A randomised controlled feasibility trial (the HARMONIC Trial) of a novel modular transdiagnostic intervention—Shaping Healthy Minds—versus psychological treatment-as-usual, for clinic-attending adults with comorbid mood, stressor-related and anxiety disorders

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Abstract

This trial introduces a novel transdiagnostic intervention (Shaping Healthy Minds) to address the gap in effective interventions for people with complex and comorbid presentations including anxiety, disturbed mood, and trauma sequelae. Shaping Healthy Minds is a modular intervention which synthesises several evidence-based treatment techniques that allows for standardised, yet flexible, treatment delivery. We conducted a patient-level two-arm randomised controlled trial (HARMONIC) that compared Shaping Healthy Minds to psychological treatment-as-usual (PTAU) for individuals aged >18 years (*n* = 42) with at least two comorbid mood, anxiety, obsessive-compulsive or trauma/stressor disorder diagnoses, recruited from outpatient psychological services within the UK National Health Service (NHS). This early phase trial aimed to estimate the efficacy, feasibility, and acceptability of the transdiagnostic intervention. We obtained estimates of likely effect size, and acquired basic demographic, cognitive and behavioural data to assess potential mediators and moderators of outcome in preparation for a later phase fully-powered efficacy trial. On the co-primary outcomes at post-treatment and 3-month follow-up of self-reported depression symptoms, anxiety symptoms, and disability and functional impairment, the trial provided point estimates of efficacy for SHM versus PTAU with moderate effect sizes in favour of SHM for the quadratic effects from baseline through post-treatment to follow-up. Secondary outcomes included number of diagnoses and changes in transdiagnostic processes. The project has demonstrated that a full trial is feasible, and that the SHM treatment approach appears likely to be efficacious compared to PTAU. The trial procedures were approved by the Health Research Authority of the NHS of the UK (East of England, Reference: 16/EE/0095). The results of this feasibility trial will inform future large-scale trials of how to effectively treat co-occurring mood, anxiety, and stressor-related disorders.
Trial registration NCT03143634.

A randomised controlled feasibility trial (the HARMONIC Trial) of a novel modular transdiagnostic intervention—Shaping Healthy Minds—versus psychological treatment-as-usual, for clinic-attending adults with comorbid mood, stressor-related and anxiety disorders

Mood, posttraumatic, obsessive-compulsive and anxiety disorders—the so-called common mental health problems (National Institute for Health and Care Excellence (NICE), 2011)—are one of the largest causes of disability in the world, with 16%–20% of adults affected at any given time (Kessler et al., 2003; Medical Research Council, 2010). Maximising our ability to treat common mental health problems in cost-effective, efficient and effective ways that can be widely disseminated is a priority (Medical Research Council, 2010). NICE recommends a range of complex psychological treatments at various points in the care pathway to all those suffering from such problems, although specific recommendations for individuals experiencing more than one problem are limited (Pilling et al., 2011). Between 40% and 80% of patients experiencing a common mental health problems also experience an additional comorbid mental health problems (Brown et al., 2001; Kessler et al., 2005). Even our best available psychological treatments only achieve clinical recovery for 40%–70% of patients, depending on their primary mental health problem, with people suffering complex comorbid conditions faring significantly worse (Moses & Barlow, 2006). For the majority of patients who receive treatment, there remains a significant risk of future relapse (Bockting et al., 2015; Loerinc et al., 2015). A key challenge therefore is how we can extend current psychological treatments for common mental health problems to increase efficacy, and facilitate sustained recovery, particularly for those with comorbid, recurrent and complex presentations (Ellard et al, 2010).

Over the past decade, there has been a major shift in the conceptualisation of common mental health problems, away from a single-diagnosis approach in favour of a transdiagnostic model (Craske, 2012; Dalgleish et al., 2020; Newby et al., 2015). There is also a strong empirical and theoretical support for a transdiagnostic approach to treatment development, as many of the

cognitive, emotional, behavioural and interpersonal factors which drive symptomatology are consistent across disorders (Brown & Barlow, 2009; Harvey et al., 2004). A transdiagnostic treatment approach thereby has the potential to improve treatment for people with anxiety, stress and depression, improving the efficacy and efficiency of treating co-morbid difficulties within a single treatment, as well as reducing the need for clinicians to learn multiple single-diagnosis treatment protocols.

There is a mismatch between the available evidence base and the clinical reality faced by practitioners. Despite the fact that the majority of people with any given common mental health problem have at least one or more disorders comorbid to their primary diagnosis (Brown at al., 2001), manualised treatment are relatively inflexible. This leaves patients with a wide range of problems and presentations receiving the same treatment package, regardless of their symptoms, goals, and concerns (Barlow et al., 2004). Third, in practice, many clinicians already tailor evidence-based psychological treatments to address individual concerns and goals. Manualised treatment protocols, therefore, need to better reflect the realities of service user presentations and experiences to deliver interventions that are more efficient, effective, and personalised.

Existing single-disorder psychological treatment protocols for individual common mental health problems share more similarities than differences (Chorpita & Daleiden, 2009). The widespread availability of so many treatment options has the potential to elicit considerable decision-making difficulties for the treating clinician. In both formulation and treatment planning, challenging decisions occur when selecting the order in which to treat multiple difficulties, in evaluating the most appropriate treatment approach, and identifying which treatment option will be acceptable and effective for the client. Our systematic review and meta-analysis supported the overall efficacy of transdiagnostic treatments for anxiety and depression (Newby et al., 2015) in this burgeoning area of research. This meta-analysis and a later narrative review (Dalgleish et al., 2020) called for more high-quality studies to resolve uncertainties surrounding the heterogeneity of treatment effects and to determine the best treatment approaches and designs.

The present study evaluates a novel transdiagnostic intervention which combines a number of evidence-based treatment strategies into a flexible protocol for adults with common mental health problems. The intervention we developed—Shaping Healthy Minds —targets the processes and symptoms that are deemed to be common to common mental health problems and offers a number of advances in transdiagnostic treatment by incorporating the best available techniques from existing manual-based treatments into the one treatment package. Rather than using integral interventions (where all patients receive the same relatively fixed, complete protocol), Shaping Healthy Minds is a modular intervention, whereby the assessment of core problematic emotional, cognitive, interpersonal and behavioural processes informs the selection and sequence of treatment modules targeted at specific problem areas for patients (Chorpita et al., 2005; Jeppesen et al., 2021). This modular approach allows for standardised, yet flexible treatment that is personalised to the individual concerns, problems and goals for the patient. In using a modular approach, this trial will contribute to identification and evaluation of effective treatment components and delivery method. Finally, it expands beyond interventions that typically focus on alleviating negative symptomatology (e.g., negative thoughts, excessive negative emotions) by incorporating interventions designed to increase positive emotions, capture strengths and enhance resilience for sustained recovery (Craske et al., 2019; Dunn et al., 2019).

Objectives

We developed a novel psychological intervention (Shaping Healthy Minds [SHM]) for the treatment of complex and comorbid adult mood, stressor-related and anxiety disorders, and aimed to evaluate this intervention within UK NHS psychological services. We aimed to examine the feasibility of SHM in reducing symptoms of depression, anxiety, distress, disability and functional impairment through an early stage RCT, in line with recommendations for the development of complex interventions (Craig et al., 2008). In particular, we gathered data on the extent to which SHM performs comparably to psychological treatment-as-usual (PTAU) for a given service user's primary diagnosed problem (Newby et al., 2015; Reinholt & Krogh, 2014) as well as for other

significant additional, secondary and/or comorbid difficulties. In addition, this trial provided a preliminary evaluation of the efficacy of a modular transdiagnostic treatment approach in reducing the distress and impairment associated with common mental health problems (Newby et al., 2015).

The trial also provided an indication of the feasibility and acceptability of the transdiagnostic intervention to service users and clinicians. This was achieved by recruiting through post-primary care UK National Health Service (NHS) psychology services where complex comorbidity represents the modal clinical presentation. In addition, the trial provided feasibility for data gathering as well as initial estimates of cost-effectiveness in terms of service use and potential quality-adjusted life years (QALYs) added. The trial employed co-primary outcomes, examining the effect of SHM on primary and comorbid diagnoses. The aim was to provide a plausible range of point estimates of the efficacy of SHM on standardised continuous symptom measures for primary and secondary diagnoses to inform this key question, refine the treatment manual and contribute to the design of future scaled-up trials (Craig et al., 2008).

The study thus comprised a pre-registered (Black et al., 2018) patient-level 2-arm randomised-controlled feasibility trial to evaluate the viability of a later-phase efficacy trial. We aimed to: 1) evaluate core procedural and protocol uncertainties regarding the later-stage trial; 2) enable decisions about the design and powering of the efficacy trial (including an estimate of the effect size, the nature of the comparison intervention, and the trial design); 3) explore the feasibility of conducting cost-effectiveness/utility analyses alongside the planned efficacy trial; and 4) identify potential key moderators and mediators of the impact of SHM.

Method

Study design

The design was a parallel-arm RCT comparing SHM to PTAU. Participants were assessed three times—at baseline, at post-treatment and at 3-month follow-up. At each timepoint a face-to-face assessment was conducted, including the full battery of primary and additional outcomes and process measures described below. For the full trial protocol, see Black et al. (2018).

Participants and recruitment

We recruited 42 people aged >18 years through UK National Health Service mental health services, including the high-intensity team of the Cambridge Psychological Wellbeing Service, and secondary care services with expertise in treatment of more complex and comorbid affective disorders. Participants had a primary diagnosis of either a unipolar mood, anxiety, obsessive-compulsive, or trauma-related or stressor-related disorder (common mental health problems) with at least one additional comorbid diagnosis, according to the DSM-5 (APA, 2013). Diagnosis of common mental health problems was determined by trained clinical research staff using the Structured Clinical Interview for DSM-5 (SCID-5; First et al., 2015). Primary and secondary diagnoses were determined by a combination of clinician judgement, scores on disorder-specific measures, and top problems ratings (SCID-5; First et al., 2015). To be eligible, participants also scored >10 on either the Patient Health Questionnaire (PHQ-9; Kroenke et al., 2001) and/or the Generalised Anxiety Disorder Questionnaire (GAD-7; Spitzer et al., 2006). Exclusion criteria were current/past diagnosis of psychosis or bipolar disorder, current diagnosis of alcohol or substance use disorder (all assessed via the SCID-5), organic brain damage, complex trauma history or recurrent self-injury requiring specialist services, or current suicidality that warranted immediate clinical attention and constituted a current risk of harm to the individual (all assessed via participant self-report, the NHS service clinical care team, and the SHM clinical team). Some participants were receiving multidisciplinary input from secondary care services, but those randomised to SHM agreed not to receive any *additional* psychological services while participating in the trial. All other services (e.g., medication review with psychiatrist or general practitioner, occupational therapy, social support services) were continued, and there were no medication exclusions.

Service users waiting for NHS treatment who were potentially eligible for the trial were identified by an Assistant Psychologist at the clinical service, who provided them with a letter outlining the study. Interested service users then contacted the research team to opt into the study.

Initial eligibility was screened over the telephone, and suitable participants were invited to complete the SCID-5, either at the clinical service or the research unit. At the beginning of this session, all participants provided written informed consent. Eligible participants completed an additional baseline assessment session including additional self-report questionnaires and experimental tasks, not discussed here.

Figure 1 summarises participant flow through the trial.

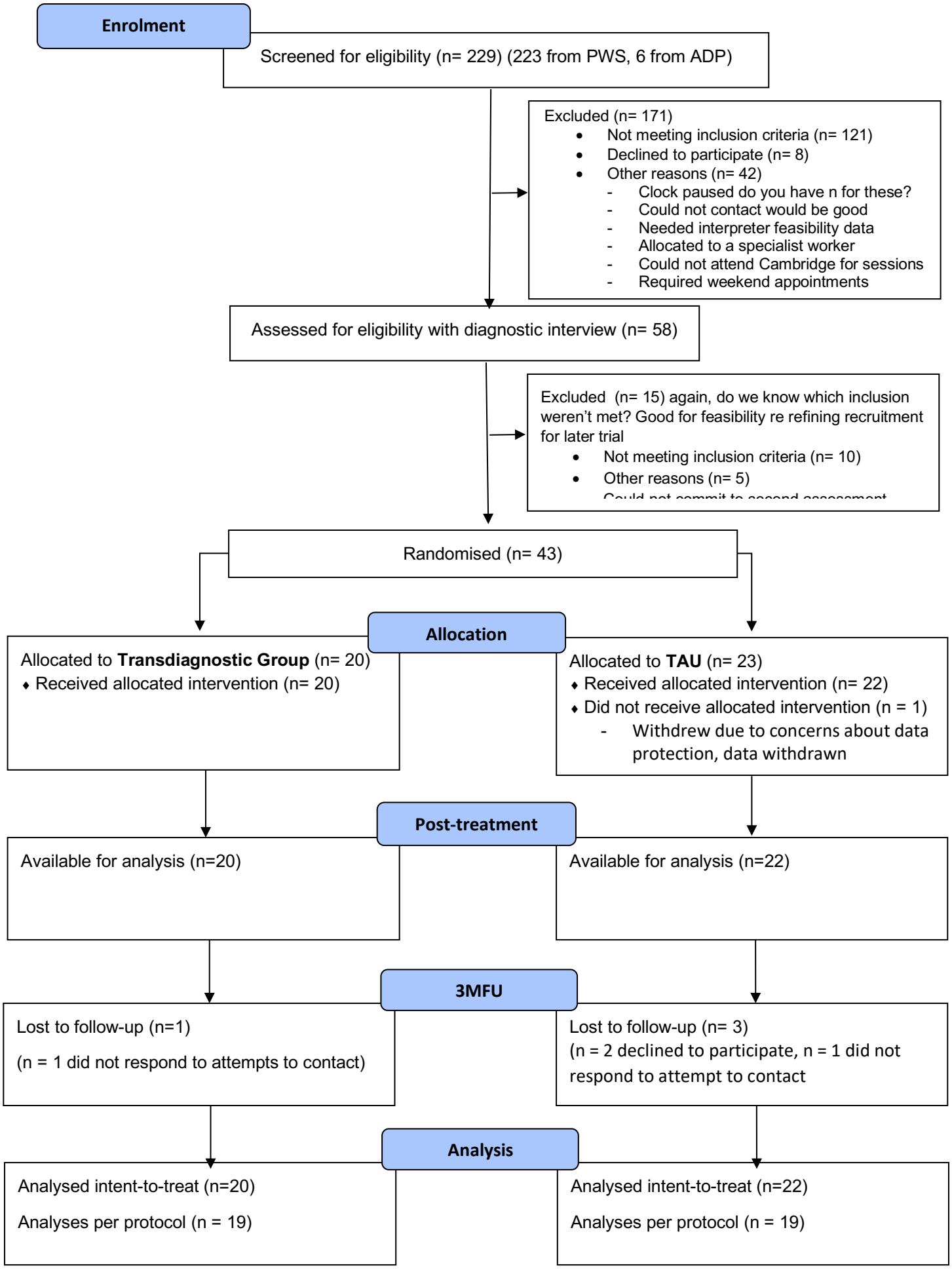

Figure 1. Participant flow through the trial (CONSORT Diagram)

Note. PWS = Psychological Wellbeing Service; ADP = Affective Disorders Pathway, Secondary Care; 3MFU = 3-month Follow-Up

Interventions

Shaping Healthy Minds is a modular intervention, comprising 10 independent modules that comprises up to 20 sessions (1 hour per week). The content of the modules is drawn from a number of evidence-based psychological therapies, including Cognitive Behavioral Therapy (CBT; Beck, 2010), Dialectical Behaviour Therapy (DBT; Linehan, 1993), Acceptance and Commitment Therapy (ACT; Hayes, Strosahl, & Wilson, 1999), mindfulness-based interventions (e.g. Mindfulness-Based Cognitive Therapy [MBCT]; Segal, Williams, & Teasdale, 2002), rumination-focused CBT (RF-CBT, Watkins et al., 2011; Watkins, 2016) and behavioural activation (BA; Martell, Dimidjian, & Ruth, 2010). SHM aims to bring together the core and unique therapeutic techniques from the best available disorder-focused treatment packages into the one transdiagnostic treatment package. For example, behavioural experiments (Bennett-Levy et al., 2004) and graded exposure (Norton, 2012) from CBT, value exercises and mindfulness strategies from ACT (Harris, 2009), activity scheduling from BA (Martell et al., 2010), emotion regulation strategies from DBT (Linehan, 1993), and present moment awareness exercises from MBCT (Segal et al., 2002). Selection of the elements of SHM was guided by recent meta-analyses supporting the effectiveness of these treatment strategies (Ekers et al., 2014), and the respective manuals were reviewed by experienced clinical psychologists (TD, JMN, AB, CH and MB). In addition, co-authors who are experts in particular fields (e.g., WK for mindfulness and case formulation; EW for rumination) were consulted on the content of specific modules. A Clinical Psychologist (MB) and Assistant Psychologist (DJ), both with postgraduate training in CBT and with experience in treating adult common mental health problem s delivered the transdiagnostic intervention. They received fortnightly individual and group clinical supervision from a Senior Clinical Psychologist (AB). The modular approach is standardised, yet can be flexibly delivered according to an individual's concerns, problems and goals.

For PTAU, clinical psychologists and high-intensity CBT therapists in teams specialising in common mental health problems provided the course of psychological therapy that they deemed

appropriate, in addition to referral to other health/social services and medication management. The delivered

treatment was documented to ensure systematic understanding of the duration, frequency and type of treatment administered.

Treatment fidelity and clinician adherence for the SHM group was rated with a bespoke Treatment Fidelity Checklist by trial clinicians. Additionally, an independent rater scored a randomly-selected 10% sample of session recordings with the Treatment Fidelity Checklist and Cognitive Therapy Scale-Revised (CTS-R). For additional details about the interventions see Black et al. (2018).

Primary outcome measures

The co-primary outcome measures were self-reported symptoms of depression (PHQ-9; Kroenke et al., 2001; Cronbach's α = .60 in the current sample) and anxiety (GAD-7; Spitzer et al., 2006; α = .68 in the current sample), as well as levels of disability and functional impairment on the Work and Social Adjustment Scale (WSAS; Mundt et al., 2002; α = .69 in the current sample).

Secondary outcomes

Secondary outcomes were self-reported symptoms of the specific diagnoses that participants met criteria for at trial baseline. These were indexed by the Improving Access to Psychological Therapies (IAPT) Phobia Scales (social phobia, agoraphobia, specific phobia; Department of Health, 2011), the Social Phobia Inventory (Connor et al., 2000), the Penn State Worry Questionnaire (generalised anxiety; Meyer et al., 1990), the Obsessive-Compulsive Inventory (Foa et al., 1998), the Revised Impact of Event Scale (post-traumatic stress; Wilson et al., 2007), the Agoraphobia-Mobility Inventory (Chambless et al., 1985), the Fear Questionnaire (specific phobias; Marks & Mathews, 1979), the Panic Disorder Severity Scale - self report version (Shear et al., 1997), and the Health Anxiety Inventory-short version (Salkovskis et al., 2002). Participants completed a selection of these measures depending on their concerns and primary/secondary diagnoses identified from the SCID. In addition to these disorder-specific measures, the Inventory of Depression and Anxiety Symptoms (IDAS) captured both disorder-specific and transdiagnostic

symptom dimensionality within a single measure (Watson et al., 2012; α = .97 in the current sample) and the Sheehan Disability Scale (Sheehan, 1983) captured functional impairment.

Process measures

We included a number of process-related measures at baseline, post-intervention and at 3-month follow-up to begin to explore mechanisms of change and the feasibility of conducting embedded process outcome research within this type of trial (see Supplementary Table S1).

Health economics measures

Data collection for the health economic evaluation took a patient-level perspective (Dixon et al., 2016; Salisbury et al., 2016), recording the cost per session of treatment and productivity losses resulting from time off work as a consequence of their mental health difficulties. Data were collected using the Healthlines Resource Use Questionnaire (Dixon et al., 2016; Salisbury et al., 2016), which is a measure of the participants' use of healthcare services (including NHS, help at home, medication expenses), occupational productivity (i.e., time off work) and cost of transdiagnostic treatment delivery (e.g., direct and indirect time spent in service delivery). Costs were then derived from the Unit Costs of Health and Social Care 2017/2018 (Curtis, 2019) in conjunction to using NHS reference costs for the year of 2017/2018.

The Medical Outcomes Study Questionnaire Short Form 36 Health Survey (SF-36; Ware & Sherbourne, 1992), a generic quality of life questionnaire, measured overall health and well-being, daily functioning and general life satisfaction across multiple domains. The SF-36 is not in itself suitable for economic evaluation; to overcome this limitation Brazier et al. (2002) developed an algorithm to generate a continuous index for health, which can be then used as a healthy utility measure. This allowed calculation of the additional number of quality-adjusted--life years (QALYs) the treatment yielded. Together, collecting these data also allowed for preliminary estimates of the potential cost utility of the transdiagnostic intervention and also of the feasibility of acquiring these data within the trial protocol.

Treatment expectancy

Participants' beliefs about the credibility of the treatment and expectancy of treatment outcomes were measured at the beginning of treatment for those in the SHM group (Devilly & Borkovec, 2008), capturing beliefs about how logical and successful the treatment seemed, whether they would recommend the treatment to a friend, and the expected percentage improvement in their symptoms.

Sample Size

Although a standard power calculation based on detecting treatment effects is the conventional approach to determining sample sizes for trials, the main aim of this trial was to elucidate feasibility for a larger later-stage evaluation (Black et al., 2018). At this stage, we therefore sought primarily to provide a point estimate of the efficacy of SHM whih could inform a power calculation for a putative fully powered later-phase evaluation. Our previous experience with such early phase trial platforms indicated that 50 patients will provide sufficient numbers and diagnostic diversity to evaluate feasibility, acceptability and procedural uncertainty for SHM and a plausible test of recruitment protocols.Assuming a 20% attrition rate, this would allow a complete case sample of n=40 (Black et al., 2018). As we had had good participant retention throughout the trial (insert attrition rate here), we closed recruitment at 42 participants and collected at least primary outcome post-treatment data for all of them. This has provided a reasonable range of point estimates of effect on our set of candidate outcome measures sufficient to guide later phase trial work.

Randomisation

Sequence Generation and Allocation concealment mechanism

Following both baseline assessment sessions, eligible participants were stratified according to gender, depression (PHQ-9; <= 17, >= 18;) and anxiety (GAD-7; <= 14, >=15) severity scores, and randomised to either SHM (n=20) or PTAU (n=22). This was achieved using computer-generated, quasi-random numbers and was conducted by the trial statistician (PW), who was blind to study objectives.

Implementation

Once generated, this information was passed to the project coordinator responsible for delivering the intervention. Once a participant began treatment, they were free to discontinue participation at any time. There was one participant in each group who discontinued the intervention (after one and eight sessions, respectively) but both participants provided post-treatment primary outcome measures and were included in Intent-to-treat analyses.

Blinding

Outcome assessments were conducted by independent raters who had no therapeutic relationship with the patients, were not part of the core trial team, and were blind to treatment condition. Double blinding of patients and therapists was not possible due to the nature of the trial (i.e., a psychological intervention). The trial statistician was also blind to treatment condition.

Statistical methods

The main aim of this trial was to elucidate feasibility for a larger later-stage evaluation, so fully-powered analyses were not conducted for this trial. Data summarising participants and outcomes and analyses of the trial outcomes were conducted by the trial statistician, blind to trial condition, following Consolidated Standards of Reporting Trials (CONSORT; Schulz et al., 2010) standards (see online Supplementary Figure S2). There were no planned interim analyses. Initial analyses of primary and secondary outcomes? were conducted on an intention-to-treat basis, with subsequent exploratory? analyses being per protocol. Mixed-model analyses of variance was used to compare groups on outcomes at the three assessment points—baseline, post-intervention and 3-month follow-up. Baseline levels on relevant measures were included as covariates, as appropriate. Both intent-to-treat and per-protocol analyses were conducted with our range of outcome measures following CONSORT standards. Group single mean imputation was used to account for missing data. There was insufficient power for analysis of process variables as potential moderators and mediators (Kraemer et al., 2008) and we simply report completion rates for evaluation of feasibility.

Health-related quality of life utilities were measured at baseline, and post-intervention and 3 months and QALYs were calculated from responses to the SF-36 (Ware & Sherbourne, 1992). To derive the cost of work loss attributable to absenteeism, total daily compensation was based on median weekly earnings for workers in the United Kingdom in 2018 (£113.66 per day). Average hourly wage was calculated by using the average hours worked for a full-time worker (37hrs)[1], which equates to an hourly wage of £15.36. Increment cost-effectiveness (ICERs) were calculated with the net monetary benefit being estimated at the NHS threshold values suggested by NICE of £20 000–£30 000 per QALY. This derived preliminary estimates of the cost utility of the transdiagnostic intervention to inform comprehensive health economics evaluations in a later stage trial.

Results

Recruitment

Key questions were whether a later-stage scaled-up trial was feasible and the protocol acceptable. Participants were recruited between 21st July 2017 and 28th August 2019. The protocol appeared to be feasible and acceptable, as recruitment was steady (229 referrals), and we were able to recruit eligible participants through the identified pathways. We also observed a high level of retention through to follow-up, with only 4 patients out of 42 lost to 3-month follow up.. . Regarding attitudes towards randomisation, anecdotally some participants reported initial disappointment at being assigned to PTAU rather than SHM, but did not echo this disappointment post-treatment.

Baseline data

Demographic information and diagnostic data for the 42 participants who entered the study are presented in Table 1.

[1] https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/timeseries/ybuy/lms

Table 1. Participant characteristics at trial baseline

	Total Sample (*N* = 42)		PTAU (*n* = 22)		Shaping Healthy Minds (*n* = 20)		Group effect
	Mean/Freq	*%*	Mean/Freq	*%*	Mean/Freq	*%*	
Female	28	67	14	64	14	70	χ^2 = .19, *p* = .66
Age	33.11	10.23 (SD)	38.2	14.01 (SD)	28.1	6.42 (SD)	*t* = 2.96, *p* = *.005*
Service							
PWS	39	93	20	91	19	95	
ADP	3	7	2	9	1	5	
No. of Diagnoses	3.76	1.41 (SD)	3.86	1.36 (SD)	3.65	1.49 (SD)	*t* = .49, *p* = .63
Primary Diagnosis (SCID)							
MDD	10	23	6	27	4	20	
PDD	2	52	1	5	1	5	
PTSD	1	2	1	5	0	0	
Panic Disorder	1	2	1	5	0	0	
Agoraphobia	1	9	1	5	0	0	
SAD	4	43	0	0	4	20	
GAD	19	7	9	41	10	50	
OCD	3	2	2	9	1	5	
SSD	1		1	5	0	0	
Secondary Diagnosis (SCID)							
MDD	15	34	7	32	8	40	
PDD	4	9	3	14	1	5	
PTSD	3	777	3	14	0	0	
Agoraphobia	3	25	2	9	1	5	
SAD	3	5	0	0	3	15	
GAD	11	2	4	18	7	35	
OCD	2		2	9	0	0	
BED	1		1	5	0	0	

Note. PTAU = Psychological treatment as Usual, ADP = Affective Disorders Pathway (Secondary Care), MDD = Major Depressive Disorder, PDD = Persistent Depressive Disorder, PTSD = Post-traumatic Stress Disorder, SAD = Social Anxiety Disorder, GAD = Generalised Anxiety Disorder, OCD = Obsessive Compulsive Disorder, SSD = Somatic Symptom Disorder, AN = Anorexia Nervosa, BN = Bulimia Nervosa, BED = Binge Eating Disorder, SCID = Structured Clinical Interview for DSM-5.

Description of the Interventions Delivered

Psychological Treatment-as-usual

Most participants (20/22) in PTAU received a version of CBT which included a combination of: psychoeducation; self-monitoring; behavioural activation; emotion regulation including relaxation, mindfulness; cognitive therapy techniques including work on core beliefs; exposure; exposure and response prevention; sleep strategies; strategies to reduce drinking; assertiveness training; managing anger; trauma-focused CBT techniques; compassion exercises; and values

exercises. One participant received brief psychoeducation, and one participant received integrative counselling. Many courses of therapy were based on disorder-specific manuals (e.g., managing low mood, exposure and response prevention for OCD), but many courses also included elements from a variety of treatment manuals or adiagnostic work on low self-esteem and positive data logs, highlighting the somewhat transdiagnostic nature of interventions delivered in PTAU to suit this group.

SHM

At the beginning of treatment (following description of the treatment and rationale), participants in SHM reported that the treatment was credible (*M* = 6.77, *SD* = 1.34, range 3.00 – 8.67 out of a maximum of 10) and that they expected the treatment to lead to an average 54.72% reduction in symptoms (*SD* = 16.66%). Participants received varying combinations of treatment modules depending on their top problems and strengths and goals for therapy. Table 2 shows the modules completed for each participant.

Table 2. Use of Modules for the 20 participants who completed *Shaping Healthy Minds*.

	MODULE									
	1	2	3	4	5f	6	7	8	9	10
Participant ID										
2	X	X		X		X		X		X
4	X	X	X	X		X				X
5	X	X	X			X				X
7	X	X	X	X		X	X	X		X
12	X	X	X			X			X	X
17	X	X	X	X		X				X
18	X	X		X		X				X
19	X	X	X	X		X				X
24	X	X	X			X				X
25	X	X	X			X				X
27	X	X	X			X				X
28	X	X	X			X				X
30	X	X	X			X				X
31	X	X	X			X				X
32	X	X	X	X		X				X
33	X	X		X		X		X		X
34	X	X	X	X		X				X
39	X	X		X		X				X
41	X	X		X		X				X
43*	X	X	X							

Note. Modules: 1 - Getting Acquainted, 2 - Emotional Awareness, 3 - Managing and Tolerating Emotions, 4 - Behavioural Activation, 5 - Overcoming Avoidance, 6 - Tackling Unhelpful Thoughts, 7 -Tackling Unhelpful Habits, 8 - Overcoming Repetitive Thinking, 9 - Managing Upsetting Memories and Images, 10 - Relapse Prevention and Future Orientation. Modules 1, 2 and 10 are included in SHM for all participants. Modules 3 – 9 are optional and were delivered in the order deemed most appropriate for each participant. * - this participant ended treatment after 8 sessions following a change in personal circumstances.

The two clinicians who delivered SHM found it straightforward to work through and that the manuals provided a useful structure for working with complexity and comorbidity. The exact way in which the manuals were used differed between participants – the draft therapist manual always provided useful guidance as to the principles that were essential to each module and useful exercises, but the use of the client manual depended on participant needs and preferences.

Fortnightly supervision was important in navigating the manual and determining module selection in collaboration with the participants. As can be seen from the module use summary (Table 2), not all modules were utilised during the trial, and some were used more than others. There were a few reasons for this: 1) not all modules were relevant to participants' presenting problems (e.g.,

there were no participants with a primary or secondary diagnosis of PTSD in the SHM group so Module 9 – Managing upsetting memories and images was not used); 2) Even though each module had a specific focus, there was some overlap in strategies that could target particular problems (e.g., Module 5 – Overcoming Avoidance could have been used for managing many types of anxiety, but the behavioural experiments in Module 6 – Tackling Unhelpful Thinking proved to be a more appropriate way to address these difficulties to incorporate belief change); and 3) Module 6 (Tackling unhelpful thinking) proved to be the most utilised "optional" module due to the range of strategies including identifying unhelpful thinking patterns, flexible thinking skills, behavioural experiments, and examining affective styles/core themes that were relevant to all participants' difficulties.

Length of the interventions

On average patients in SHM received a longer intervention with a greater number of sessions than patients in PTAU (see Table 3) reflecting the emphasis in SHM on tacklingtackling multiple diagnostic problems relative to PTAU.

Table 3. Treatment length for Psychological Treatment-as-Usual and *Shaping Healthy Minds.*

	Psychological Treatment as Usual *n* = 22 M (*SD*)	Shaping Healthy Minds *n* = 20 M (*SD*)	*t*	*Sig.*
No. of treatment sessions	11.32 (5.09)	18.55 (3.00)	5.53	.000
Treatment length (days)	139.09 (71.06)	202.85 (52.23)	3.29	.002

Trial Outcomes

Our aim was to derive estimates of the likely treatment efficacy of SHM versus PTAU at post-treatment and follow-up for core symptom outcomes and diagnostic data. Although the trial was not powered to detect effects at traditional levels of significance, for completion we report both inferential statistics and effect sizes.

For the intent-to-treat (ITT) analyses, we compared changes in our primary outcomes for SHM against PTAU from baseline to post-treatment to follow-up (see Table 4 for data and inferential statistics). As can be seen from Figure 2, both intervention arms appeared efficacious in reducing symptoms and diagnoses[2]. There were statistically significant quadratic effects (see Figure 2) in favour of SHM for depression, anxiety, functioning and numbers of diagnoses with medium η_p^2 effect sizes ranging from .12 to .19.

[2] As the SHM and Intervention Groups differed in age, we also ran an analysis of covariance with age as a covariate. This did not alter the pattern of results so we have reported the ANOVA here. ANCOVA results can be found in the supplementary materials.

Table 4. Observed outcome measures at each assessment.

	Psychological Treatment-as-Usual (n = 22)		Shaping Healthy Minds (n = 20)		Intervention effect[a]
	Mean	*SE*	Mean	*SE*	
Depression symptoms (PHQ-9)					$F_{(2, 39)} = 2.70$, $p = .08$, $\eta_p^2 = .06$
Baseline	15.91	.83	15.65	.88	Linear: $F_{(1, 40)} = 1.17$, $p = .29$, $\eta_p^2 = .03$
Post-treatment	11.68	1.29	7.35	1.35	Quadratic: $F_{(1, 40)} = 5.50$, $p = .02$, $\eta_p^2 = .12$
3-month follow up*	9.82	1.27	7.43	1.33	
Anxiety symptoms (GAD-7)					$F_{(2, 39)} = 4.79$, $p = .01$, $\eta_p^2 = .11$
Baseline	14.46	.74	14.70	.77	Linear: $F_{(1, 40)} = 2.46$, $p = .13$, $\eta_p^2 = .06$
Post-treatment	11.05	1.15	6.2	1.21	Quadratic: $F_{(1, 40)} = 9.39$, $p = .004$, $\eta_p^2 = .19$
3-month follow up*	8.11	1.04	6.11	1.09	
Impact on functioning (WSAS)					$F_{(2, 39)} = 3.92$, $p = .03$, $\eta_p^2 = .09$
Baseline	22.91	1.65	24.45	1.73	Linear: $F_{(1, 40)} = 2.95$, $p = .09$, $\eta_p^2 = .07$
Post-treatment	20.74	1.86	15.65	1.96	Quadratic: $F_{(1, 40)} = 7.91$, $p = .008$, $\eta_p^2 = 0.17$
3-month follow up*	15.29	1.62	13.19	1.70	
No. of diagnoses					$F_{(2, 32)} = 2.49$, $p = .10$; , $\eta_p^2 = .07$
Baseline	3.94	.36	3.58	.33	Linear: $F_{(1, 33)} = .47$, $p = .50$, $\eta_p^2 = .01$
Post-treatment	2.38	.42	1.00	.38	Quadratic: $F_{(1, 33)} = 5.13$, $p = .03$, $\eta_p^2 = 0.14$
3-month follow up*	1.69	.40	.95	.36	

Note. Data are observed cases only. *Presented data are n=19 per group due to loss to follow-up Depression, Anxiety and Impact of functioning analyses are intent-to-treat analyses using imputed data for the follow-up time point. No. of diagnoses is for completers only.

[a] Intervention effect, repeated measures ANOVA across baseline, post-treatment and 3-month follow up; followed by linear and quadratic within-subjects contrasts, on intent-to-treat imputed data.

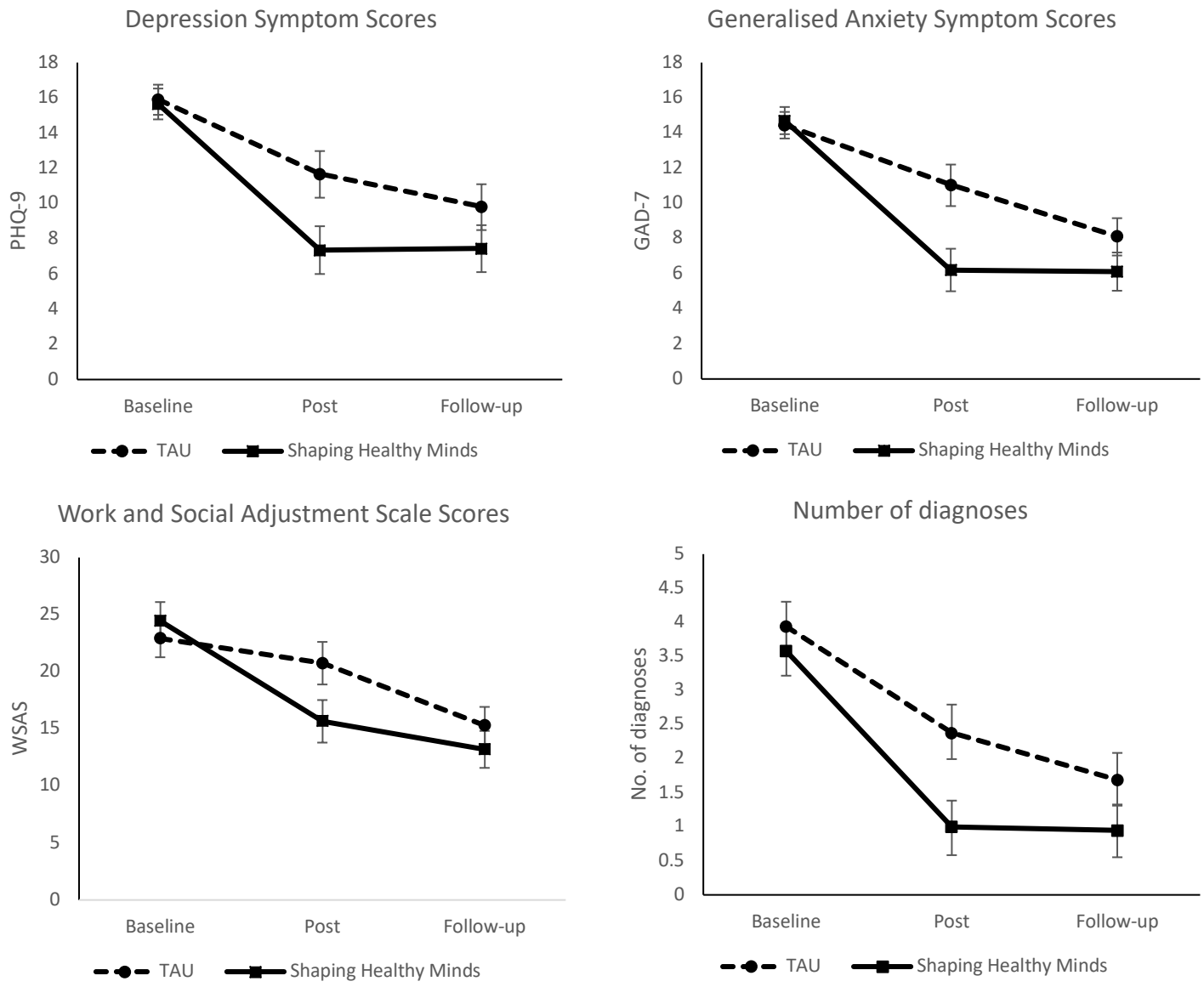

Figure 2. Primary outcomes (Depression symptom scores on the Patient Health Questionnaire – 9-item version (PHQ-9), Anxiety symptom scores on Generalised Anxiety Disorder Questionnaire – 7-item version (GAD-7), Work and Social Adjustment scores on Work and Social Adjustment Scale (WSAS), and number of diagnoses following assessment using Structured Clinical Interview for DSM-5, for Psychological Treatment as Usual (TAU) and Shaping Healthy Minds. *Note.* Error bars represent one standard error.

Because between-arm differences were greater at post-treatment and reduced at follow up, we next examined statistical differences at each post-treatment time point. For the ITT analyses, the SHM group scored significantly lower than the PTAU group at post-treatment on depression (PHQ-9; mean difference 4.33, 95% CI .54 – 8.12, p = .03, d = 0.73) and anxiety (GAD-7; mean difference 4.85,

95% CI 1.46 – 8.23, p = .006, d = 0.92, but the difference between the groups on impact on functioning was only a statistical trend (WSAS; mean difference 2.70, 95% CI -.37 – 10.55, p = .07, d = 0.60). Further, the SHM group met criteria for significantly fewer diagnoses at post-treatment (SCID diagnoses; mean difference 1.38, 95% CI .22 – 2.53, p = .02, d = 0.85).

At 3-month follow-up, there were no statistically significant differences between the groups on depression (PHQ-9; mean difference 2.39, 95% CI -1.34 – 6.11, p = .20, d = 0.41), anxiety (GAD-7; mean difference 2.01, 95% CI -1.03 – 5.04, p = .19, d = 0.42), impact on functioning (WSAS; mean difference 3.10, 95% CI -1.64 – 7.84, p = .19, d = 0.42), or number of diagnoses (SCID diagnoses; mean difference .74, 95% CI -.35 – 1.83, p = .18, d = 0.48), although effect size estimates remained moderate in favour of SHM.

The proportions of participants meeting criteria for primary and secondary diagnoses at baseline, post-treatment and 3-month follow up are shown in Figure 3. Analyses based on the observed data showed that there was no significant difference between the groups at post-treatment on primary diagnosis (χ^2 (1, *N* = 37) = 3.05, p = .08, *d* = 0.60), but there were significantly fewer participants in the SHM condition who met criteria for their secondary diagnosis (χ^2 (1, *N* = 37) = 4.38, p = .04, *d* = 0.73). There were no significant differences at 3-month follow-up on primary diagnosis (χ^2 (1, *N* = 35) = .05, p = .83, *d* = 0.07) or secondary diagnosis (χ^2 (1, *N* = 35) = 2.76, p = .10, *d* = 0.59).

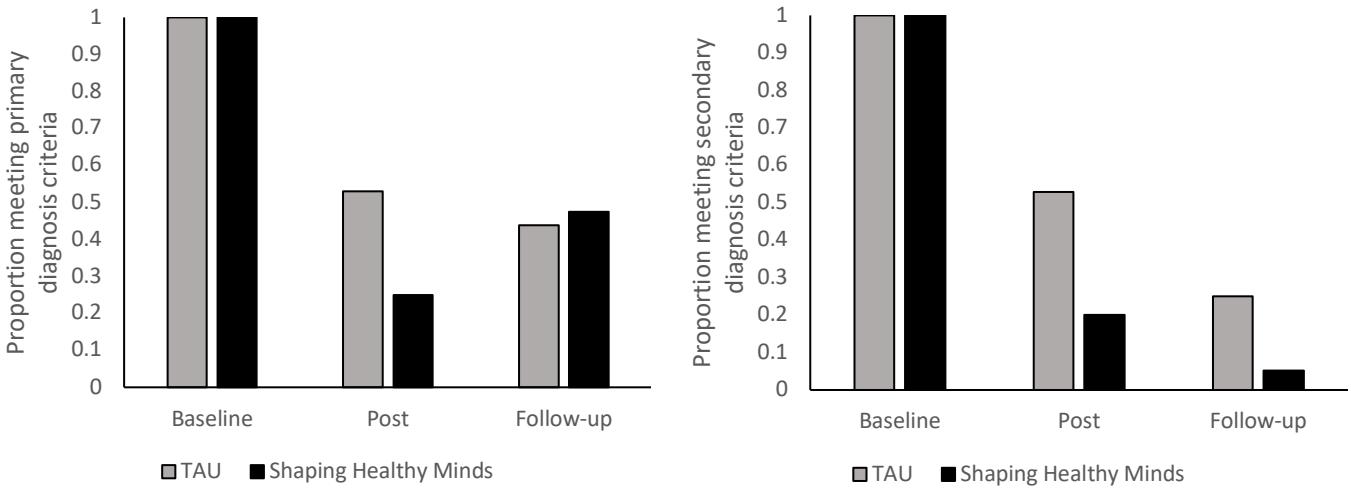

Figure 3. Proportions of participants meeting criteria for primary and secondary diagnosis.
Note. SHM: Baseline *n* = 20; Post-treatment *n* = 20; 3-month Follow-Up *n =19*. PTAU: Baseline *n* = 22; Post-treatment *n =17*; 3-month Follow-Up *n* = 16.

The individual participant trajectories on depression symptoms, anxiety symptoms, work and social adjustment, and number of diagnoses are presented in the Supplementary Figures S1 – S4. These results suggest that a small number of participants in the SHM arm experienced a deterioration in symptoms between post-treatment and 3-month follow-up assessments, which in such a small sample may have had a disproportionate effect on the averaged results reported above.

SHM

We also collected data on a number of secondary outcomes and process measures to evaluate the feasibility of acquiring this information in a later phase trial. Data completion rates are detailed in Table 5. Data completion was good for process measures (86% at post-treatment assessment; 83% at 3-month follow-up) though less than for our primary outcomes. We also collected disorder-specific self-report measures for participants according to their diagnostic profile to evaluate the feasibility of acquiring this information in a later phase trial. The completion rates for these measures are also presented in Table 5 and varied as a function of the presence/absence of the diagnosis as a primary diagnosis across the trial participants.

Health economic analyses

Data completion for our health economics measures (quality of life and health resource use) was good (81% completion) indicating feasibility of acquiring health economics indices in a scaled-up trial. For information, the Quality of Life descriptive data are presented in Table 6 and Table 7.

Table 6. Mean (SD) quality of life descriptive data measured on the Medical Outcomes Study Questionnaire Short Form-36 Health Survey (SF-36; Ware & Sherbourne, 1992) for the Psychological Treatment-as-Usual (PTAU) and Shaping Healthy Minds (SHM) groups across the trial timepoints

	Baseline			**Post-treatment**			**Follow up**		
	Total sample	PTAU	SHM	Total sample	PTAU	SHM	Total sample	PTAU	SHM
Physical Functioning	83.21 (21.97) (n =42)	76.14 (25.21) (n=22)	91.0 (14.74) (n=20)	85.56 (19.66) (n=36)	77.06 (23.98) (n =17)	93.16 (11.58) (n=19)	88.57 (18.89) (n=35)	80.63 (24.55) (n =16)	95.26 (8.25) (n=19)
Role Limitations due to physical health	59.77 (44.33) (n =41)	45.24 (45.15) (n=21)	75.00 (38.90) (n=19)	68.57 (40.83) (n=35)	50.00 (44.72) (n =16)	84.21 (30.29) (n=19)	76.47 (40.33) (n=34)	59.38 (48.20) (n =16)	95.26 (8.25) (n=18)
Role Limitations due to emotional problems	18.70 (26.92) (n =41)	18.18 (30.40) (n=22)	19.30 (23.08) (n=20)	33.33 (34.73) (n=36)	19.61 (29.01) (n =17)	45.61 (35.50) (n=19)	59.80 (38.30) (n=34)	52.08 (43.83) (n =16)	66.67 (32.33) (n=18)
Energy	24.88(16.07) (n =41)	25.95(17.79) (n=21)	50.0(23.75) (n=20)	41(19.28) (n=35)	38.75(21.72) (n =16)	42.89(17.35) (n=19)	44.71(19.34) (n=34)	45.33(22.64) (n =15)	44.21(16.93) (n=19)
Emotional well-being	34.19 (14.20) (n =42)	34.55 (16.59) (n=22)	33.80 (11.42) (n=20)	52.33 (20.04) (n=36)	47.76 (23.13) (n =17)	56.42 (16.38) (n=19)	56.69 (19.39) (n=35)	51.50 (22.34) (n =16)	61.05 (15.82) (n=19)
Social Functioning	39.88 (26.23) (n =42)	32.95 (21.32) (n=22)	47.50 (29.41) (n=20)	58.57 (26.91) (n=35)	50.78 (27.18) (n =16)	65.13 (25.54) (n=19)	63.97 (29.32) (n=34)	50.00 (33.74) (n =15)	75.00 (19.98) (n=19)
Pain	67.74 (28.57) (n =42)	60.45 (31.46) (n=22)	75.75 (23.21) (n=20)	69.58 (28.19) (n=36)	61.76 (34.84) (n =17)	76.58 (18.90) (n=19)	73.46 (26.80) (n=34)	66.72 (32.97) (n =16)	79.44 (18.82) (n=18)
General Health	46.43 (19.58) (n =42)	42.95 (17.43) (n=22)	50.25 (21.49) (n=20)	88.57 (18.89) (n=35)	46.47 (15.69) (n =17)	56.67 (17.99) (n=18)	58.38 (19.26) (n=34)	52.33 (20.17) (n =15)	63.16 (17.58) (n=19)

Table 7. Quality of Life Metrics measured on the Medical Outcomes Study Questionnaire Short Form-36 Health Survey (SF-36; Ware & Sherbourne, 1992) for the Psychological Treatment-as-Usual (PTAU) and Shaping Healthy Minds (SHM) groups across the trial timepoints

	Baseline			**Post-Treatment**			**Follow-up**		
	Total	PTAU	SHM	Total	PTAU	SHM	Total	PTAU	SHM
SF-6D Preference Based Measure of Health	.58 (.07) n = 42	.56 (.07) n = 22	.60 (.06) n = 20	.63 (.09) n = 35	.60 (.09) n = 16	.65 (.09) n = 19	.67 (.09) n = 31	.65 (.12) n = 14	.68 (.06) n = 17

Cost effectiveness. Summary statistics were estimated for all variables used in the economic analysis. Eleven participants had missing data of whom eight were from the PTAU group and three from the SHM group. Listwise deletion of cases was applied when data was missing at either follow-up period. There was no significant difference between the SF-36 scores at baseline (PTAU: M = .56, SD = 0.06; *SHM*: M = .60, SD = 0.06; $t(29) = 1.64$, p = .113)

Cost-Effectiveness

Cost-effectiveness was calculated from an NHS perspective for SHM over PTAU. The Incremental Cost Effectiveness Ratio is £29, 096.77 between Baseline and Post-Treatment. This suggests that SHM improves clinical results but at an increased cost, with the cost-effectiveness ratio within NICE guidelines (£20, 000 – £30, 000/QALY). However, at follow up, the Incremental Cost Effectiveness Ratio was - £489903.29, suggesting the SHM intervention was both more costly and less effective than TAU. PTAUTAU. Notably, the difference in SF-6D score at post treatment was 0.02, whilst at follow-up was smaller at -0.001, indicative of the small differences which separated both active interventions.

Direct costs to the NHS. We carried out sensitivity analyses in two areas of uncertainty to test the robustness of the results. First, we varied the cost per service use of two items which have been costed differently in different studies. In Permutation 1 the cost of calling an NHS Call Centre was changed from £38.00/call to £7.00/call. In Permutation 2, the cost of calling the NHS Direct line was similarly changed from £38.00/call to £7.00/call. In Permutation 3, two outliers were removed as their total costs to the NHS were two standard deviations beyond the mean. The permutations all result in changes to the ICER, highlighting the instability of the results although the direction of the effects remain constant. Results of the sensitivity analysis and permutations are presented in Table 8. Additional health economic analyses can be found in the supplementary materials.

Table 8. Effects of different permutations and the resulting changes to the incremental cost-effectiveness ratio (ICER) for *Shaping Healthy Minds* over Psychological Treatment-as-Usual

ICER	Original	Permutation 1	Permutation 2	Permutation 3
Baseline to Post-treatment	£29, 096.77	£26, 099.62	£29, 031.01	£27, 800.40
Baseline to Follow-up	-£489903.29	-£435462.04	-£483810.63	-£45335.20

Note. Minus figures for baseline to follow-up indicate that compared to PTAU, SHM is associated with a relative negative benefit associated with each unit of additional cost, such that SHM is not cost-effective.

Safety aspects

No adverse events were reported throughout the trial.

Treatment Fidelity and Cognitive Therapy Scale – Revised

A Clinical Psychologist with experience of working on transdiagnostic treatment trials served as an independent rater, and scored 10% of randomly selected sessions on the Cognitive Therapy Scale-Revised (Blackburn et al. 2011) for the delivery of SHM. All scores for both therapists indicate that they reached the cut-off score for competence of over 40 (Kazantzis et al., 2018; Vallis et al. 1986), with mean scores of 46.50 (*SD* = 3.05, range 43 – 51), and 44.69 (*SD* = 2.97, range 40 – 51), of a potential range of 0 – 72.

Treatment Fidelity Checklist data were recorded by the trial therapists after every session, demonstrating that delivery of the SHM intervention was feasible and that module components could be covered. These data provide an insight into which components of modules were commonly or repeatedly employed and is informing the development of future iterations of the manual. The

independent rater scored the same 10% of sessions on the Treatment Fidelity Checklist, with an average score of 1.26 out of 2 per session and median of 2 out of 2, indicating that all module components were partially or fully covered in each session. Interpretation of these data is limited due to the variability in module length and session structure. Future trials using the *SHM* protocol could use holistic or module-based ratings to derive quantitative comparisons and incorporate a rating system that allows for comparison between module components.

Discussion

This randomised controlled feasibility trial provides a platform for a scaled-up efficacy trial of a new transdiagnostic modular treatment for all common mental health problems in adults — *Shaping Healthy Minds* (SHM) — that enables the flexible delivery of evidence-based techniques. This treatment approach has the potential to improve the treatment effectiveness and dissemination of evidence-based interventions for the many individuals for whom diagnosis-specific treatments leave significant difficulties unaddressed. The results from this trial have provided a range of estimates of effect sizes that can be used to power a later-stage trial of treatment efficacy, to refine the treatment protocol and to inform future evaluation of the mechanisms underlying any treatment effects. SHM has the potential to improve outcomes for those with complex presentations, through offering a cost-effective treatment option to reduce chronic, transdiagnostic psychological difficulties.

We aimed to establish the feasibility of a clinical trial to evaluate whether SHM is an efficacious treatment for mood and anxiety disorders in adults. We gathered data on the feasibility, acceptability and point estimate of efficacy of the intervention and acquired basic demographic, cognitive and behavioural data to assess mediators and moderators of outcome in preparation for a later phase clinical trial. The data from the trial suggests that *Shaping Healthy Minds* reduces symptoms of depression and anxiety, improves work and social adjustment, and reduces both primary and secondary diagnoses of mood, anxiety, stressor-related and obsessive-compulsive disorders.

The current study evaluated core procedural and protocol uncertainties regarding the putative later-stage trial. We demonstrated that we were able to recruit eligible participants, and that the randomisation process was acceptable. Further, clinician engagement for SHM was positive, although the two trial clinicians were part of the research team. Clinician engagement for PTAU was mixed, with varying levels of interest and responsiveness. Future trials may increase direct communication with clinicians and involve them in the research process. This trial provided useful information about the selection of primary/secondary outcome measures; the PHQ-9, GAD-7 and WSAS were selected to broadly cover transdiagnostic symptoms of common mental health problems and effect on functioning. Secondary measures tended to capture an individual's primary diagnosis, so their scores may not be reflected in the primary outcome measures, and each participant completed slightly different measures.

The current study also provided valuable insights to enable decisions about the design and powering of the efficacy trial. We found that recruitment through the local UK NHS IAPT service resulted in a smoother recruitment flow compared to secondary care due to a large number of clinicians and greater predictability of wait times. In addition, psychological interventions were somewhat more standardised. The point estimates of efficacy for SHM versus PTAU comprised moderate effect sizes for the quadratic effects from baseline through post-treatment to follow-up. Effects were smallest at follow up, although still moderate in magnitude, and this overall pattern can guide sample size estimates for the later-phase efficacy trial. Further, acquisition of data for cost-effectiveness/utility analyses alongside the planned efficacy trial was feasible.

We piloted the collection of data on putative mechanisms measures within the feasibility trial, including personality functioning, emotion regulation, cognitive emotion regulation, experience of emotions, awareness of emotions, autobiographical memory and working memory/affective working memory. Data completion for these measures was good indicating that embedding a process-outcome assessment in a later trial is viable.

The longer-term potential impact of SHM is to provide an efficacious transdiagnostic modular intervention for common mental health problems in primary and secondary care. The estimated annual UK cost of depression including treatment costs, reduced ability to work and premature mortality in 2000 was £9 billion, with only £370 million for direct treatment costs. The costs of service use associated with anxiety disorders have been estimated at £1.24bn in 2007, with an additional £7.7bn in lost earnings. Significant proportions of these costs are generated by adults suffering from complex and comorbid depression and anxiety, where treatment non-response, cross-sector service-use and loss of productivity are greatest. Providing effective treatment for these mental health problems therefore has the potential of reducing both long-term treatment costs as well as preventing large productivity losses.

The modular and scalable nature of SHM also has the potential to bring simplicity, clarity, and convenience to the purchase of mental health treatment options, such that General Practitioner clusters and other commissioning bodies will be presented with clear choices for purchase, allowing selection of interventions along the single treatment-strand that are bespoke to their particular environment. Service delivery organisations would also be able to choose from a suite of such intervention products ranging from single sessions of advice or detection (e.g., for individual primary services) through to a complete range of modules across many sessions (e.g., for a mental health trust). SHM could add substantial value to existing PTAU approaches. In a primary care context, it would provide a model for working efficiently with comorbidity, and in secondary care it potentially increases access to evidence-based psychological treatment by protocolising a highly complex formulation process. We anticipate that modules will be teachable to a wider staff group and therefore implementable across all points of contact with patients including hospitals, clinics, communities, and special environments (e.g., prisons, care homes).

Although we did not conduct a formal qualitative study, overall, participants who received the *Shaping Healthy Minds* intervention provided positive feedback, with most noting that they liked the flexibility and tailoring of the treatment. Many participants found that the sequence of modules

suited their needs, while others noted that there had not been sufficient time within the allocated sessions to cover all content. A few participants suggested that it might have been helpful to map out their journey through the modules closer to the beginning. There was mixed feedback about the client manuals – some participants liked the detailed and relevant content, but others found it either overwhelming or not as relevant to their concerns. Overall, participants found the focus on the emotion cycle that is central to SHM to be relevant as it provided a clear way to describe their experiences. As all participants had comorbid and somewhat complex difficulties, a clear need arose to "move up a level" from discrete emotion cycles to the moods and patterns across their experiences. SHM seemed acceptable to patients with only 1 patient lost to follow up. As anticipated patients utilised different combinations and numbers of therapy modules (see Table 3).

Limitations and future directions

One of the challenges in working with a heterogeneous transdiagnostic sample is selecting outcome measures that will appropriately capture participants' problems, strengths and functioning. While the co-primary measures assessing depression, anxiety, and work and social adjustment covered a broad range of symptoms and functioning, it would be helpful to include a wellbeing measure such as the Warwick Edinburgh Mental Wellbeing Scale (Tennant et al., 2007) in future trials, as well as incorporate idiographic outcomes to capture person-centred and goal-focused changes (Hayes et al., 2019). Further, some of the outcome and process measures did not have good internal consistency in this sample. The generalisability of the trial findings is limited by the employment of well-supervised clinical psychologists who were very familiar with the theoretical underpinnings of the SHM approach, and the dissemination and implementation of this approach could be the focus on future studies. In addition, for a full-scale trial it may be necessary to embed treatment-monitoring into data curation procedures throughout the trial, and ensure that standardised assessments are used to assess participant experiences (e.g., acceptability). Finally, we did not routinely collect the module-specific process measures for all participants in the SHM group due to the variability in module length and overlap between modules. It would be important to test

the effect of individual treatment modules on transdiagnostic processes and outcomes in order to demonstrate the effective components of a modular approach.

Conclusion

We conducted a patient-level two-arm randomised controlled trial (HARMONIC) that compared SHM to psychological treatment-as-usual (PTAU) for adults with at least two comorbid mood, anxiety, obsessive-compulsive or trauma/stressor disorders diagnoses, recruited from outpatient psychological services within the UK National Health Service (NHS). On the co-primary outcomes of self-reported depression symptoms, anxiety symptoms, and disability and functional impairment, the trial provided point estimates of efficacy for SHM versus PTAU with moderate effect sizes in favour of SHM for the quadratic effects from baseline through post-treatment to follow-up. The project has demonstrated that a full trial is feasible, and that the SHM treatment approach appears likely to be efficacious compared to PTAU. Although a feasibility trial, the results will inform future revisions of clinical guidelines with recommendations of how to effectively treat co-occurring mood, anxiety, and stressor-related disorders.

Registration

Clinicaltrials.gov: NCT03143634

Protocol

https://bmjopen.bmj.com/content/8/8/e024546

http://dx.doi.org/10.1136/bmjopen-2018-024546

Author contributions

Contributors MB managed the trial, co-delivered the intervention, co-developed the treatment manuals and has helped draft the manuscript; DJ conducted assessments, co-delivered the intervention, and assisted with data collation and analyses; AB supervised and advised on the delivery of the interventions and has provided guidance on the protocol; JC provided practical and NHS service support for the trial; COL and RE provided support for the trial management; JP, SP, AS, KG and KK assisted with trial assessments; PW was the trial statistician responsible for the randomisation, advice on analysis strategy, and analysis of the data; LL provided support for the health economics component; SR provided service user support for the trial; SG, EW and WK have advised on the treatment manual; CH assisted with trial management and assessments; JMN co-developed and adapted the treatment manuals and with TD initially compiled the *Shaping Healthy Minds* protocol; TD designed the study, co-developed the treatment manuals, acted as Chief Investigator and helped to draft the manuscript. All authors have read and approved the final manuscript.

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References

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders*. Fifth ed. Arlington, VA: American Psychiatric Publishing.

Barlow, D.H., Allen, L.B., & Choate, M.L. (2004). Toward a unified treatment for emotional disorders. *Behavior Therapy, 35*, 205–30. doi:10.1016/S0005-7894(04)80036-4

Barlow, D.H., Farchione, T.J., Bullis, J.R., Gallagher, M.W., Murray-Latin, H., Sauer-Zavala, S. et al. (2017). The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders compared with Diagnosis-Specific Protocols for Anxiety Disorders: A Randomized Clinical Trial. *JAMA Psychiatry, 74,* 875-884. doi:10.1001/jamapsychiatry.2017.2164

Beck, J. (2011). *Cognitive Behavior Therapy: Basics and Beyond (Second Edition)*. New York: Guilford Press.

Black, M.J., Hitchcock, C., Bevan, A., O Leary, C., Clarke, J., Elliott, R., Watson, P., LaFortune, L., Rae, S., Gilbody, S., Kuyken, W., Johnston, D., Newby, J., & Dalgleish, T. (2018). The HARMONIC trial: study protocol for a randomised controlled feasibility trial of Shaping Healthy Minds—a modular transdiagnostic intervention for mood, stressor-related and anxiety disorders in adults. *BMJ Open, 8,* e024546. doi: 10.1136/bmjopen-2018-024546

Blackburn, I.-M., James, I.A., Milne, D.L., et al. (2001). The Revised Cognitive Therapy Scale (CTS-R): Psychometric Properties. *Behavioural and Cognitive Psychotherapy, 29*, 431-446. doi: 10.1017/S1352465801004040

Bockting, C.L., Hollon, S.D., Jarrett, R.B., et al. (2015). A lifetime approach to major depressive disorder: The contributions of psychological interventions in preventing relapse and recurrence. *Clinical Psychology Review, 41*, 16–26. doi: 10.1016/j.cpr.2015.02.003

Brazier, J., Roberts, J., & Deverill, M. (2002). The estimation of a preference-based measure of health from the SF-36. *Journal of Health Economics, 21(2),* 271-292.

Brown, T.A., & Barlow, D.H. (2009). A proposal for a dimensional classification system based on the shared features of the DSM-IV anxiety and mood disorders: Implications for assessment and treatment. *Psychological Assessment, 21*, 256–71. doi:10.1037/a0016608

Brown, T.A., Campbell, L.A., Lehman, C.L., et al. (2001). Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. *Journal of Abnormal Psychology, 110*, 585–99. doi: 10.1037/0021-843X.110.4.585

Chambless, D.L., Caputo, G.C., Jasin, S.E., et al. (1985). The Mobility Inventory for Agoraphobia. *Behaviour Research and Therapy, 23*, 35–44. doi:10.1016/0005-7967(85)90140-8

Chorpita, B.F., Daleiden, E.L., & Weisz, J.R. (2005). Modularity in the design and application of therapeutic interventions. *Applied and Preventive Psychology, 11*, 141–56. doi: 10.1016/j.appsy.2005.05.002

Chorpita, B.F., & Daleiden, E.L. (2009). Mapping evidence-based treatments for children and adolescents: application of the distillation and matching model to 615 treatments from 322 randomized trials. *Journal of Consulting and Clinical Psychology, 77*, 566–79. doi:10.1037/a0014565

Clark DM , Ehlers A , Hackmann A , et al . Cognitive therapy versus exposure and applied relaxation in social phobia: A randomized controlled trial. J Consult Clin Psychol 2006;74:568–78.doi:10.1037/0022-006X.74.3.568

Connor KM , Davidson JR , Churchill LE , et al . Psychometric properties of the Social Phobia Inventory (SPIN). New self-rating scale. Br J Psychiatry 2000;176:379–86.

Craig P , Dieppe P , Macintyre S , et al . Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ 2008;337:a1655.doi:10.1136/bmj.a1655

Craske MG . Transdiagnostic treatment for anxiety and depression. Depress Anxiety 2012;29:749–53.doi:10.1002/da.21992

Craske, M.G., Meuret, A., Ritz, T., *Treanor, M., *Dour, H., & Rosenfield, D. (2019). Positive affect treatment for depression and anxiety: a randomized clinical trial for a core feature of anhedonia. *Journal of Consulting and Clinical Psychology, 87(5)*, 457-471. doi: 10.1037/ccp0000396.

Curtis, L. & Burns, A. (2019). *Unit Costs of Health and Social Care 2019*. Unit Costs of Health and Social Care. PSSRU, University of Kent. doi: 10.22024/UniKent/01.02.79286).

Dalgleish, T.*, Black, M.J.*, Johnston, D., & Bevan, A. (2020). Transdiagnostic Approaches to Mental Health Problems: Current Status and Future Directions. Journal of Consulting and Clinical Psychology. 88(3), 179-195. doi: 10.1037/ccp0000482.

Department of Health. The IAPT data handbook version 2.0.1. 2011: Published to DH Website, in electronic PDF format only.

Devilly GJ , Borkovec TD . Psychometric properties of the credibility/expectancy questionnaire. J Behav Ther Exp Psychiatry 2000;31:73–86.doi:10.1016/S0005-7916(00)00012-4 C

Dixon P , Hollinghurst S , Edwards L , et al . Cost-effectiveness of telehealth for patients with depression: evidence from the Healthlines randomised controlled trial. BJPsych Open 2016;2:262–9.doi:10.1192/bjpo.bp.116.002907

Dugas MJ , Ladouceur R , Léger E , et al . Group cognitive-behavioral therapy for generalized anxiety disorder: treatment outcome and long-term follow-up. J Consult Clin Psychol 2003;71:821–5.doi:10.1037/0022-006X.71.4.821

Dunn, B.D., Widnall, E., Reed, N., Taylor, R., Owens, C., Spencer, A., … & Kuyken, W. (2019). Evaluating Augmented Depression Therapy (ADepT): study protocol for a pilot randomised controlled trial. *Pilot Feasibility Studies, 5*, 63. doi: 10.1186/s40814-019-0438-1

Ellard KK , Fairholme CP , Boisseau CL , et al . Unified Protocol for the Transdiagnostic Treatment of Emotional Disorders: Protocol Development and Initial Outcome Data. Cogn Behav Pract 2010;17:88–101.doi:10.1016/j.cbpra.2009.06.002

First MB , et al Arlington, VA: American Psychiatric Association. First MB , et al . Structured Clinical Interview for DSM-5 - research Version (SCID-5 for DSM-5, Research Version, SCID5-RV, Version 1.0.0). 2015.

Fisher AJ, Bosley HG, Fernandez KC, Reeves JW, Soyster PD, Diamond AE, Barkin J. Open trial of a personalized modular treatment for mood and anxiety. Behav Res Ther. 2019 May;116:69-79. doi: 10.1016/j.brat.2019.01.010. Epub 2019 Feb 21. PMID: 30831478.

Foa, E.B., Kozak, M.J., Salkovskis, P.M., et al. (1998). The validation of a new obsessive-compulsive disorder scale: The Obsessive-Compulsive Inventory. *Psychological Assessment, 10*, 206–14. doi: 10.1037/1040-3590.10.3.206

Harvey, A.G., Watkins, E.R., Mansell, W., & Shafran, R. (2004*). Cognitive behavioural processes across psychological disorders: A transdiagnostic approach to research and treatment.* Oxford: Oxford University Press, 2004.

Hayes, S.C., Strosahl, K.D., & Wilson, K.G. (1999). *Acceptance and commitment therapy: An experiential approach to behavior change*. New York: Guilford Press.

Hayes, S.G., Hofmann, S., Stanton, C.E., Carpenter, J.K., Sanford, B.T., Curtiss, J.E., & Ciarrochi, J. (2019). The role of the individual in the coming era of process-based therapy, *Behaviour Research and Therapy, 117*, 40-53, doi: 10.1016/j.brat.2018.10.005.

Jeppesen, P., Wolf, R.T., Nielson, S.M., Christensen, R., Plessen, K.J., Bilenberg, N., et al. (2021). Effectiveness of Transdiagnostic Cognitive-Behavioral Psychotherapy Compared With Management as Usual for Youth With Common Mental Health Problems: A Randomized Clinical Trial. *JAMA Psychiatry, 78,* 250-260. doi:10.1001/jamapsychiatry.2020.4045

Kazantzis, N., Clayton, X., Cronin, T.J., Farchione, D., Limburg, K., & Dobson, K.S. (2018) The Cognitive Therapy Scale and Cognitive Therapy Scale-Revised as Measures of Therapist Competence in Cognitive Behavior Therapy for Depression: Relations with Short and Long Term Outcome. *Cognitive Therapy and Research,* doi: 10.1007/s10608-018-9919-4

Kessler, R.C., Berglund, P., Demler, O., et al. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62,* 593–602.doi:10.1001/archpsyc.62.6.593

Kessler, R.C., et al. (2003). The epidemiology of major depressive disorder: results from the National comorbidity survey replication (NCS-R). *Journal of the American Medical Association, 289*, e3105.

Kraemer, H.C., Kiernan, M., Essex, M., et al. (2008). How and why criteria defining moderators and mediators differ between the Baron & Kenny and MacArthur approaches. *Health Psychology, 27,* S101–S108. doi:10.1037/0278-6133.27.2(Suppl.).S101

Kroenke, K., Spitzer, R.L., & Williams, J.B. (2001). The PHQ-9: validity of a brief depression severity measure. *Journal of General Internal Medicine, 16*, 606–13.

Linehan, M.M. (1993). *Cognitive-Behavioral Treatment of Borderline Personality Disorder*. New York: Guilford Press.

Loerinc, A.G., Meuret, A.E., Twohig, M.P., et al. (2015). Response rates for CBT for anxiety disorders: Need for standardized criteria. *Clinical Psychology Review, 42*, 72–82. doi: 10.1016/j.cpr.2015.08.004

Marks, I.M., & Mathews, A.M. (1979). Brief standard self-rating for phobic patients. *Behaviour Research and Therapy, 17*, 263–7. doi: 10.1016/0005-7967(79)90041-X

Medical Research Council. (2010). *Review of mental health research: Report of the strategic review group*. London: Medical Research Council.

Meyer, T.J., Miller, M.L., Metzger, R.L., et al. (1990). Development and validation of the Penn State Worry Questionnaire. *Behaviour Research and Therapy, 28*, 487–95. doi: 10.1016/0005-7967(90)90135-6

Moses, E.B., & Barlow, D.H. (2006). A New Unified Treatment Approach for Emotional Disorders Based on Emotion Science. *Current Directions in Psychological Science, 15*, 146–50. doi: 10.1111/j.0963-7214.2006.00425.x

Mundt, J.C., Marks, I.M., Shear, M.K., et al. (2002). The Work and Social Adjustment Scale: a simple measure of impairment in functioning. *British Journal of Psychiatry, 180*, 461–4. doi: 10.1192/bjp.180.5.461

Newby, J.M., McKinnon, A., Kuyken, W., Gilbody, S., & Dalgleish, T. (2015). Systematic review and meta-analysis of transdiagnostic psychological treatments for anxiety and depressive disorders in adulthood. *Clinical Psychology Review, 40*, 91–110.doi:10.1016/j.cpr.2015.06.002

Norton, P.J. (2012). *Group cognitive-behavioural therapy of anxiety: A transdiagnostic treatment manual*. New York: Guilford Press.

Pilling, S., Whittington, C., Taylor, C., et al. (2011). Identification and care pathways for common mental health disorders: summary of NICE guidance. *British Medical Journal, 342*, d2868. doi: 10.1136/bmj.d2868

Reinholt, N., & Krogh, J. (2014). Efficacy of transdiagnostic cognitive behaviour therapy for anxiety disorders: a systematic review and meta-analysis of published outcome studies. *Cognitive Behaviour Therapy, 43*, 171–84. doi: 10.1080/16506073.2014.897367

Salisbury, C., O'Cathain, A., Edwards, L., et al (2016). Effectiveness of an integrated telehealth service for patients with depression: a pragmatic randomised controlled trial of a complex intervention. *Lancet Psychiatry, 3*, 515–25. doi: 10.1016/S2215-0366(16)00083-3

Salkovskis, P.M., Rimes, K.A., Warwick, H.M., et al. (2002). The Health Anxiety Inventory: development and validation of scales for the measurement of health anxiety and hypochondriasis. *Psychological Medicine, 32*, 843–53. doi: 10.1017/S0033291702005822

Schulz, K.F., Altman, D.G., Moher, D., for the CONSORT Group. (2010). CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *Trials, 11*, 32. doi:10.1186/1745-6215-11-32

Segal, Z.V., Williams, J.M.G., & Teasdale, J.D. (2002). *Mindfulness-based Cognitive Therapy for Depression: A new approach to preventing relapse.* New York: Guilford Press.

Shear, M.K., Brown, T.A., Barlow, D.H., et al. (1997). Multicenter collaborative panic disorder severity scale. *American Journal of Psychiatry, 154*, 1571–5. doi: 10.1176/ajp.154.11.1571

Sheehan, D.V. (1983). *The Anxiety Disease*. New York: Charles Scribner and Sons.

Spitzer, R.L., Kroenke, K., Williams, J.B., et al. (2006). A brief measure for assessing generalized anxiety disorder: the GAD-7. *Archives of Internal Medicine, 166*, 1092–1097. doi: 10.1001/archinte.166.10.1092 C

Tennant, R., Hiller, L., Fishwick, R., Platt, S., Joseph, S., Weich, S., Parkinson, J., Secker, J., & Stewart-Brown, S. (2007). The Warwick-Edinburgh Mental Well-being Scale (WEMWBS): development and UK validation. Health and quality of life outcomes, 5, 63. doi: 10.1186/1477-7525-5-63

Vallis, T.M., Shaw, B.F., & Dobson, K.S. (1986). The Cognitive Therapy Scale: Psychometric properties. *Journal of Consulting and Clinical Psychology, 54*, 381–385. Doi: 10.1037/0022-006X.54.3.381.

Ware, J.E., & Sherbourne, C.D. (1992). The MOS 36-item short-form health survey (SF-36). Conceptual framework and item selection. *Medical Care, 30*, 473–83.

Watson, D., O'Hara, M.W., Naragon-Gainey, K., et al (2012). Development and validation of new anxiety and bipolar symptom scales for an expanded version of the IDAS (the IDAS-II). *Assessment, 19*, 399–420.doi:10.1177/1073191112449857

Wilson, J.P., Tang, C.S., & Weiss, D.S. (2007). In: Wilson JP , Tang CS , eds. *The Impact of Event Scale: Revised, in Cross-cultural assessment of psychological trauma and PTSD*. New York: Springer, 219–38.