

BMJ Open Protocol for a sequential, multiple assignment, randomised trial to test the effectiveness of message-based psychotherapy for depression compared with telepsychotherapy

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To cite: Arean P, Hull D, Pullmann MD, *et al.* Protocol for a sequential, multiple assignment, randomised trial to test the effectiveness of message-based psychotherapy for depression compared with telepsychotherapy. *BMJ Open* 2021;**11**:e046958. doi:10.1136/bmjopen-2020-046958

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2020-046958>).

Received 18 November 2020
Accepted 11 October 2021



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ABSTRACT

Introduction Digital mental health tools have become popular alternatives to traditional psychotherapy. One emerging form of digital mental health is message-based care, the use of text messages or asynchronous voice or video messaging to provide psychotherapy. There has been no research into whether this is an effective method of psychotherapy as a stand-alone treatment or in combination with traditional psychotherapy.

Methods and analysis This is a sequential, multiple assignment randomised trial to compare message-based care, videoconference-psychotherapy and a combination of the two treatments in 1000 depressed adults. Participants will be recruited through Talkspace, a digital mental health company, and randomised to receive 6 weeks of either message-based care only or videoconference-psychotherapy only. At 6 weeks, participants will be evaluated for their response to treatment. Those with a 50% or more response to treatment will continue with their assigned condition. Those who do not respond will be randomised to either monthly videoconference-psychotherapy or weekly videoconference-psychotherapy plus message-based care. Primary outcomes will be depression and social functioning. We will also explore moderators of treatment outcome.

Ethics and dissemination The study received ethics approval from the University of Washington Institutional Review Board. Results of this study will be presented in peer-reviewed journals and at professional conferences.

Trial registration number NCT04513080; Pre-results.

INTRODUCTION

Depression is the leading cause of disability and mortality worldwide and is associated with increased suicide risk, poor school and work performance, poor quality of life and significant economic burden.^{1–3} Psychotherapy is an effective treatment for depression, with 60% of those with depression preferring psychotherapy to medication.^{4–8} Only 42% of people with depression use psychotherapy^{9 10} and of those who do access psychotherapy, few do not receive a

Strengths and limitations of this study

- This study is a large-scale clinical trial of 1000 people who will answer important questions about the effectiveness of message-based care, either alone or in combination with telepsychotherapy, for treating adults suffering from depression.
- Because this study uses a sequential, multiple assignment randomised trial design, we will be able to determine who responds to different sequences of digital treatment.
- This study will also determine whether comorbid anxiety moderates response to treatment and whether number of contacts per week, participants' perception of treatment match to mental health challenges and working alliance mediate response to treatment.
- A limitation to this study is that clinicians will not be blind to the participant's treatment condition. However, assessment procedures allow for such blinding and the statistician completing the analyses will be blind to study arm.

full course of treatment.¹¹ The disconnect between treatment preferences and service use can be explained by access and inconvenience. Psychotherapy is commonly offered as in-person care, with most psychotherapists concentrated in large urban areas.¹² The typical psychotherapy dose is 12–16 1 hour, in-person meetings, yet available appointments are often during inconvenient times (9–5, M–F).¹³ Psychotherapy as it is currently delivered is limited to weekly or every other week 1 hour visits, and in some settings (integrated primary care), is as infrequent as once a month.^{14 15} Originally, evidence-based psychotherapies were designed to be delivered 1–2 times a week in the initial phases of treatment to enhance engagement and speed response,^{16 17} and research now finds two or more psychotherapy contacts per week

results in greater engagement and faster recovery.^{18 19} The delivery of psychotherapy as it is currently designed is inaccessible to most patients in need of care, and is not provided as frequently as recommended, reducing its clinical impact.

Advances in technology and ubiquitous ownership of mobile technology can be leveraged as novel methods of delivery to move the needle on rates of depression. Research has consistently shown videoconferencing-based psychotherapy (VCP) to be an engaging form of delivery that enhances access, has high levels of patient satisfaction and is comparable to conventional treatment among diverse patient populations, ages and diagnostic groups.^{20–33} It is considered to be equivalent and more accessible than face-to-face psychotherapy.³⁴ While telepsychotherapy addresses location barriers effectively, it suffers from the same time barriers as face-to-face psychotherapy.

Message-based psychotherapy (MBP), defined as the use of text messages or asynchronous voice or video messaging, is an interesting alternative to VCP and is becoming a widely available form of psychotherapy delivery, with as many as 21 companies providing MBP³⁵ in the USA and an estimated 82 start-up companies offering this care globally as of this writing.³⁶ It differs from VCP in that patient–therapist contact can be done asynchronously, as often as needed and can be delivered when it matters most to the patient. Studies show that asynchronous messaging between therapists and patients supports action plan implementation, results in better therapeutic alliance and overall adherence to treatment recommendations by patients,^{37–43} and in small studies, results in significant reductions in depression. MBP is based on the theory that interventions have their biggest clinical impact when the consumer is at their greatest level of receptivity, and through better timing and tailoring, improve the consumers' readiness to change, self-efficacy to implement the intervention and in goal-directed⁴⁴ behaviour.⁴⁵ Recent research further suggests that more than once a week therapeutic contact results in better depression outcomes.^{46–48} However, the impact of MBP as a stand-alone treatment for depression is still unknown, and for this reason is in further need of study.

The combination of MBP with either occasionally or regularly scheduled VCP may be particularly helpful to people who do not respond to either VCP or message-based care alone. To date, there is limited information on the relative effectiveness of message-based and VCP, and what is the best 'step-up' in treatment for people who may need more intensive care. Thus research is needed to (1) determine the relative effectiveness of MBP, compared with weekly VCP, (2) determine whether a switch to monthly VCP+MBP or weekly VCP+MBP is better for people who do not respond to VCP or MBP alone, (3) determine who responds to best to VCP, MBP or the combined conditions and (4) test the assumptions about the frequency and timeliness of treatment on working alliance and hence treatment outcomes.

STUDY OBJECTIVES

The purpose of this paper is to publish the protocol of a study recently funded by the National Institute of Mental Health to determine the impact of MBP compared with VCP as stand-alone interventions, and for whom a combined approach to care is needed. Our specific aims and hypotheses are:

Aim 1

Determine the relative effectiveness of MBP to VCP on depression and functioning at 6 weeks of care. Because of the evidence suggesting that more frequent contact with a therapist results in great treatment outcomes, we hypothesise that:

Hypothesis 1A

Patients randomised to MBP will have greater improvements in depression (9-Item Patient Health Questionnaire, PHQ-9) and anxiety (7-Item Generalised Anxiety Scale, GAD-7) and are more likely to show a response to treatment than patients randomised to weekly VCP.

Hypothesis 1B

Patients randomised to MBP will have greater improvements in functioning (Sheehan Disability Scale) from baseline to week 6 assessment than those randomised to weekly VCP.

Hypothesis 1C

For those who respond to their assigned treatment, a greater proportion of those in MBP will show response to treatment and remission as reported on PHQ-9 (primary) and GAD-7 (secondary) than those in weekly VCP.

Aim 2

For those who fail to respond to level 1 care, compare the addition of 6 weeks of monthly VCP with weekly VCP on depression and functional outcomes.

Hypothesis 2A

Patients *who do not respond to MBP* and are randomised to weekly VCP will have greater improvements in depression, anxiety and function and are more likely to show a response to treatment than patients randomised to monthly VCP.

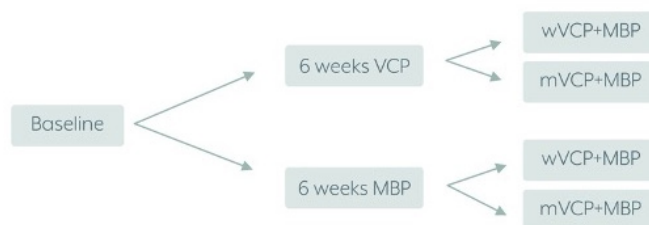


Figure 1 Sequential randomisation approach. MBP, message-based psychotherapy; VCP, videoconferencing-based psychotherapy.

Hypothesis 2B

Patients *who do not respond to VCP* and are randomised to weekly VCP with MBP will have greater improvements in depression, anxiety and function and are more likely to show a response to treatment than those randomised to monthly VCP with MBP.

METHODS AND ANALYSIS

This clinical trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials guidelines (see online supplemental file 1). This study has been approved by the University of Washington (UW) (STUDY00010391).

Study design

This study is a sequential, multiple assignment randomised trial (SMART). Although our first primary aim is to compare message-based care only (MBP) to once-a-week videoconferencing therapy sessions (VCP), we are further interested in which augmentation sequences are most effective for those who do not respond to their randomised condition. Sequenced interventions are customised to patients' needs with a *tailoring variable*. In this study, the tailoring variable is PHQ-9, as it is collected routinely in clinical practice and based on an indication of inadequate clinical response (<50% reduction in PHQ-9) after 6 weeks of treatment.⁴⁹ After 6 weeks of active treatment, we will readminister the PHQ-9. If participants do not respond to their initial treatment assignment, they will be randomised to receive either monthly or weekly VCP with MBP (see figures 1 and 2).

Patient and public involvement

No patients were involved in planning the study methods.

Participants

We will recruit 1000 participants representative of the typical patient seeking care through an online platform for symptoms of depression. Inclusion criteria are that participants must be 18 years old or older, live in the USA, speak English or Spanish, have a score of 10 or greater on the PHQ-9 screening and have received a diagnosis of depression during baseline assessment. Participants with active suicidal ideation or with a primary diagnosis of psychosis will be excluded and referred to intensive care. We will not exclude participants with other psychiatric co-morbidities.

Recruitment methods

We will recruit from Mental Health America's website, a US-based mental health advocacy and referral service. Individuals identified as eligible for and interested in the study will participate in an informed consent.

Interventions

General treatment procedures

Procedures for treatment initiation are the same for each treatment option. Participants contact therapists any time

after a therapist is assigned. Therapists respond within 15 min to 24 hours. Participants will be offered 12 weeks of care. In addition to text and video chat services, Talkspace maintains a virtual bookshelf of articles, worksheets and educational videos therapists can share with patients. See table 1 for timeline.

Message-based psychotherapy (MBP)

In this condition, therapists work with participants over a secure messaging platform. Participants have unlimited access to this platform and can message their therapist as often as they like. Therapists respond to messages within 15 min to an hour during office hours, and within 14 hours outside of office hours. MBP is not fully synchronous.

Video chat only (VCP)

This condition consists of weekly evidence-based psychotherapy appointments that last between 30 and 45 min. These sessions are conducted using Agora, a secure, Health Insurance Portability and Accountability Act (HIPAA)-compliant videoconferencing service that is seamlessly integrated into the Talkspace platform application. This is an evidence-based model of care.⁵⁰

Message-based psychotherapy with monthly video chat/Preferred Plan (PP)

This condition allows patients unlimited messaging with their therapist and once a month, 30–45 min video chat with the same therapist. Therapist and participants schedule their video chat appointment to occur at once a month intervals during therapist office hours.

Message-based psychotherapy with weekly video chat/Ultimate Plan (UP)

In this condition, participants will have access to both unlimited MBP, but will be able to schedule weekly, 30–45 min video chat with the same therapist.

Therapists

Talkspace therapists will provide all treatments in this study; we will select therapists who have been trained to provide evidence-based psychotherapy, and who are known to be expert in one of three models: cognitive-behavioural therapy (CBT), problem-solving therapy (PST) or interpersonal therapy (IPT). We will not assign therapists to treatment model or study arm, but rather each therapist will provide all types of care. Our rationale is as follows (1) this reduces conflating the effects of therapist and condition; (2) when patients switch or argument care currently, they typically do not switch therapists. The ability for therapists to add services to treatment is more in-line with usual care; (3) we would be less likely to lose participants if they could stay with the same therapist throughout the study. Therapists providing care in this study must be able to provide CBT, IPT or PST. We will employ two strategies to ensure clinicians are using evidence-based practices: (1) UW will provide yearly trainings with study therapists to review best practices in the application of evidence-based psychotherapies; this

TIMEPOINT**	STUDY PERIOD															
	Enrollment	Allocation	Post-allocation											Close-out		
	-t ₁	0	t ₁	t ₂	t ₃	t ₄	t ₅	t ₆	t ₇	t ₈	t ₉	t ₁₀	t ₁₁	t ₁₂		
ENROLLMENT:																
Eligibility screen	X															
Informed consent	X															
Level 1 Random Assignment & Allocation		X														
Level 2 Random Assignment & Allocation							X									
INTERVENTIONS:																
[Unlimited messaging]		X	_____													
[Weekly Video]		X	_____													
[Unlimited messaging & weekly video]								_____								
[Unlimited messaging & monthly video]								_____								
ASSESSMENTS:																
Health Concerns	X															
Use of Mental Health Services	X															
Impact	X															
NIAAA	X															
MDE Screener	X															
Depression	X		X	X	X	X	X	X	X	X	X	X	X	X		
Anxiety	X		X	X	X	X	X	X	X	X	X	X	X	X		
Functioning	X		X	X	X	X	X	X	X	X	X	X	X	X		
Treatment Rationale Scale			X													
Health Concerns, Use of Mental Health Services	X															
Patient Global Improvement Scale			X	X	X	X	X	X	X	X	X	X	X	X		
Major Life Changes						X				X				X		
Satisfaction with Care						X				X				X		
CAHPS ECHO						X						X				
WAISR						X						X				
Exit Survey														X		

Figure 2 Schedule of enrolment, interventions and assessments. ECHO, Experience of Care and Health Outcomes Survey; MDE, Major Depressive Episode; WAISR, Working Alliance Inventory, Short Form.

practice is in-line with programmes that Talkspace already offers their clinicians and (2) we will randomly select texts and video chat encounters and rate these encounters on use of CBT, IPT or PST strategies. To ensure real-world generalisability, feedback will not be provided, as this is not currently a quality control measure in any health plan or system of care in the USA. Rating forms we use for these purposes are the Use of Psychotherapy Elements Rating Scale.^{51–53}

Randomisation

Participants will be assigned to one of two conditions, VCP or MBP, on entry to the study using stratified systematic random assignment, to ensure roughly equivalent

numbers of participants within each condition across therapists. This will minimise confounding that may occur due to nesting of client within clinicians while maximising the reliability of clinician intraclass correlation estimates and increasing statistical power in mixed-effects regression analyses. For stage 2, those who have made a 50% reduction to PHQ-9 scores to their assigned treatment at their 5-week timepoint will continue in that same treatment for six more weeks. If the week 5 PHQ-9 scores are missing, we will use the week 4 or 3 PHQ-9 assessments for randomisation. If these are also missing, we will use the therapists' rating on the Clinician Global Impression-Improvement Scale⁵⁴ at 5 weeks. Participants who do not

Table 1 Study timeline

Year 1												
Task	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
Finalise protocol, IRB, training, DSMB			XX	XX	XX							
Participant recruitment (n=500)					XX	XX	XX	XX	XX	XX	XX	XX
Participant follow-up					XX	XX	XX	XX	XX	XX	XX	XX
Progress report, DSMB												XX
Year 2												
Participant recruitment (n=500)	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX
Participant follow-up	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX	XX
Progress report, DSMB												XX
Year 3												
Participant follow-up	XX	XX	XX									
Data analysis				XX	XX	XX	XX	XX				
DSMB				XX								
Progress/final report									XX	XX	XX	XX

DSMB, Data and Safety Monitoring Board; IRB, Institutional Review Board.

show improvement (eg, 50% reduction in PHQ-9 scores or therapist rating of improvement, if PHQ-9 scores are missing) will be randomised to either the weekly VCP with MBP (Ultimate Plan or PP) to monthly VCP with MBP (Preferred Plan or PP). The randomisation protocol will be developed by the study statistician and embedded in the Research Electronic Data Capture (REDCap)^{55 56} tracking and data collection system to facilitate automated condition assignment.

Assessment measures, methods and timeline

Participants will be involved in the study for a total of 12 weeks. They complete an initial screening survey, baseline assessment, 4 follow-up assessments (4-weeks, 6-weeks, 10-weeks and 12weeks), daily ratings and weekly assessments. The initial screening is completed after entering Talkspace's digital platform. After review of results by study team member for inclusion criteria and presence of depression, eligible participants are contacted by a Talkspace staff member and sent the consent form. Data collection for all time points, including screening, baseline, daily and weekly surveys, takes place via Short Message Service (SMS)-delivered REDCap surveys (see [table 2](#) and [figure 2](#)).

Baseline assessment

Demographics: Participants will complete a survey to determine gender, age, ethnicity, income categories and education.

The Major Depressive Episode (MDE) Screener.^{57 58} The MDE screener will assess the prevalence of MDE by screening for the nine DSM-IV MDE symptoms. The MDE screener was shown to have excellent agreement with clinical interviews using the Structured Clinical Interview for DSM-CV (SCID-CV kappa=0.76; sensitivity=0.97, specificity=0.97).

9-item Patient Health Questionnaire (PHQ-9).⁵⁹ The PHQ-9 consists of nine depression items and one disability item. The participant rates on a 0–3 scale if they have experienced the symptom over the last 2 weeks.

The Social Life and Family Life Scales of the Sheehan Disability Scale (SDS).⁶⁰ The SDS is a measure of disability/functional status. This is a brief analogue disability scale, which uses visual–spatial, numeric and verbal anchors.

7-item Generalised Anxiety Scale (GAD-7).⁵⁹ To assess for co-occurring anxiety, we will use the GAD-7, a seven-item screener for generalised anxiety. It consists of items related to GAD. Participants rate on a scale of 0–3 how much they have experienced in the last 2 weeks.

National Institute of Alcohol Abuse and Addictions Alcohol Screening Test (AST).⁶¹ The AST is a four-item screener developed by the NIAAA to quickly identify people who may be at-risk drinkers, dependent on or abusing alcohol. Participants are asked if they drink alcohol, and those who do are asked if in the past year they have had more than 4–5 drinks a day, more than once in the year. Those who indicate that they have are asked additional questions about the impact their drinking has had on their personal and work life.

IMPACT assessment of mania and psychosis.⁶² To document current or history of bipolar or psychosis diagnosis, we will use the four-item mania and psychosis-screening instrument used in the IMPACT study.

Treatment Rationale Scale (TRS).⁶³ To assess participant expectations about treatment, which influences outcomes, we will administer TRS, a four-item scale administered before the second and last session. The scale assesses patient expectations about the success of treatment.

Table 2 Schedule of assessments

Assessments	Timepoint													
	Screening	Baseline	1	2	3	4	5	6	7	8	9	10	11	12
Demographics	X													
The Major Depressive Episode (MDE) Screener		X												
9-Item Patient Health Questionnaire (PHQ-9)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
The Social Life and Family Life Scales of the Sheehan Disability Scale (SDS)		X	X	X	X	X	X	X	X	X	X	X	X	X
7-Item Generalised Anxiety Scale (GAD-7)		X	X	X	X	X	X	X	X	X	X	X	X	X
National Institute of Alcohol Abuse and Addiction Alcohol Screening Test (AST)		X												
IMPACT assessment of mania and psychosis		X												
Self-reported health and health concerns		X												
Use of Mental Health Services		X												
Treatment Rationale Scale (TRS)			X											
Patient Global Improvement Scale			X	X	X	X	X	X	X	X	X	X	X	X
Major Life Changes						X				X				X
Satisfaction with Care						X				X				X
Experience of Care and Health Outcomes Survey (ECHO)						X						X		
Working Alliance Inventory, Short Form (WAI-SR)						X						X		
Exit Survey														X

Assessments are collected via REDCap at all timepoints.

REDCap, Research Electronic Data Capture.

Weekly assessments

Participants will complete the PHQ-9, SDS and GAD-7. In addition to these measures, we will administer the *Patient Global Improvement Scale*, a five-item measure of participant perception of improvement since beginning treatment. Participants are asked to rate whether their rate of improvement since using the apps. Specifically, participants are asked, 'since starting treatment, I feel that I am: (1) much worse (2) worse (3) no different (4) improved (5) much improved'

Tailoring variable

SMART designs require a tailoring variable that is a measure to determine when a switch or augmentation should take place. Tailoring variables are measures that are commonly employed in practice. We will use the PHQ-9 as our tailoring variable, as this is currently a measure that Talkspace uses for clinical decision-making. If the PHQ-9 is unavailable, we will use the therapist's rating on the Clinician Global Impression-Improvement Scale as our tailoring variable.

12-week outcomes

The PHQ-9 (depression) and SDS will serve as our primary clinical outcomes.

Process of care

Other hypothesised mediators of clinical and functional outcomes are (1) intervention intensity, (2) working alliance and (3) timeliness of treatment. These measures will be collected at weeks 4 and 10, as they are hypothesised treatment mediators.

Treatment intensity: These data will be collected from Talkspace's electronic records, consisting of time spent in treatment, number of 'sessions'/messages over 12 weeks and treatment attendance.

Working Alliance Inventory, Short form (WAI-SR):⁶⁴ The WAI-SR is a 12-item measure of therapeutic alliance (relationship between the consumer and therapist or coach). It is a reliable measure of alliance, with $\alpha=0.92$.

Experience of Care and Health Outcomes Survey (ECHO):⁶⁵ ECHO items assess whether consumers received timely treatment, enough information to support

self-management and were involved in treatment as much as they wanted. ECHO is a reliable instrument with $\alpha=0.85$.

DATA ANALYSIS PLAN

Data management

All data will be kept in a secure server in the UW's School of Medicine behind a firewall system we have used for our other mobile studies. All participant specific data will be encrypted, time stamped and identified using a non-descript value unrelated to any participant identification information. Only the researchers will have the information necessary to translate from the non-descript identifier value to the actual patient identification. That translation information will be stored in a separate secure location from the trial clinical data. All analyses reported from this study will only contain aggregate data. The data from individual participants may be reported, anonymously, as examples of the flow through the study portal app site.

Missing data

Baseline and follow-up variables with missing values will be imputed using multiple imputation methods described by Rubin.⁶⁶

Sample size

Our sample size was chosen to provide adequate power to both aims 1 and 2. Since the second aim focuses on the subset of 6-week non-responders, we have powered the second aim for an effect size midway between a small (0.20 SD) and a moderate (0.50) effect size and then ensure that the resulting initial enrolment sample size would be adequate for a small effect size (0.20 SD). Furthermore, we ensure that we have sufficient power for clinically meaningful binary 'success' outcomes which are key secondary outcomes.

Aim 1 analysis

To test aim 1, the explanatory variable of interest will be group randomisation status (MBP vs VCP) with outcomes collected over the first 6 weeks. Three-level longitudinal mixed-effects regression models (baseline and weekly outcomes through the 6-week timepoint nested within client nested within clinician) will be specified with appropriate distribution and link functions to match the dependent variables (eg, linear for PHQ-9, SDS and WAI scores, binomial/logistic for PHQ remission at week 6, negative binomial/log for number of messages/sessions). Client-level and clinician-level effects will be random effects. Covariates will include participant demographic and symptom severity and comorbidity variables. Each model will include a time x condition interaction to evaluate differences slopes (rates of change over time). Time will be entered as a categorical variable to allow general response trajectories, and in secondary analyses as a linear variable that assumes a constant rate of improvement

over the first 6 weeks. Models with time centred at BL and 6 weeks will be run separately to statistically test for conditional mean differences at those timepoints, in addition to testing for differences in slopes. The primary outcome in 1A and 1C is the PHQ-9 at week 6, and for 1B is the SDS at week 6.

Power for aim 1

For the quantitative primary outcome (PHQ-9), we will have greater than 80% power to detect a 0.20 SD across groups, which corresponds to a clinically meaningful small difference, if we obtain approximately 800 participants after an estimated 20% attrition. For a binary success outcome, we will consider a 50% reduction in PHQ-9 from baseline to 6 weeks as success, and we have greater than 80% power to detect an absolute difference of 10% (eg, 60% of subjects with >50% improvement vs 70% of subjects with >50% improvement).

Aim 2 analysis

To test aim 2, the explanatory variable of interest will be second-stage sequence group randomisation status and the analysis population will be the subset of non-responders based on their 6-week PHQ-9. Covariates will include original randomisation group, demographics, symptoms severity and comorbidities. Regression models will be specified with the appropriate distribution and link functions to match the dependent variable. The aim 2 analysis will use data collected from weeks 7–12 with a primary focus on the 12-week timepoint

Power for aim 2

For the second-stage randomisation, we anticipate that approximately 40% of subjects would not show >50% improvement and therefore undergo a second-stage randomisation. The primary comparison in the second stage is the comparison of UP versus PP for each of the first-stage randomisation groups (MBP and VCP). We conservatively assume that 40% of 800 subjects followed through 6 weeks would be eligible, and that 80% of these subjects would be followed through 12 weeks. In this case, we expect a second-stage analysis sample of 256 subjects, and this corresponds to 80% power to detect a 0.35 SD difference across the UP and PP groups when pooling across the primary MBP and VCP strata.

Exploratory analyses

Moderators of clinical outcomes for aims 1 and 2. We can expand the aim 1 and aim 2 analyses to consider baseline factors as moderators for the initial randomisation assignment over weeks 1–6, and then can consider 6-week measures as potential moderators of the second-stage randomisation over weeks 7–12. Specifically, for aim 2, we will use data from the non-responders to evaluate candidate moderators for the second-stage conditions and we will consider interactions between intervention status at the second sequence and baseline anxiety symptom severity, depression severity and comorbidities, number of texts/sessions per week, perceived timeliness of



treatment and working alliance as moderators. Each analysis will use the same multilevel regression specifications that were used for the primary analysis but will include the possible moderator and condition x moderator as covariates. We will run separate models to obtain parallel tests for each moderator. The significance of the interaction effects will be used to determine whether anxiety is a treatment moderator, using Benjamini-Hochberg false discovery rate procedure to avoid type I errors.⁶⁷

Full study longitudinal model

Aims 1 and 2 each focus on specific time periods, and aim 2 focuses only on those subjects randomised in the second stage. Given the SMART design, we can also characterise over the full longitudinal time course the differences across the embedded dynamic treatment strategies based on both the initial randomisation and the second-stage augmentation. For such analysis, we need to properly account for the fact that the 6-week outcome also determines the second-stage randomisation. Therefore, we will use both weighted analysis^{68 69} to characterise each of the four embedded dynamic treatment strategies (initial VCP or MBP, combined with either of the step-up options for non-responders), and will use Q-learning to consider potential additional moderating variables that could potentially generate more individualised treatment sequences.^{69 70}

LIMITATIONS

As with all clinical trials, this study has limitations. It will not be possible to blind participants and therapists to study condition, however, all assessments will be blind, as they will be collected through an automated survey system. Participants are volunteers and therefore may not be fully representative of the general adult population with depression. Finally, as a real-world study that emphasises generalisability, we will not be providing supervision to ensure that therapists have high fidelity to evidence-based treatment protocols.

RECRUITMENT STATUS AND TRIAL DATES

We will begin recruitment for this study in January of 2021 and will continue to recruit through December of 2023. Data collection is planned to be complete by April 2024, with data analysis and dissemination to be conducted between April 2024 and October of 2024.

ETHICS AND DISSEMINATION

Ethics

This study has been approved by the UW's Institutional Review Board (STUDY00010391), which is serving as the single IRB for this study with Talkspace relying on UW's IRB. All protocol modifications and amendments will be submitted to UW's IRB for review and approval prior to updates to the study's ClinicalTrials.gov listing.

Consent

Participants will provide informed consent for treatment through Talkspace and study procedures and research data collection through Research Electronic Data Capture (REDCap), which is HIPAA and Federal Information Security Management Act (FISMA) compliant. Adequacy of the Informed Consent procedure and the feasibility of obtaining a truly informed consent for an internet-based and mobile health app intervention projects has been studied in Dr Arean's research group. The informed consent procedures have been thoroughly prepiloted and refined to maximise the understanding of the informed consent process and content. The consent form will provide detailed information about the study and its procedures, assure participants that they are free to discontinue at any time and reiterate that non-participation or discontinuation will not impact their care at Talkspace. Follow-up questions will be asked to ensure that the participant has clearly understood the main aspects of the consent form. Correct answers to questions assessing for participants' understanding of the limitations of participation will be necessary to sign the consent form and advance to the baseline assessment. The consent form will also specify that participants need to seek immediate care if they feel in danger of hurting self or others. Participants are encouraged to contact the study team via email if parts of the informed consent form are unclear, or if additional information is desired. In addition to correctly answering questions about the informed consent document, participants need to provide consent by selecting a checkbox indicating provision of consent. A record of each participant having provided consent will be kept in a secure database.

Harms

If a participant is determined to be in need of a higher level of psychiatric care than what can be provided by the study and/or expresses any risk of self-harm, the Talkspace therapist will be responsible for appropriate referral and treatment. Adverse events, including those reported by participants, are routinely reported to the UW IRB. After the first 50 participants have entered the trial, we will review any adverse events that have occurred. Should any unexpected serious adverse events occur, our study protocol will be modified to prevent other similar events. If this effort fails to prevent additional similar adverse events, the study will be discontinued. A copy of the IRB protocol is provided in online supplemental file 2.

Data safety and monitoring plan

We will convene a Data and Safety Monitoring Board (DSMB) prior to the launch of the study and will engage this external body to provide critical evaluation of our protocol, and to provide on-going oversight to ensure patient safety and high-quality research conduct. The DSMB will be comprised of at least three members who can represent expertise in psychology/psychiatry, clinical trial methodology/biostatistics, and ethics.

Dissemination

We will deposit participant data into the National Institute of Mental Health (NIMH) informatics infrastructure in order to enable sharing of clinical research data. We anticipate submitting to the NIMH Data Archive. Data will also be made available as a part of the process of manuscript publication and presentation. Manuscripts will be submitted for publication to high-quality peer-reviewed journals, following the NIH Public Access Policy guidelines. Findings will be presented at public lectures, scientific institutions and relevant national conferences.

Contributors Each author has contributed significantly to, and is willing to take public responsibility for, one or more aspects of the study. PA, DH, MDP and PJH participated integrally in the study design. All authors contributed to design of the study protocol, data acquisition and analysis plan. PA drafted the initial manuscript; all other authors provided critical revisions and approved the final revisions.

Funding This work is supported by National Institutes of Mental Health grants R44MH124334 and P50MH115837.

Competing interests DH is a contracted employee at Talkspace and Noom.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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