e.g. Jitsy Meet). These changes were approved by the WHO (the organization developed the original version of the PM+ intervention). In these 60-minute sessions participants may talk to trained non-professional helpers (who are supervised by registered (clinical) psychologists). We will follow this outline, except that we excluded all assessment instruments from the manual, since they are administered at the assessments instead of at the intervention sessions. PM+ has four core features, and it is brief (five sessions).

In this study, the delivery mode of the PM+ intervention will be flexible, with remote delivery in phases of the pandemic when physical distancing rules apply. This is a future-oriented attempt towards a more holistic mental health care system that can flexibly switch between modes of delivery (e.g. remotely (e.g. Jitsy Meet) or face-to), depending on the needs and the specific containment measures that apply, and the specific preferences and needs of the participant.

Protocol adherence

Protocol adherence will be ensured by weekly supervisions provided by the PM+ trainers/supervisors as well as the fidelity checklist (Dawson et al., 2016). In addition to these, audio records of the sessions will be used for fidelity checks. The sessions will be recorded with professional equipment and only the helper audio will be recorded. The same procedure will be used for teleconferencing systems (e.g., Jitsy Meet), only the helper audio will be recorded, and downloaded right after the session is over. Audio recordings will be stored in PSSJD servers.

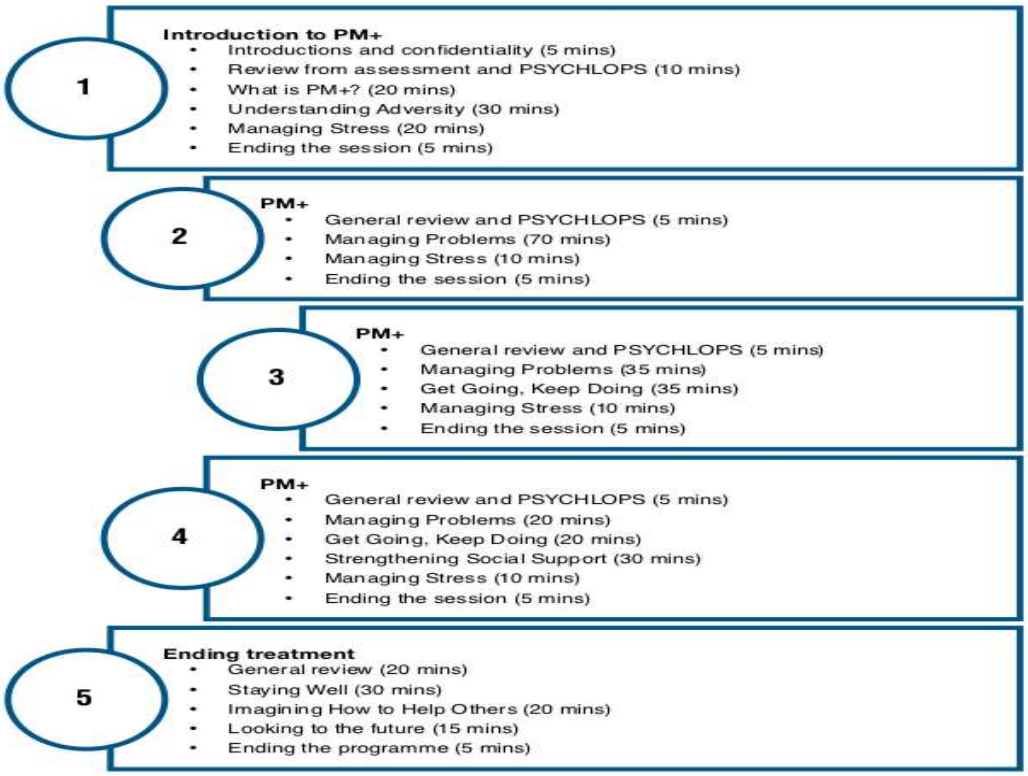

Figure 2. Outline of five PM+ sessions (figure from PM+ Manual, WHO, 2016). We will follow this outline, apart from the PSYCHLOPS assessment which is excluded.

Helpers in PFA, DWM and PM+ interventions

Helpers selected to provide support to users will be resident physicians/psychologist or clinical psychologist (graduated and with Master's degree in clinical psychology). Helpers should speak the same language as the participant. For DWM but particularly PM+ helpers, it is also recommended that helpers experience receiving support using the stress management guide (i.e., practice using the stress management guide as a user with a colleague acting as the helper). If support is provided remotely, it is preferable that helpers have experience with remote support and receive training in this approach (e.g., EQUIP REMOTE). Practice sessions (e.g., providing support to other helpers, practice supporting persons with impairments) can help identify issues that may arise prior to working with users and build helper capacity. Helpers need to sign a confidentiality agreement. Helpers may deliver either PFA, DWM and/or PM+, if they are trained (and supervised) in each intervention delivered.

Training PFA helpers

Before providing PFA, helpers need training to enhance knowledge and gain better understanding of appropriate psychosocial responses and skills in providing support to individuals exposed to adversity (Sijbrandij et al., 2020). This half- or one-day training (WHO, 2013) includes explanations of the basic concepts and PFA principles, how to support (very) distressed people, and how not to cause further harm by using participatory learning (i.e. role-play).

Training DWM helpers

Similar to PFA-helpers, the role of the coach in DWM is to provide brief motivational support to the participants; not provide specialized mental health services. Helpers should be empathetic and motivated to do this. Before working as a helper, helpers will receive a short training (2 or 3 days depending on whether they are already trained in PFA) by academics and/or mental health-care professionals. Helpers will be trained in providing support using the stress management guide (i.e., practice using the stress management in role-plays with other helpers) and practice to deliver support remotely (i.e. practice providing support in role-play settings). Helpers will receive a written manual as a guide for the brief support sessions.

Training PM+ helpers

PM+ helpers will receive eight days of training, followed by three practice cases, on-the-job training, and close supervision during the whole trial by the PM+ trainers/supervisors. Audio records of PM+ sessions will also be used for supervision. The training program comprises of education about common mental disorders, basic counseling skills, delivery of intervention strategies and self-care (Rahman et al., 2016a).

Trainers/supervisors

All DWM/PM+ helpers will be actively trained and supervised by more senior psychologist and psychiatrists and will be continued to be monitored throughout the process. These clinicians will also independently assess and monitor treatment sessions at-random in order to ensure treatment adherence and fidelity. Furthermore, these expert clinicians will supervise the entire assessment and therapeutic process to reduce the burden on and risks for participants. DWM/PM+ trainers/supervisors will be approximately five licensed mental health care professionals such as health-care psychologists or psychiatrists. They will be trained by a Master Trainer via a training-of-trainers program, consisting of the same elements as the training for helpers, but also of training and supervision skills (Rahman et al., 2016a). The PM+ trainers/supervisors will be responsible for close supervision of the PM+ helpers. Therefore, as a next step, they will train DWM/PM+ helpers. Figure 3 shows how the training-of-trainers of PM+ is planned.

[*The research team at PSSJD/FSJD will be responsible for arranging the trainings and supervision for the helpers at the Barcelona site. Supervision of the helpers by the trainers/supervisors will take place on a weekly basis (Dawson et al., 2016). This will be done remotely or face-to-face, depending on the preference of the trainers/supervisors and accounting for COVID-19 regulations. The trainers/supervisors will also receive supervision by the Master trainer when necessary.]*

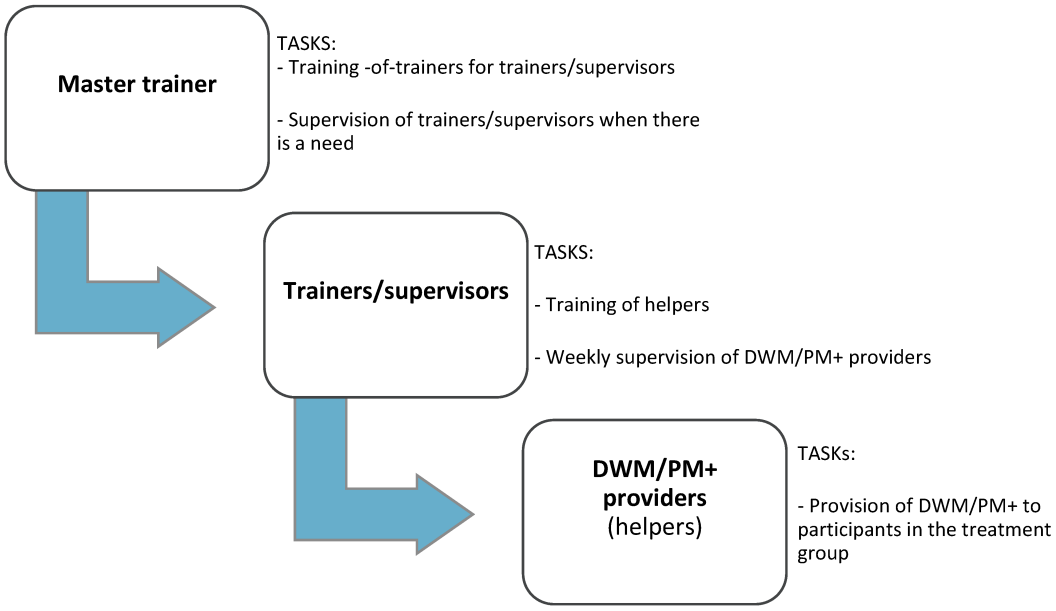

Figure 3. Training of Trainers/Supervisors and DWM/PM+ Helpers.

16. Methods

16.1. STUDY PARAMETERS/ENDPOINTS

All participants will have five assessments (T0-T4), mostly by filling out online questionnaires. The five assessments take place at the following time-points (see also Figure 1):

T0: Screening for eligibility including psychological distress

T1: Baseline assessment

T2: within 1 week post DWM intervention assessment

T3: 1-week post PM+ intervention assessment

T4: 2-months post PM+ intervention assessment

The hypothesis to be tested is that the stepped-care program consisting of DWM (step 1) and PM+ (step 2) plus PFA and CAU will be more effective in decreasing psychological distress compared to PFA and CAU alone.

16.1.1. Main study parameter/endpoint

The main study parameter will be the decrease in symptoms of depression from baseline to two-month follow-up after the PM+ intervention ended, measured through the combined sum score of the PHQ-9 and GAD-7 previously validated as the PHQ-ADS (Kroenke et al., 2016; 2019). A description of the measure(s) can be found under 'Study Procedures'. Based on prior studies on PM+ in Pakistan and Kenya (Rahman et al., 2016b; Bryant et al., 2017) where PM+ was administered as a standard treatment, we expect to detect a Cohen's *d* effect size of 0.4 in the PM+ group at 2 months post-treatment.

16.1.2. Secondary study parameters/endpoints

1. Level of depression (PHQ-9)
2. Level of anxiety (GAD-7)
3. Severity of posttraumatic stress disorder (PCL-5)
4. Quality of life (EQ-5D-5L)
5. Cost of care: impact on use of health system, other services, time out of employment and other usual activities and need for informal care (*Client Service Receipt Inventory*, CSRI schedule)
6. Resilience factors (PASSc)

The measurement instruments are described under 'Study procedures'.

16.1.3. Other study parameters

1. Demographic data

2. Exposure to adverse life-events (*Life Events Checklist,* LEC)
3. Treatment fidelity (DWM: tracking app usage based on meta-data, PM+: audio records, checklists)
4. Satisfaction (qualitative assessment in study phase 3)
5. Acceptability of the program (qualitative assessment in study phase 3)
6. Implementation indicators: reach, dose, resource use, costs of recruiting, training and retaining staff delivering the stepped-care program, program costs, adaptation, the process, quality

16.2. RANDOMIZATION, BLINDING AND TREATMENT ALLOCATION

After the screening and the baseline assessment, participants will be randomized in either the treatment group (n=105) Barcelona and Madrid) or the comparison group (n=105 Barcelona and Madrid) , with an equal probability of assignment to each group (allocation ratio 1:1). The trial is a single-blind RCT (i.e. outcome assessors are blind to treatment allocation). Randomization will be carried out through computerized software (e.g. Castor) and it will be performed by an independent person who is not involved in the assessment. If participants are randomized into the treatment group, they will be allocated to a DWM helper and given access to the DWM online app. This is also done blind by an independent person who is not involved in the assessment. The allocated helper will contact the participant through a method agreed at assessment (e.g. telephone, message or email) to set up a time and date for a first acquaintance telephone call before the intervention starts. During this call, the weekly support calls of the DWM helper will be discussed and planned. If participants still meet the inclusion criteria 1 week after the DWM program ended, they will be contacted by the PM+ helper (might be the same helper as for DWM) to plan five consecutive (tele-conferencing) meetings of 60 minutes with the participant. The first session will be scheduled within a few days and no longer than one week after the pre-intervention assessment.

16.3. STUDY PROCEDURES

All participants will receive an information sheet with details about the study aims and procedures (appendix I), as well as the informed consent (appendix II). The informed consent will be presented electronically via Qualtrics software during baseline assessment (T1), thus allowing remote consenting.

Screening (T0)
Following informed consent, participants will be invited to complete step 1 of the first assessment: screening. Screening consists of using several (self-administered) measurement instruments to see if people meet the inclusion criteria. Also, specific questions are asked to check whether participants should be excluded because of fulfilling exclusion criteria. More detailed explanations of all measures are described under *'Measurement Instruments'.*

- When participants are not selected for the trial because they score below the cut-off scores for the K10 or when they meet the exclusion criteria, they will immediately be provided feedback e.g. on the screening outcomes (including K10 score) and an explanation why they are not eligible for the study (p. 86 of the PM+ intervention manual; WHO, 2016). When participants are excluded because of an imminent suicide risk, expressed acute needs/protection risks (for example, a young woman who expresses that she is at acute risk of being assaulted or killed) or observed (suspicion of) severe mental disorders or severe cognitive impairment they will be referred for appropriate treatment and support (e.g., general practitioner, mental health specialized support)

Baseline assessment (T1)
If participants meet the eligibility criteria and score above the cut-off of the K10, they will continue with the baseline assessment. This step includes the informed consent, administration of contact information, preferences for remote contact (e.g. video-conferencing, e-mail/telephone) questionnaires about socio-demographic characteristics; suicidal

ideation questions, COVID-19-related questions, the BTQ; the PCL-5; the PHQ-9, the GAD-7, the EQ-5D-5L,LIRs stressors list, the PASSc, and the CSRI.

Post-intervention and follow-up assessment (T2, T3, T4)
Quantitative assessments will take place four times for all participants: at screening (T0) and baseline (T1: before the intervention), at 1 week after DWM (T2) and at 1 week (T3) and at 2 months after the PM+ program has finished (T4). All instruments used in the baseline assessment (T1) will be used for each of the post-intervention and follow-up assessments, see Table 1. The screening instrument K10 (T0) will be re-assessed at T2 only. In case participants do not respond to a scheduled assessment, they are called a maximum of five times (on different days) for scheduling a new appointment.

Assessors
Screening T0 data will be collected using the collective program CASTOR EDC. Assessments T1 to T4 will be conducted online (collective program Qualtrics).

Assessment of treatment fidelity
DWM: Participants' usage of the DWM app will be tracked, such as who accesses what page, how often, how much time participants spend on the app, etc. This way, we can track protocol adherence to the DWM app afterwards, once they finished the intervention. During the intervention, we will only use meta-data to track participants' progress in the sense that participants will receive an e-mail that the next module has been unlocked and is accessible for them to use one week after they finished the previous module. Additionally, participants receive a weekly phone call from a helper to see how they are doing and check on their progress.
PM+: Audio tapes of the treatment sessions will be recorded and stored to monitor treatment fidelity. The audio tapes can be used for supervision by the trainers/supervisors and will be used to rate treatment fidelity.

Measurement instruments
The measurement instruments that will be used for the four quantitative assessments, i.e. at screening (T0) and baseline (T1), post-intervention 1 (T2), and post-intervention 2 (T3), and follow-up (T4), as well as during the DWM/PM+ intervention are depicted in Table 1. In case there is no translation of a measurement instrument in Spanish, the instrument will be translated and back-translated by the research team.

[PLEASE FIND TABLE 1 below with Overview of the concepts, their measures, the type of study parameter in the study, and the moment of measuring during study phase 2]

Concept	Measures	Type of study parameter	Moment of measuring						
			Screening (T0)	Baseline (T1)	DWM	Post-assessment 1 (T2)	PM+	Post-assessment 2 (T3)	Follow-up assessment (T4)
Psychological distress	K10	Screener	x			x			
Suicide risk:									
- Face-to-face *or*	PM+ tool	Screener	x			x	x		
- Self-administered	Step-by-step question	Screener	x			x		x	x
Mental, neurological or substance use disorders	PM+ tool	Screener	x						
Depression and Anxiety:	PHQ-ADS	Primary							
Subscale depression	PHQ-9	Secondary		x		x		x	x
Subscale anxiety	GAD-7	Secondary		x		x		x	x
Posttraumatic stress reactions	PCL-5	Secondary		x		x		x	x
Resilience factors	PASSc	Secondary		x		x		x	x
Quality of life	EQ-5D-5L	Secondary		x		x		x	x
Impact on resource use/costs	CSRI	Secondary		x		x		x	x
Socio-demographics		Other		x					
Treatment fidelity:	Metadata	Other			x				
- DWM									
- PM+	Audio records	Other					x		

Screeners

Screening instruments

K10: psychological distress

Psychological distress will be measures using the Kessler-10 Psychological Distress Scale (Kessler et al., 2002). The K10 is a ten-item self-report questionnaire to screen broadly for psychological distress (e.g. anxiety and depression related distress) experienced in the past 30 days. Items are rated on a five-point Likert scale ranging from *none of the time* to *all of the time*. The sum of the ten items gives a total score ranging from 10 to 50. Higher scores represent higher levels of distress. The K10 has strong psychometric properties and has strong discriminatory power to distinguish Diagnostic and Statistical Manual of Mental Disorders-IV cases from non-cases (Kessler et al., 2002). The K10 has been validated in various population samples and is a useful instrument in both primary care (Kessler et al., 2002) and general population samples (Furukawa, Kessler, Slade & Andrews, 2003; Kessler et al., 2005). Moreover, the K10 has been found to not have any substantial bias in regards to education level and gender, thus making it useful for research (Baillie, 2005).

There is no standard cut-off score for the K10 present. In addition to a cut-off score of 20, also lower cut-off scores have been found, e.g. a cut-off score of 12 (Lace et al., 2019) or a cut-off score of 14 (Baggaley et al., 2007). When determining the appropriate cut-off point, it is important to take into account the context in which the measurement instrument is used. In order to not miss potential participants, in research a low cut-off score with a low rate of false negatives and a high sensitivity is favored (Smits, Smit, Cuijpers & De Graaf, 2007). In STRENGHTS, a similar study to the RESPOND project, among Syrian refugees in the Netherlands, a cut-off point of 15 was used to indicate moderate to high levels of psychological distress (de Graaff et al., 2020). This was based on a study among Afghan and Kurdish refugees asylum seekers in New Zealand and Australia where they used the following cut-off scores: 10–15.9 (low risk of psychological distress), 16–21.9 (moderate levels of distress consistent with a diagnosis of moderate depression and/or anxiety disorder), 22–29.9 (high level of distress) and 30 or more (possibility of very high or severe levels of distress) (Sulaiman-Hill & Thompson, 2010). A cut-off score of 15.9 which we believe is appropriate for this varying target population.

Screening instruments for exclusion criteria

Suicidal ideation

Suicidality will be explored at several time-points (at T0, at T1, during PM+ and at follow-up assessments) with either the 'assessment of thoughts of suicide' risk tool (from PM+; WHO, 2016, pp. 86) when assessed in face-to-face contact (e.g. in person or remotely through teleconferencing or telephone) or with the self-administered step-by-step suicidality question (Van 't Hof et al., 2021) when assessed with an online questionnaire. People who have plans to end their life (as indicated by an answer of "yes" on the screening question - "In the past week/month, have you had serious thoughts or a plan to end your life?") will be excluded from the study. Participants who answer "yes" to this additional screening question will be considered at imminent risk of suicide (Van 't Hof et al., 2021). In case of imminent suicidal risk, people are excluded from participation. They will be explained (on-screen or by telephone/teleconferencing or in person) that they cannot participate but that they may need additional mental health support with advice to go to an emergency room or call the national suicide hotline. They will also be presented suggestions for steps to follow in order to receive mental health care (e.g. contact general practitioner), encouraged to seek help, and provided with additional self-care tips.

Severe mental disorder

(Suspicion of) a severe mental disorder will be assessed during the screening phase before starting the PM+ intervention 'Impairments possibly due to severe mental, neurological or substance use disorders'. This is a tool which is to be filled in by the assessor based on their observations and judgment of the participants' behaviors. No questions are asked to the participant. The tool asks 4 questions related to the participant's behavior: 1) does the participant understand you (even though they speak the same language or dialect)?; 2) Is the participant able to follow what is happening in the assessment to a reasonable extent?; 3) Are the participants' responses bizarre and/or highly unusual?; 4) From the participants' responses and behaviors, does it appear that they are not in touch with reality or what is happening in the assessment? If the answer is no to question 1 or 2, or yes to question 3 or 4, the participant will be excluded.

Primary outcome measure

The PHQ-ADS is the sum of the PHQ-9 and GAD-7 scores (details of both instruments summarized below) and thus can range from 0 to 48, with higher scores indicating higher levels of depression and anxiety symptomatology. Two validation studies of the PHQ-ADS in trial data-sets of patients with chronic (musculoskeletal) pain and oncologic diseases have been

published (Kroenke et al., 2016; Kroenke et al., 2019). Evidence shows high internal reliability (Cronbach's alpha of 0.8 to 0.9), strong convergent and construct validity, sufficient unidimensionality and evidence for sensitivity to change (i.e. differentiating between individuals classified as worse, stable, or improved by a reference measure at three months post-intervention).

Secondary outcome measures

PHQ-9: depression (PHQ-9; subscale of PHQ-ADS)
Depressive symptoms during the past two weeks will be measured using the Patient Health Questionnaire depressive module. It asks how often someone was bothered by each of the nine DSM-5 criteria and scores answers on a four-point Likert scale ranging from 0 (not at all) to 3 (nearly every day) (Kroenke, Spitzer, & Williams, 2001). In addition to the nine items, the PHQ-9 asks: "If you checked off *any* problems, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?", which is to be answered with "Not difficult at all", "Somewhat difficult", "Very difficult", or "Extremely difficult". For the current study, we will examine changes in caseness in depression. We will use a cut-off score of 10, which has been found to be a valid cut-off point for diagnosis (Manea, Gilbody & McMillan, 2021).
The PHQ-9 has been translated to and is available in many languages (see https://www.phqscreeners.com/). The PHQ-9 has been found to be a reliable and valid instrument to measure depressive severity. Furthermore, due to its brevity, PHQ-9 is a useful instrument for usage in a clinical or research setting (Kroenke et al., 2001).

GAD-7: anxiety symptoms (GAD-7; subscale of PHQ-ADS)
The GAD-7 questionnaire is a seven-item, self-report anxiety questionnaire which assesses the degree to which the patient has been bothered by feeling nervous, anxious or on edge over the last two weeks. Items also include other generalized anxiety symptoms such as being unable to stop worrying about multiple things, having trouble relaxing or sitting still, feeling irritable and being afraid of something bad happening at all times (Spitzer et al., 2006). Items are scored from 0 to 3, respectively for experiencing symptoms 'not at all', for 'several days', for 'more than half the days' and for 'nearly every day'. The total score ranges from 0 to 21. Cut-off points for mild, moderate and severe anxiety, are scores of 5, 10 and 15, respectively (Spitzer et al., 2006). A score of 10 has been identified as the optimal cut-off score to balance specificity and sensitivity (Spitzer et al., 2006).
The GAD-7 has been translated to and is available in many languages (see https://www.phqscreeners.com/).

PCL-5: PTSD Symptoms
PTSD symptoms during the past week according to the DSM-5 PTSD diagnosis will be measured using the PCL-5 (Weathers et al., 2013). A shortened 8-item version of the original PCL-5 (a 20-item checklist which correspond with the 20 DSM-5 PTSD symptoms) will be used. Items are rated on a 0-4 scale. Added up, the maximum severity score is 32. Higher scores indicate higher symptomatology.

Resilience related constructs (Dynacore-C study; Veer et al., 2021)
Resilience factors (i.e. underlying factors that lead to resilience) may also be measured by assessing factors like optimism, positive appraisal style, perceived social support (in general and related to COVID-19), perceived self-efficacy and behavioral coping style. In RESPOND, we will assess positive appraisal style with the Positive Appraisal Style Scale – content focused (PASSc). The PASSc is based on positive appraisal style theory of resilience (PASTOR; Kalisch et al, 2015; Kalisch et al, 2021). The PASTOR theory conceptualizes resilience as an outcome: the maintenance of mental health after stressor exposure. Positive appraisal style would therefore not be a measure of resilience, but a resilience factor. It intends to capture the underlying mechanism which leads to resilience. The PASSc is currently used in a number of longitudinal studies (Mainz Resilience Study; Longitudinal Resilience Assessment study, and several studies of the DynaMORE project). The PASSc was originally developed as a 29 items questionnaire featuring generalized positive

appraisals of and attitudes towards difficulties, covering specifically the 3 main dimensions of stressor/threat appraisal - appraisal of threat magnitude/cost (relating to catastrophizing vs. trivialization), of threat probability (relating to pessimism vs. optimism), and of one's coping potential (relating to helplessness vs. overconfidence). Internal validity testing and a factor analysis resulted in a reduced list of 12 items, which is the PASSc. A paper (R. Kalish and P. Petri-Ramao) currently being prepared shows internal consistency α = .87 and reliability Cronbach's α = .84. The PASSc shows convergent validity with other underlying resilience factors as it correlates with optimism .52 (SOP-2), with stress recovery (BRS): .50, with well-being (WHO-5): .42, with trait anxiety (STAI-Y2): -.51 , with neuroticism (from BFI-10): -.49. Discriminant validity is shown in low correlation with I-8 impulsivity subscales urgency, intention <=.13; with openness (from BFI-10): .17, with conscientiousness (from BFI-10): .19.

EQ-5D-5L: quality of life

The EQ-5D-5L measures quality of life and consists of two parts, the EQ-5D and the EQ VAS. Part 1, the EQ-5D, rates the level of impairment across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The EQ-5D-5L is an adapted version of the EQ-5D(-3L), which only had three response options for each dimension and was therefore thought to not sufficiently capture milder health issues and small changes between different states of health (Herdman et al., 2011). The EQ-5D-5L has been used widely and is available in over 150 languages, also for laptop, tablet or Castor EDC (https://euroqol.org/eq-5d-instruments/eq-5d-5l-available-modes-of-administration/self-complete-for-use-in-castor-edc/). Country specific utility weights will be attached to data from the EQ-5D-5L and changes in participant quality of life years gained between intervention and control groups will be determined. Part 2, the EQ VAS, is a visual, vertical, analogue scale. The endpoints of the scale are called 'The best health you can imagine' and 'The worst health you can imagine' and the current health status of that day needs to be indicated, after which the number checked on the scale also needs to be written down.

CSRI schedule: cost of care

The CSRI was developed for the collection of data on service utilization (e.g. use of health system, other services, time out of employment and other usual activities, need for informal care) and related characteristics of people with mental disorders, as the basis for calculating the costs of care for mental health cost-effectiveness research. It has been used cross-culturally and is available for Spain.

Other measures

Socio-demographic information

Socio-demographic information will be collected with predefined items based on the REDEFINE and STRENGTHS studies (i.e. age, gender, nationality, years of education, relationship status, and main work-status and additional questions regarding country of birth, household population (incl. children < 18 and elderly people), household income on average, occupational area working, mental health condition and overall current health status and housing (square meters of the house, outdoor space available).

Treatment fidelity

Process monitoring of the full stepped-care intervention includes review of helpers' records of DWM phone calls and PM+ sessions with participants; helpers' supervision records including intervention fidelity monitoring, and supervision of supervisors by intervention trainers. Tracked app usage information of the DWM app and audio records of the PM+

sessions will be analyzed. The data will be collected throughout the intervention delivery (see Table 1) and reviewed as it is collected, leading to an iterative process of intervention monitoring informing intervention delivery.
To monitor treatment fidelity of DWM, participants' usage of the DWM app will be tracked. To monitor treatment fidelity of PM+, treatment sessions will be audio-recorded (with previous consent of the participants). Giving consent to the audio recording is no requirement to receive the PM+ program. Audio records will be coded by the local research team and used for treatment fidelity analysis. In order to determine whether the intervention-as-implemented does not differ from the intervention-as-designed, fidelity checklists filled out by the research team for a random sample, stratified on helpers, of sessions / participants. The data will be collected throughout the intervention delivery and reviewed as it is collected, leading to an iterative process of intervention monitoring informing intervention delivery. Treatment fidelity will be analyzed as manipulation check.

Implementation indicators
After the intervention has finished, various implementation indicators will be assessed, such as reach, dose, resource use, costs of recruiting and retaining staff delivering the stepped-care program, program costs, adaptation, the process and quality of the stepped-care DWM/PM+ intervention.

Additionally part of the cost-effectiveness analysis, we will estimate the incremental cost per change in the primary outcome, as well as quality of life. To do this, estimates of the resource use and costs of implementation are needed, making use of data from implementation indicators. This will involve analysis of records on resources and costs for initial training, as well as use of process and fidelity data on resources used for receipt of interventions, such as the number of PM+ sessions attended and input and support from supervisors.

Study phase 3
Study phase 3 consists of a qualitative study. The aim of this study is to explore the feasibility, i.e. identifying barriers and facilitators specific to the target population, of scaling-up the implementation on the stepped-care DWM/PM+ intervention. This will be done by conducting in-depth semi-structured interviews and focus group discussions with key informants. In these interviews, participants' satisfaction and acceptability of the program will also be explored.

Key informants will include participants in the treatment group who completed the DWM intervention (n=6; improved and not improved) or the PM+ intervention (n=6; improved and not improved), who dropped-out during DWM (n=6) or during PM+ (n=6), and family members (or close persons) of participants in the treatment group who completed the DWM or PM+ intervention (n=6) or dropped out during DWM or PM+ (n=6). Participants and their family members will be asked questions concerning the satisfaction and acceptability of the intervention, barriers and facilitators to adherence, and to what extent they think that the stepped-care program has actually contributed to improving participants' functioning. Recruitment for participants of the treatment group and their family members will start at 3 months post-PM+.

Additionally, we will interview (a) mental health practitioners of the participating centers, (b) local stakeholders of the participating centers, e.g. mental health specialists and supervisors, with a role in policy development or implementation, (c) clinical staff in primary (e.g. GPs, social workers) and secondary (e.g. psychologists) care, and (d) local and national policy makers with knowledge on mental health care (20-25 participants in total). Policy decision makers will be interviewed to obtain their perceptions of the benefits and challenges of integrating the stepped-care DWM/PM+ intervention into routine service provision. Health care professionals will be interviewed to explore their views on the potential for scaling-up the stepped-care DWM/PM+ intervention and integrating the program into the health system in Spain. Furthermore, we will conduct focus group discussions with facilitators (n=4-8) of the DWM/PM+ intervention. Facilitators will include both helpers and trainers/supervisors and we will balance for power of various stakeholders. Facilitators will be interviewed on their experience in providing the DWM/PM+ intervention and to obtain their ideas in implementing this intervention in Spain.

Interviews and focal group discussions will be conducted online or in person, depending on the preferences of the participant and will in accordance with COVID-19 regulations. Key informant interviews and focal group discussions will

be audio-recorded and transcribed. The transcribed data will be coded and analyzed using the qualitative data analysis software program NVIVO.

16.4. WITHDRAWAL OF INDIVIDUAL PARTICIPANTS

Participants can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a participant from the study for urgent medical reasons, e.g. imminent suicide risk. Since only individuals with imminent suicide risk will be excluded, those with suicidal thoughts at inclusion/screening will be followed up by the helpers. When during calls with DWM/PM+ helpers, participants show deterioration with imminent suicidal plans than the helper will discuss this immediately with one of the DWM/PM+ supervising mental health specialists. Also, when there is clear suspicion of worsening of (severe) mental health problems, participants will be asked to withdraw from the study and contact their general practitioner for a referral to specialized mental health treatment.

16.5. REPLACEMENT OF INDIVIDUAL PARTICIPANTS AFTER WITHDRAWAL

No new subjects will be included for each withdrawn subject. In our power calculation for the sample size, we have taken into account 30% attrition.

16.6. FOLLOW-UP OF SUBJECTS WITHDRAWN FROM TREATMENT

If a subject decides to withdraw from the study, the investigator will ask for the reason. It will be enquired whether the subject wishes to withdraw from the study or from a specific time point only and so whether the subject can be re-contacted at a later time. Withdrawal from the study will have no effect on the regular treatment. Subjects who leave the study for medical reasons will be followed until the interfering condition has resolved or reached a stable state.

16.7. TEMPORARY HALT FOR REASONS OF SUBJECT SAFETY

We will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited medical research ethics committee without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited medical research ethics committee. The investigator will take care that all subjects are kept informed.

16.8. ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, FOLLOW-UP OF ADVERSE EVENTS.

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the trial procedure or the stepped care DWM and PM+ intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. All adverse events will be

followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

A serious adverse event is any untoward medical occurrence or effect that:

- results in death
- is life threatening (at the time of the event)
- requires hospitalisation or prolongation of existing inpatients' hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all serious adverse events to the sponsor without undue delay after obtaining knowledge of the events, except for the following serious adverse events: Not applicable.

17. Ethical considerations

17.1. ANONYMISATION AND PSEUDONYMISATION

Anonymization will be applied to personal data to achieve irreversible de-identification and optimal solution will be decided on a case-by-case basis by using a combination of different techniques:

1. Pseudonymization: personal data (i.e., names and surnames, contact information, department) will be removed from the dataset and kept separately and securely stored in PSSJD's secure servers. Organization and departments will be also assigned with a unique ID code. Original values will be securely kept in PSSJD and will be able to be retrieved and linked back to the pseudonym, should the need arise. The ID number will be unique, and shall not have relationship with the original values. Security controls (including administrative and technical ones) will be used to protect the identity database.
2. Generalization: a deliberate reduction in the precision of data, such as converting a person's age into an age range. This technique will be used for values that can be generalized and still be useful for the intended purpose.
3. Synthetic Data: mainly used to generate synthetic datasets directly and separately from the original data, instead of modifying the original dataset.

Since pseudo-anonymised data might still be attributed to a natural person by using additional information such as a decryption key, the General Data Protection Regulation will remain applicable in this particular case.

17.2. DATA ACCESS AND MANAGEMENT

Data access and management

All data from the Barcelona site will be securely stored in PSSJD's secure servers.

3) Data collection platform (assessments). Data collection for the assessments will be managed using Castor EDC. This platform complies with all the relevant General Data Protection Regulation obligations and HIPAA regulations. More specific information can be found here: https://www.castoredc.com/wp-content/uploads/2021/04/Castor-Assessment-of-GDPR-and-HIPAA-Compliance.pdf. Since teleconferencing platforms do not allow do record only audios, videos from PM+ sessions will be directly eliminated once the PM+ is finished, and only the audio will be stored.
4) Metadata (DWM-app). The web application DWM used as first step intervention, will collect metadata (e.g. usage of the app such as when someone logs in, when a lesson is opened for the first time, when it has ended, when an answer is given or changed within a lesson, when a exercise is logged, when a journal entry is added, when a message to the helper is written). An ID code is used to link with the Castor EDC data. No personal data will be routinely collected with the app. The data is stored in a MySQL database on a managed VPS which is located in a datacenter in the Netherlands (managed by the full EU-study coordinators). Internet provider is ISO 9001, ISO 27001 certificated. All privacy sensitive data is stored encrypted and is pseudonymized: i.e. the record that contains the data from a lesson that has been filled in by a participant does not contain a referring key (an ID) that points directly to the corresponding record in the user table but contains a hash that is the result of a computation by an algorithm based on info from the user record. The database is backed-up daily by the provider and goes back 7 days. Only the helpers and the researcher coordinator of the trial will have access to participants' metadata.
5) Qualitative study (phase 3). The material recorded in audio, as well as the field notes will be stored on a server within the information systems of the PSSJD. This information will be accessible to the FSJD research team only. The transcripts will be stored in the PSSJD server and a proprietary license will be used for the data analysis software to which only FSJD researchers will have access to.

Management, communication and transfer of personal data of all participants will be in compliance with Regulation EU 2016/679 of the European Parliament and of the Council of April 27, 2016 on the protection of natural persons as regards to the treatment of personal data and the free circulation of data, being mandatory from May 25, 2018 and to Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights. The legal basis that justifies the treatment of the data is the consent signed by the patient, in accordance with the provisions of article 9 of the EU Regulation 2016/679.

The data collected will be only identifiable by a code, thus no information will be included to identify participants. Only researchers from PSSJD with the right of access to the source data will be able to link the data collected in the study to the participants' personal data. The identity of the participants will not be available to any other person except for a medical emergency or legal requirement.

Those who might have access to the identified personal information are: health authorities, the Research Ethics Committee and personnel authorized by the study promoter, when necessary to check study data and procedures, but always maintaining confidentiality in accordance with current legislation.

Only the encrypted data will be transferred to third parties and other countries, which in no case will contain information that can directly identify the participant (such as name and surname, initials, address, social security number, etc.).

If the event that encrypted data transfer is conducted outside the European Union, either in entities related to the hospital center where the patient participates, to service providers or researchers who collaborate with us, the data of the participants will be protected by safeguards such as contracts or other mechanisms established by the data protection authorities.

In addition to the rights that the previous legislation already contemplates (access, modification, opposition and cancellation of data, deletion in the new Regulation), the participants can also limit the management of data collected for the project that is incorrect, request a copy or limit moving data to a third party (portability). To exercise these rights, they shall contact the principal investigator of the study or the Data Protection Officer of the PSSJD through genis.parra@pssjd.org. Likewise, they have the right to contact the Data Protection Agency if they are not satisfied.

Data cannot be deleted even if a participant leaves the study, to ensure the validity of the research and to comply with legal duties and medication authorization requirements.

The Investigator and the Sponsor are obliged to keep the data collected for the study for at least 10 years after its completion. Subsequently, personal information will only be kept by the health care center and by the sponsor for other scientific research purposes if the participant has given his/her consent, and if permitted by applicable law and ethical requirements.

17.3. MEDICAL DEVICE

The first step of the step-care intervention is the DWM program presented via a mobile app. We consider that this app does not meet the criteria to be considered a medical device for the following reasons: (i) the population to which this app is directed is the working and healthy adult population. Those who present imminent suicide risk, those with a severe mental disorder, cognitive impairment or currently receiving specialized psychological treatment will be excluded from the study (ii) DWM-app is based on a manual that is considered a low-intensity intervention. It aims to improve well-being, not treating severe mental disorders (iii) other intervention studies are being currently conducted employing apps with similar aims (but for other target populations such as workers of small and medium enterprises, BEST and EMPOWER project), and these apps were not considered to be a medical device by the *Fundació* Ethics Committee.

17.4. ETHICS AND DATA ADVISORY BOARD (EDAB)

The RESPOND' Ethics and Data Advisory Board (EDAB) will monitor and provide expert advice on data management and all ethical, legal and societal issues that arise within the project, promoting integrity and a better alignment of RESPOND with social needs and expectations that may arise within or as a result of RESPOND. This includes monitoring the safety, rights, and wellbeing of study participants, and providing input for ethics reports. In addition, the EDAB will provide advice on FAIR data management, including data privacy and adherence to the General Data Protection Regulation. The EDAB will ensure that the trial and data collection in RESPOND are conducted in accordance with the International Conference on Harmonisation, the WHO Good Clinical Practice standards, Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013), and (inter)national laws (e.g, Medical Research Involving Human Subjects Act (WMO)). In addition, the ethical, legal of the participants and research staff members will be reviewed and interim analyses will be considered in case safety issues are (suspected to be) violated. Incidental findings within RESPOND refer to an extreme score on study instruments (questionnaires or interviews) that need additional follow-up. Other issues that will be considered include privacy and intellectual property rights. Relevant issues will be discussed in an annual meeting, but if issues arise between these meetings, the EDAB will be requested to plan an additional meeting. Additional meetings will be held before submission of ethics documents for formal approval as well as before submission of ethics reports. The EDAB compromises of independent members having no conflict of interest with the sponsor of the study, i.e. dr. Christopher Dowrick, dr. Victor Perez, and dr. Sonja Rutten, member of the Ethics Review Committee Board member (VUA). For RESPOND principal investigator Prof. dr. Marit Sijbrandij will join the EDAB meetings together with assistant professor Dr. Anke Witteveen. Tom Paffen LL.M (VU) will join for matters of data protection and privacy.

The management team and EDAB will ensure that all necessary actions will be undertaken to minimize risks and suggest necessary measures to counter these risks. Through efficient communication between the EDAB, overall management (Work Package 1), and leader of individual Work Packages, the consortium will ensure that mitigation measures will be undertaken in a timely and effective manner.

The advice(s) of the EDAB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the EDAB, the sponsor will send the advice to the reviewing medical research ethics comitees, including a note to substantiate why (part of) the advice of the EDAB will not be followed. The EDAB should conclude each review with their recommendations to RESPOND as to whether the study should continue without change, be modified, or be terminated. Recommendations regarding modification of the design and conduct of the study could include: modifications of the study protocol based upon the review of the safety data; suspension or early termination of the study or of one or more study arms because of serious concerns about subjects' safety, inadequate performance, or rate of enrolment; suspension or early termination of the study or of one or more study arms because study objectives have been obtained according to pre-established statistical guidelines.

17.5. PUBLIC DISCLOSURE AND PUBLICATION POLICY

The trial will be registered in a public trial registry before the first patient is recruited. The results of the study will be submitted for publication in international, peer-reviewed journals. Moreover, findings may will be presented in scientific conferences and be disseminated to stakeholders working in the field. In addition to all, the results of the study will be disseminated through the WHO website and other dissemination channels of WHO. A preliminary version of the RESPOND Communication and Dissemination Plan has been delivered to the EU in February 2021.

18. STATISTICAL ANALYSYS

18.1. PRIMARY STUDY PARAMETERS

The statistical analysis of the RCT will estimate effectiveness of the stepped-care DWM/PM+ intervention with PFA and CAU compared to PFA and CAU alone, with PHQ-ADS score as the primary study parameter.

The primary outcome will be summarized using number of subjects (*n*), minimum and maximum; and means, standard deviations (*SD*) for normally distributed data, or medians and inter-quartile ranges for non-normally distributed data. To measure comparisons at baseline between the two treatment arms, either independent-sample *t* or Mann-Whitney tests will be performed on continuous variables, and Fisher's or chi-squared tests on categorical variables.

Both intention-to-treat (ITT) and per-protocol (PP) analyses will be conducted. ITT will include all randomized participants ($n \sim 210$) while PP will include only those who completed the intervention program. The main conclusion of the trial will be based on the ITT analysis of the primary outcome. A secondary analysis of the primary outcome will also be presented using the PP population.

The statistical analysis will be masked, i.e. the trial statistician will be blinded to the treatment groups until the analysis has been completed. Moreover, the trial statistician will not be involved in determining participants' eligibility, in administering the intervention, in measuring the outcomes or in entering data.

To estimate the treatment effect, either linear or generalized mixed models will be employed for the primary endpoint analysis, which will have treatment as fixed effects, baseline measurement of primary endpoint as covariate, and subject as random effects. The mean difference between two treatment arms at each visit/time together with its 95% confidence interval will be derived from the mixed model. Covariate-adjusted mixed model of primary endpoint will also be performed by adding pre-specified covariates at baseline (gender, age, education, adverse (traumatic) events, COVID-19 related events, and severity of symptoms) into the above model. Post-hoc sensitivity (i.e., moderation) analyses will also be conducted based on baseline characteristics (e.g., different treatment effects for men and women).

Missing data

Missing data will be treated as missing at random. No imputations of missing values will be made, as multilevel models can deal with missing data (Singer, Willett & Willett, 2003).

18.2. SECONDARY STUDY PARAMETERS

Economic outcomes

Health economic analysis will be conducted to determine the difference in costs and outcomes in the intervention arm as compared to the care as usual group. Primary analysis will be the total costs over the 2-month follow-up treatment period. Between-group comparison of mean costs will be completed using standard *t*-test with ordinary least squares regression used for adjusted analysis, with the validity of results confirmed using bootstrapping. Pseudonymized data will be sent to the London School of Economics and Political Science, partner in RESPOND under Work Package 3, for the health economics analysis of the CSRI.

Analysis of secondary outcomes with repeated measurements

Additionally, linear or generalized mixed models as mentioned for the primary outcome analysis (PHQ-ADS) will be carried out for analyzing the following clinical outcomes measured at baseline, at 1 week after DWM, at 1 week and at 2 months after finishing PM+: posttraumatic stress reactions (PCL-5), depressive symptoms (PHQ-9), generalized anxiety (GAD-7), and quality of life (EQ-5D-5L).

Analysis of other secondary outcomes
Changes in caseness of the composite measure anxiety and depression will be calculated for the PP sample using the recommended cut-off of >20 for moderate severity on the PHQ-ADS questionnaire (Kroenke et al., 2016; Kroenke et al., 2019) and will be analyzed using a hierarchical logistic model with the same fixed and random effects as the hierarchical linear models above, from which odds ratio of having a depression together with 95% CI at each time point will be derived.

Corrections for multiple testing

Models will be tested on $\alpha = .05$; we will not apply a post-hoc correction to deal with problems associated with multiple testing, but instead report the number of tests that are carried out.

18.3. OTHER STUDY PARAMETERS

Phase 3 will consist of qualitative interviews and/or focus group discussions among participants and key stakeholders to evaluate possible barriers and facilitators to treatment engagement and adherence to the PM+/DWMS program. The outcomes of these assessments will be used to make informed-decisions for potential mediators or moderators of PM+/DWMS treatment effectiveness.

Treatment fidelity:

In order to determine whether the intervention-as-implemented does not differ from the intervention-as-designed, fidelity checklists filled out will be completed for a random sample, stratified on peer-health care workers, intervention providers of sessions/participants. Treatment fidelity will be analyzed as manipulation check.

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