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Examining the effectiveness of a web-based intervention for symptoms of depression and anxiety in college students: Study protocol of a randomised controlled trial.

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Abstract

Introduction The college years are a peak period for the onset of common mental disorders. Poor mental health is associated with low academic attainment, physical, interpersonal and cognitive impairments. Universities can use online approaches to screen students for mental disorders and treat those in need. The present study aims to assess the effectiveness of a guided web-based transdiagnostic individually-tailored intervention to treat students with symptoms of depression and/or anxiety.

Methods and analysis The present study is a randomised controlled trial. Participants are Dutch college students (≥ 18 years) with mild to moderate depression and/or anxiety symptoms. The intervention is a guided web-based transdiagnostic individually-tailored intervention that targets symptoms of depression and/ or anxiety. The intervention consists of 7 online sessions with a duration ranging from 4 to 7 weeks depending on individual progress. A booster session is administered four weeks after the completion of the 7th session. Primary outcome measures are the Patient Health Questionnaire (PHQ-9) for depression and the Generalised Anxiety Disorder-7 items scale (GAD-7) for anxiety. These scales are administered at screening, post-treatment and follow-up assessments (6 and 12 months post-randomisation).

Ethics and Dissemination The Medical ethics committee of the Vrije Universiteit Medical Centre has approved the protocol (registration number 2016.583, A2017.362 & A2018.421). Results of the trial will be published in a peer-reviewed journal.

Trial registration Netherlands Trial Register NTR6797 Registered on 03-11-2017

Keywords College Students; Depression; Anxiety; Web-Based Interventions; Transdiagnostic Treatment; Individually-Tailored; Cognitive Behavioural Therapy; Youth

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Article Summary

Strengths

- This study aims to advance current knowledge on the effects of web-based interventions in college students with depression and anxiety.
- A transdiagnostic and individually-tailored therapeutic approach is employed to target both symptoms of depression and anxiety.
- Both Dutch and International students will be included to increase generalizability of the findings.

Limitations

- The power calculation has been based on the primary aims of this study, thereby limiting the power to detect moderators of treatment outcome.
- The assessment of study dropout relies on self-report answers due to privacy restrictions.

Introduction

Mental health problems, such as depression and anxiety, have a significant impact on college students' functioning and are notably burdensome [1]. College years are a peak period for the first onset of common mental disorders [2] College students experience a variety of stressors (e.g., exams, living away from family, financial hardships), which make them prone to mental disorders. Research has shown that depression and anxiety are highly prevalent among college students while the majority of lifetime cases begin before 24 years of age [2]. Not surprisingly, there is a positive association between mental health and academic attainment. Mental disorders are related to physical, interpersonal and cognitive impairments, which adversely affect educational participation and exam performance [3-5]. Consequently, there is a high chance of study dropout or delay in higher education, which in turn, leads to high direct and indirect costs for both individuals and society [6 7].

Addressing student mental health might thus be effective in improving students' well-being and academic results. However, not many college students with depression or anxiety seek or can find help for their condition. Less than twenty-five per cent of college students with mental disorders utilise mental healthcare services [8]. The university can be an excellent environment for detecting students at high risk of mental disorders and for applying evidence-based treatment approaches to prevent and treat common mental disorders at an early stage. However, the limited resources of college counselling services hamper the detection of students with mental issues. In many universities, student psychologists treat only study related problems (e.g., exam anxiety, procrastination) and not symptoms of mental disorders, such as depression and anxiety. In addition, the fear of stigmatisation makes students reluctant to consult university counselling services [9]. As a result, depression and anxiety are considerably underdiagnosed and typically untreated during college years with an unnecessary chance of aggravation of problems [10].

The question arises as to how we can provide treatment, which is effective, timely, available at low cost, accessible, and that overcomes worries about stigmatisation by maintaining students' anonymity. The Internet can play a crucial role in this endeavour. Presently, internet-based approaches have a high penetration rate and are particularly popular among youth.

Many young people with mental disorders seek information on their symptoms online [9]. Universities can use electronic media to screen for students with mental disorders but also treat those in need [11]. Recently, web-based psychological interventions have been developed and examined in research and clinical settings. Several randomised controlled trials (RCTs) and meta-analyses have addressed the effectiveness of web-based and other computerised interventions in treating depression and anxiety symptoms. So far, the results have shown that web-based interventions with therapist support are superior to control groups [12-16] with similar effect sizes to conventional face-to-face treatments [17].

Furthermore, several studies that examine the effects of web-based transdiagnostic and individually tailored interventions have emerged [18-21]. Given that depression and anxiety are highly comorbid, interventions aimed at improvement of both depression and anxiety symptoms are needed. Transdiagnostic interventions target common disorder mechanisms, such as avoidance [22]. Results from a recent meta-analysis showed a medium to large effect size in favour of web-based transdiagnostic/ individually tailored interventions compared to controls in treating anxiety (g = .82) and depression (g = 79) [22].

Nevertheless, up to now, there have been relatively few studies focusing on the effectiveness of web-based interventions in treating college students with depression and/or anxiety disorders. Farrer and colleagues [9] conducted a systematic review of technology-based interventions for tertiary students with mental disorders and showed mixed evidence for the effectiveness of technology interventions targeting depression and/or anxiety [9]. However, the focus of this review was broad; it included studies, which employed either prevention or treatment interventions [23-26].

Similarly, few studies have specifically focused on the effectiveness of transdiagnostic web-based interventions in college students with depression and anxiety. Day and colleagues found that web-based guided transdiagnostic Cognitive Behavioural Therapy (iCBT) is more effective in treating depression (d = 0.55) and anxiety (d = 0.66) compared to a waitlist control in college students [27]. Moreover, Mullin and colleagues conducted an RCT examining the effects of transdiagnostic web-based Cognitive Behavioural Therapy in treating anxiety and depression of college students [28]. The authors found significant results in favour of the

transdiagnostic web-based intervention compared to a waiting list (anxiety: d = 1.33; depression d = 1.59) [28]. Given these encouraging findings, it is important to examine further the effects of these novel therapeutic approaches in treating college students with symptoms of depression and/or anxiety.

Objectives

Primary objectives

The present study aims to assess the effectiveness of a guided web-based transdiagnostic individually-tailored intervention in treating college students with symptoms of depression and/or anxiety.

Secondary objectives

Additionally, the present study aims to (a) explore participant characteristics as moderators of treatment outcome, (b) examine the acceptability of the treatment and (c) assess whether the investigated intervention prevents university dropout and increases educational achievement.

Hypothesis

We hypothesize that the interventions will outperform the control condition in reducing depressive and anxiety symptoms of college students.

Methods and analysis

Trial Design

The present study is a two-arm superiority RCT (1:1 allocation ratio), which compares a guided web-based transdiagnostic individually-tailored intervention to treatment as usual (TAU).

=Figure 1- Flow chart of the participant's inclusion process =

Study setting

The present study is conducted in Dutch universities and colleges. The recruitment of participants and the study procedures are managed by two main centres (the Vrije Universiteit and the Universiteit van Amsterdam).

Eligibility criteria

Participants are young adults (≥ 18 years) enrolled as bachelor or master students at a university or college in the Netherlands. Students will participate in an online survey, which is part of an epidemiological study assessing the prevalence rates of mental disorders in a college student population. This epidemiological study is embedded within the WHO World Mental Health International College Student initiative (WMH-ICS). Students are invited to participate in the RCT if they: (a) experience mild to moderate depression defined as scoring above the cut-off score of 4 on the Patient health questionnaire (PHQ-9) [29] and/ or anxiety symptoms defined as scoring above the cut-off score of 4 on the Generalised Anxiety Disorder scale – 7 items (GAD – 7) [30], (b) speak Dutch or English fluently and (c) provide written informed consent before participation.

Students are excluded if they: (a) have co-morbid bipolar disorder or psychotic disorder according to the MINI International Neuropsychiatric Interview (MINI) [31], (b) experience severe depression defined as scoring above the cut-off score of 14 on the PHQ-9 and/ or anxiety symptoms defined as scoring above the cut-off score of 14 on the GAD-7 scale, (c) currently receive psychological treatment for depression and/or anxiety or have received treatment in the past 12 months and (d) have slow or no Internet connection (e.g. no broadband Internet).

Intervention

The intervention used in this study, "ICare Prevent", is a guided web-based transdiagnostic individually-tailored intervention with mobile support and is targeted at symptoms of depression and/or anxiety. It can be used on laptops, computers, and mobile devices. This intervention has been initially developed in the German language for use in the general population and is based on adaptions of a range of evidence-based interventions [32 33]. Thus, it has been translated into Dutch and English and adapted to college student needs after a series

of focus group discussions with college students [34]. The intervention strategies have been based mainly on cognitive behavioural techniques. It uses text, homework exercises, audio-visual components, and information sheets that can be downloaded. Testimonials are used to explain homework.

The participants receive seven weekly online sessions: 1) introduction into the intervention and its technical aspects, setting goals and importance of pleasant activities, 2) tackling problems and behavioural activation, 3) psychoeducation, 4) cognitive restructuring and challenging negative thoughts, 5) choosing the most prominent complaints and accordingly for depression: problem-solving; for anxiety: exposure, 6) continuation of strategies selected from session 5, and 7) plan for the future. Four weeks after completion of the seventh sessions, participants will be invited for a booster session. The individually-tailored aspect of the intervention is applied in sessions 5 and 6. Therein, participants follow disorder-specific exercises by choosing either problem solving targeted at depressive symptoms or exposure to anxiety-provoking situations, depending on individual preference. Based on their personal needs, participants are free to choose elective modules that are integrated into sessions 2 to 7 (worry and rumination, acceptance of unfulfilled needs, relaxation, alcohol consumption as emotion regulator, self-worth, perfectionism, appreciation and gratitude and sleep hygiene). Table 1 gives an overview of the intervention.

Each session takes between 45 and 60 minutes. Participants are advised to follow one or maximum two sessions per week. Thus, the total duration of the intervention ranges from 4 to 7 weeks. The online sessions are delivered with written support given by coaches via the messaging function of the intervention platform. Participants are allowed to use the content of the intervention 24/7, as long and as often they want through the online treatment platform. In addition to the online sessions, participants have access to diaries (e.g. for tracking positive activities and monitoring sleep), mood graph, homework assignments, and the messaging system that allows participants to contact their online coach. The optional mobile app provides access to, e.g. diaries. A username and a self-generated password protect participants' access to the intervention.

=Table 1 - Intervention content =

Online treatment platform

Minddistrict is the e-health platform hosted by Minddistrict BV, which is an enterprise responsible for the provision and maintenance of the Minddistrict platform. Minddistrict provides the content management system to researchers to upload interventions/ questionnaires and to enrol participants/ e-coaches. This platform has been repeatedly used by several research projects and routine care services. Minddistrict complies with all European data safety regulations and quality standards.

Support

Trained psychology master students will deliver support to participants. The training lasts for one day and consists of three parts: (a) theory (e.g. intervention materials), (b) assignments and (c) practice. Research staff experienced in web-based interventions give the training. Coaches provide individual manualized feedback via the messaging function of the intervention platform after the completion of each module, and they are available to answer questions about the treatment content. The coaches are advised to spend less than 30 minutes per individual feedback while the estimated time of feedback is 20 minutes. Thus, a coach spends in total approximately 2.5 hours per participant. A senior researcher monitors the feedback written by the coaches to ensure adherence to the treatment protocol.

Treatment as Usual

Participants in the TAU group receive information about the available regular care services in the community such as help from their general practitioner, primary and secondary mental health services from psychologists/psychiatrists. These services include mostly medications (e.g., antidepressants) and/or low intensive face-to-face psychotherapies. Students are free to decide whether they would like to seek help or not. Use of these services is recorded through self-report questionnaires at the post-treatment and follow-up assessments. This control condition has been chosen to reflect whether there is a difference between the web-based intervention and what students would normally do.

Primary outcomes

Participants who will be included in the RCT are assessed by:

Patient Health Questionnaire – 9 items (PHQ-9)

The PHQ-9 [35] is a self-report outcome measure that can be used to screen depressive symptoms. The PHQ-9 consists of 9-items. Item responses are on a 0-3 scale with total scores ranging from 0 to 27. Higher scores indicate more severe depression. PHQ-9 shows good psychometric properties with a sensitivity of .77 (.71-.84) and a specificity of .94 (.90-.97)[36]. The PHQ-9 is administered at the screening (t0), post-treatment (t2) and follow-up (t3 & t4) assessments in the intervention group.

Generalised Anxiety Disorder scale – 7 items (GAD-7)

The 7-item GAD [30] scale will be used to measure anxiety symptoms. Each of the 7 items is scored on a 0-3 scale while total score range is 0-21. Higher scores indicate more severe anxiety symptoms. The GAD-7 scale shows internal consistency with a value of Cronbach's coefficient (α) ranging from .79 to .91[37]. The GAD-7 is administered at the screening (t0), post-treatment (t2) and follow-up (t3 & t4) assessments.

Mini-International Neuropsychiatric Interview (MINI)

The diagnostic interview MINI (version 5.0) will be conducted via telephone by a trained clinical psychology master student. The MINI is a short-structured interview based on the Diagnostic and Statistical Manual of Mental disorders fourth edition (DSM-IV) and the International Classification of Diseases criteria (ICD-10). The MINI is used to determine current / lifetime diagnosis of Major Depressive Disorder, Panic Disorder, Agoraphobia, Social Phobia, Generalised Anxiety Disorder and current / lifetime diagnosis of major comorbidities (Dysthymia, Suicidality, (hypo) Manic Episode, Obsessive Compulsive Disorder, Post-Traumatic Stress Disorder, Alcohol Dependence/ Abuse, Drug Dependence / Abuse, Psychotic Disorders, Anorexia Nervosa, and Bulimia Nervosa). The MINI shows good psychometric properties with good test-retest reliability and validity [38]. The MINI is administered at baseline (t1) and 12 months follow-up (t4).

Secondary outcomes

EuroQol - 5 Dimensions (EQ-5D)

Quality of life is measured with the EQ-5D [39]. The EQ-5D is a self-report questionnaire, which measures the health-related wellbeing for clinical and economic appraisal. More precisely, EQ-5D consists of five items/ dimensions: mobility, self-care, ordinary activities, discomfort, and mood state, related to anxiety or depression. Each item/ dimension consists of three categories ranging from no problems to few and finally to many problems [40]. EQ-5D construct validity is adequate, and this type of measurement can detect meaningful changes for patients with anxiety disorders. EQ-5D is generally consistent with the measure of mood state: depression/anxiety[41]. The EQ-5D is administered at baseline (t1), post-treatment (t2) and follow-up (t3 & t4) assessments.

Client satisfaction Questionnaire – 8 items (CSQ-8)

The CSQ-8[42] is used to assess client satisfaction related to the treatment. This self-report questionnaire consists of 8 items. Item responses are on a 1-4 scale with total scores ranging from 8 to 32. Higher scores of CSQ-8 indicate higher satisfaction with the treatment. The CSQ-8 shows high internal consistency with a value of Cronbach's coefficient (α) being .93 [43 44]. The CSQ-8 is administered at the post-treatment (t2)

University dropout & Educational achievement

University dropout will be monitored through self-report questions administered at post-treatment (t2) and follow-up (t3 & t4) assessments. Regarding educational achievement, the Presenteeism Scale for Students (PSS) is used to assess presenteeism [45]. The PSS is a valid and reliable measure for the college student population [45]. Moreover, the students are asked about the number of European Credit Transfer System (ECTs) achieved during a given study period. The educational achievement is measured at the baseline (t1), post-treatment (t2) and follow-up (t3 & t4) assessments.

Treatment adherence

Adherence to treatment is measured by tracking the website usage automatically. Data related to the total number of modules completed, time spent per module and number of logging into the platform are gathered.

= Table 2 - Overview of measures and assessment points =

Assessments

Table 2 presents an overview of all measures and assessment points. As mentioned above, students are recruited through an online survey, which is part of an epidemiological study. In brief, this survey consists of a broad range of short self-administered validated scales assessing mental health problems such as attention deficit hyperactivity disorder (the Adult Attention Deficit Hyperactivity Disorder Self-Report; [46]), major depressive disorder, mania/ hypomania, generalized anxiety disorder, panic disorder, drug use disorder (Composite International Diagnostic Interview Screening Scales - CIDI; [47]), alcohol use disorder (Alcohol Use Disorders Identification Test; [48]), intermittent explosive disorder, post-traumatic stress disorder, binge-eating behavior, purging behavior, psychotic disorder (CIDI; [49 50]) and suicidal thoughts and behaviours (The Self-Injurious Thoughts and Behaviours Interview; [51]). Moreover, this survey assesses the self-reported quality of health, use of services for emotional or mental health problems, academic attainment and university expectations and adjustment. The e-survey will be administered at the screening (t0).

In the RCT, participants in both conditions are followed up to 12 months post-randomisation. After eligibility screening (t0), measures are administered at baseline (t1), post-treatment - 7 weeks post-randomisation (t2), six months (t3) and twelve months post-randomisation (t4). Figure 1 shows the flowchart of participants' inclusion.

Sample size calculation

The power calculation is based on a head-to-head comparison of the guided web-based transdiagnostic intervention versus treatment as usual (t-test). We have decided to calculate our sample size based on the effects of web-based interventions on depressive symptoms. We have made this choice because web-based interventions have overall higher effects on anxiety compared to depression. Thus, we anticipate a conservative estimate of Cohen's = .70 based on two recent meta-analyses on the effectiveness of psychotherapy in treating

depressive symptoms in college students [52 53]. If we set the statistical power at .8 and alpha at .05, according to a two-tailed hypothesis, we need 34 participants per group to obtain a Cohen's d of .70 (total N = 68). Previous literature has shown that guided web-based interventions have a dropout rate of 28% [54]. Thus, considering the potential dropouts, the minimum sample for the RCT is 88 participants (44 participants per group).

Recruitment

Participants are recruited from Dutch universities and colleges. Recruitment for the RCT is conducted through the e-survey of the WHO WMH-ICS. Recruitment for the survey is conducted in two ways: First, we recruit participants through emails and advertisements (e.g., flyers, faculty newsletters, social media, university websites). The advertisements target all college students to inform them about the study and emphasise the importance of self-help in improving wellbeing and academic achievement. We have also created a website for this study (https://caring-universities.com), which contains information and useful links for questions. The research team sends emails to students providing information about the project and a link to the screening questionnaires. A reminder is sent to non-responders biweekly. Students can unsubscribe from the reminder emails whenever they want and their participation is voluntary. Second, study advisors, students' mentors and student ambassadors inform college students about the study.

After completing the e-survey, students eligible for the RCT are notified instantly. Those who are not eligible are sent a thank-you email for their participation in the survey. The research team approaches those who have severe symptoms of depression and/or anxiety to inform them about the available treatment options in the community. Students who meet inclusion criteria (as described above) are informed about the RCT. Those who are interested in participating receive a more detailed information brochure about the study along with an informed consent form. After returning a signed informed consent form, students are invited by email for a telephone MINI diagnostic interview. After the diagnostic interview, students are randomised to either the web-based intervention or the TAU group. After randomisation, students are sent to a link (via email) to the online baseline questionnaires. Students who are assigned to the intervention arm are asked to create an account to follow the web-based

intervention. Students in the TAU group receive information about the available regular care services in the community.

Randomisation, blinding and treatment allocation

Two independent researchers who are not involved in the study generate a random sequence using a computer random sequence generator. Randomisation takes place at an individual level, stratified by recruitment location (the Vrije Universiteit or the Universiteit van Amsterdam). Participants are randomised into two groups (web-based intervention vs TAU) with an allocation ratio of 1:1. We conduct block randomisation with randomly varied block sizes (6 to 12 allocations per block). The allocation is concealed from study's researchers since the randomisation is conducted using of a computer-generated code by an independent researcher. It is not possible to mask personnel and participants to the treatment allocation because of the nature of the intervention.

Data Collection and Management

This study follows the European Union General Data Protection Regulations (GDPR). All data are driven from self-report questionnaires and are mostly collected through electronic means (Qualtrics platform). However, according to the regulations of the medical ethics committee of the VU Medical Center (VUmc), electronic informed consents are not allowed. Thus, we collect all signed informed consent forms via post. To ensure data confidentiality, participants' informed consent forms are locked in the institution allowing only authorised research staff to have access. Electronic data are password protected in a secure environment and are accessed only by authorized personnel. The primary use of the data is anonymous.

Statistical analysis

All randomised participants will be included in all analyses according to the intention to treat (ITT) principle. Missing values will be imputed using multiple imputations. Also, we will conduct per protocol analyses including only those who completed post-treatment and follow-up assessments. All analyses will be performed using STATA version SE 13.1 [55]. We will analyse the effects of the interventions on depression (PHQ-9) and anxiety severity (GAD-7)

at both post-treatment and follow-up assessment using multilevel mixed models linear regression with a restricted maximum likelihood algorithm. The post-treatment depression and anxiety scores will be used as a dependent variable and trial arm condition (web-based transdiagnostic individually-tailored intervention vs TAU) as an independent variable while adjusting for baseline depression and anxiety severity. Additionally, we will calculate the effect size, Cohen's d, by subtracting the average score on primary outcome measures (PHQ-9 and GAD-7 scales) of the intervention group from the average scores of the control group at the post-treatment and dividing the results by the pooled standard deviations. Analogously, Cohen's d will be calculated for follow-up assessments (6 and 12 months).

Possible harms

Thus far, web-based interventions have not been associated with harmful effects. On the contrary, it has been found that these interventions lead to lower symptom deterioration rates compared to controls. [56 57] Moreover, in this study participants are college students with mild to moderate symptoms of depression and/ or anxiety. This population has high degree of functioning (e.g., attending university) and is very unlikely to enter the general medical healthcare system.

Nevertheless, it is possible that the students experience suicidal ideation. If we detect a student who is at high suicidal risk, a specific protocol is followed: the e-coach calls the student to assess the risk by asking a series of questions. Afterwards, the e-coach contacts an experienced psychiatrist, who is involved in the study, to discuss the situation. If needed, the psychiatrist contacts the participant to advise him/ her to seek help from his/her General Practitioner (GP) or the student counselling services. The research team checks if the student sought help after a couple of days. Moreover, if the student permits us to use the contact details of his/ her GP, the research team notifies the GP to ensure that the student will get help timely.

Premature termination of the study

The research team will decide to terminate the ongoing trial in case of serious adverse events (e.g., suicide), which is directly related to the study procedures. The principal investigator (PC)

will prompt the discontinuation of the trial and will inform the medical ethics committee immediately. All participants will be informed about the study termination and the reason that led to this decision. Moreover, participants will receive information about available mental health care services options

Ethics and dissemination

Research Ethics Approval, Amendments & Consent

The Medical Ethics Committee of the VUmc has approved the protocol (registration number 2016.583 & A2017.362) and all amendments will be notified this committee. The study will be conducted following the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). A signed informed consent form will be requested from all eligible subjects before participation. The Medical Ethics Committee of the VUmc monitors the progress and procedures of the trial.

Discussion

Early management of depression and anxiety may improve symptoms, increase academic performance and prevent college dropout. The present protocol describes the procedures of a randomised controlled trial conducted in Dutch universities and colleges. This study aims at examining the effects of a guided transdiagnostic individually-tailored web-based intervention in reducing symptoms of depression and/ or anxiety in college student population. It is expected that the examined intervention will outperform treatment as usual in treating college students with depression and/ or anxiety.

So far, only a few trials have examined the effectiveness of web-based transdiagnostic and individually-tailored interventions in college students. The outcomes of these trials were mixed and thus, inconclusive [9]. Moreover, to our knowledge, previous studies on college students' mental health have mostly focused on one disorder. Given that depression and anxiety are highly comorbid [58-60], it is essential to test approaches with transdiagnostic components targeted at symptoms of both depression and anxiety. The present study aims at

improving existing knowledge on the effectiveness of web-based interventions in college students suffering from depression and/or anxiety by employing a transdiagnostic and individually-tailored therapeutic approach. This study targets both Dutch and international students, thereby increasing the generalizability of our findings to different cultural backgrounds.

Nevertheless, several limitations should be expected. First, the power calculation has been based on our primary aim to examine the effectiveness of the web-based transdiagnostic individually-tailored intervention in reducing symptoms of depression and/or anxiety. Therefore, the study is underpowered to examine secondary moderator analyses, which usually require larger sample sizes. If possible, we will recruit a larger number of participants to achieve sufficient power for the secondary outcomes such as college dropout, as well as the planned moderator analysis. Second, although the intervention is delivered with therapeutic guidance, retaining students in the intervention might be a challenge. However, dropout has been considered in sample size calculation and thus, we expect that it will not influence the statistical power of our sample. Third, we cannot measure educational achievement using academic records due to ethical restrictions. Information on educational attainment will be self-reported and thus, may be less objective.

Overall, the results of this study will provide valuable information about the effectiveness of web-based interventions in improving college students' mental health and may lead to the development of the infrastructure for screening and treating mental disorders within universities.

Trial Status

The trial has started in March 2018 and is expected to be completed in August 2019.

Abbreviations

CIDI: Composite International Diagnostic Interview Screening Scales

CSQ: Client Satisfaction Questionnaire

ECTs: European Credit Transfer System

EQ-5D: EuroQol 5 Dimensions

GAD-7: Generalised Anxiety Disorder – 7 item scale

GPA: Grade Point Average

iCBT: Web-based Cognitive Behavioural Therapy

MINI: Mini International Neuropsychiatric Interview

PHQ-9: Patient Health Questionnaire – 9 item scale

PSS: Presenteeism Scale for Students

RCT: Randomised Controlled Trial

TAU: Treatment As Usual

WMH – ICS: World Mental Health Surveys International College Students Initiative

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Availability of data and materials

Not applicable

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Author contributions

PC (PI), HR and RW obtained funding for this study. All authors contributed to the design of the study. EK drafted the manuscript and coordinated the recruitment of students and the

data-collection at VU. AK coordinates the recruitment of students and the data-collection at UvA. RW, HR, LW, AK, EB, SB, FB, NB, CH, PV, AK, LK, DE, RB, RCK, RA, and PC were involved in revising the manuscript critically for intellectual content. All authors read and approved the final manuscript.

Consent of publication

Not applicable

Competing interests

None

Data access

Data can be accessed only after concluding a data sharing agreement in accordance with the European regulation about general data protection.

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Table 1, Intervention content

Main Intervention	
Session	Content
1. Introduction	Goal setting and importance of pleasant activities
2. Tackling problems	Identification of problems and problem solving based on behavioural activation
3. Psychoeducation	Psychoeducation focusing either on depression or anxiety depending on individual needs
4. Cognitive restructuring	Development of functional positive thinking after identifying the relationship between thoughts, wellbeing and practising strategies
5. Choosing most prominent complaints	Problem solving targeted at either depression or exposure to anxiety provoking stimuli depending on individual needs
6. Deepening of skills chosen in session 5	Problem solving and exposure in daily life
7. Plan for the future	Reflection on goal attainment and learning experiences. Implementation of intentions until the booster session
8. Booster session (4 weeks after the completions of the 7th session)	Reflection on goal attainment and learning experiences. Implementation of intentions during the upcoming months
Elective modules	
i. Worry and rumination	Information on worry and rumination, using a worry-diary and other techniques to challenge such thoughts
ii. Acceptance of unfulfilled needs	Attending to unfulfilled needs and unsolvable problems and learning to accept them
iii. Relaxation	Exercise on progressive muscle relaxation

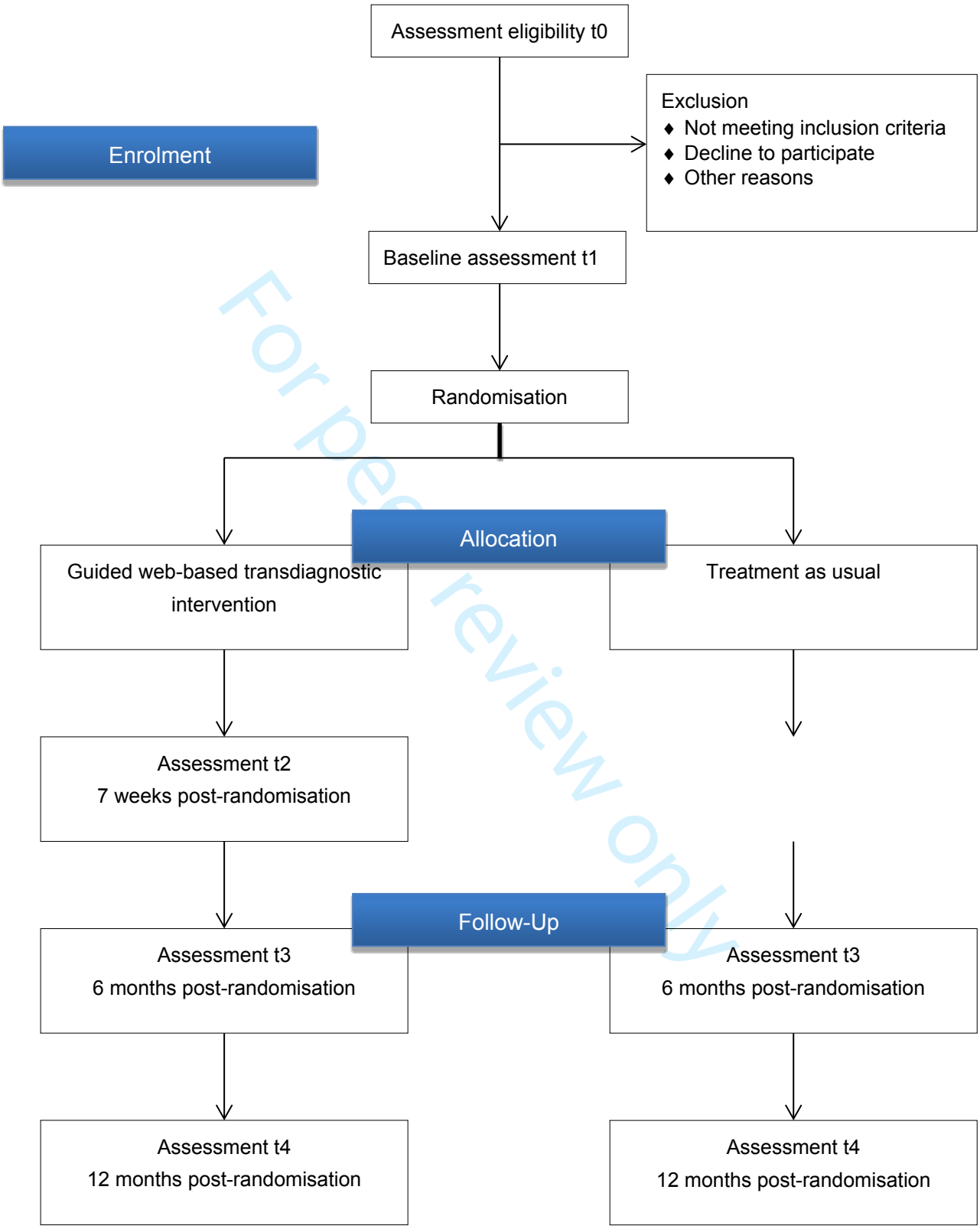
iv.	Alcohol consumption as emotion regulator	Information on the relationship between mood and alcohol, self-assessment of consumption and techniques to decrease it
v.	Self-worth	Information on the effects of low or instable self-worth and exercises to increase it
vi.	Perfectionism	Identifying personal high standards and learning techniques to exit from a vicious circle
vii.	Appreciation and gratitude	Learning how to express gratitude and how to consciously appreciate positive things in daily life
viii.	Sleep Hygiene	Sleep-limitation technique (i.e. by initially limiting sleep being able to ultimately sleep better)

Table 2. Overview of measures and assessment points

Measure (Instrument)	Assessment points				
	t0	t1	t2	t3	t4
Socio - Demographics (e-survey)	X				
DSM-IV Axis I and II disorders (e-survey)	X				
Daily functioning (e-survey)	X				
Personality traits (e-survey)	X				
Clinical measures (e-survey)	X				
Suicide plan and/or suicide attempt(s) (e-survey)	X				
Childhood maltreatment, domestic violence (e-survey)	X				
Academic experiences and functioning, participation in athletic and extra-curricular activities (e-survey)	X				
Information about lifetime and 12-month use of mental health care services (e-survey)	X				
Depressive symptoms (PHQ-9)	X		X	X	X
Anxiety symptoms (GAD-7)	X		X	X	X
The MINI International Neuropsychiatric Interview (MINI)		X			X
Quality of life (EQ-5D)		X	X	X	X
Satisfaction with treatment (CSQ-8)			X		
Presenteeism (PSS)		X	X	X	X
Educational Achievement		X	X	X	X
Study Dropout			X	X	X
Use of regular care			X	X	X

Note: t0: screening (total cohort); t1: baseline (RCT); t2: post-treatment (RCT); t3: 6 months post-randomisation (RCT); t4: 12 months post-randomisation (RCT); t5: 12 months after t0 (total cohort); t6: 24 months after t0 (total cohort)

Figure 1. Flow chart of the participant's inclusion process



Assessment t2

weeks post-randomisation

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	18
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1 & 18
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	18

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	9
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7-9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Flow chart & p.12
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12-13
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13-14
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14-15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found,	14

		if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15-16
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	16
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	16
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13-14
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	19

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Submitted to the journal
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

Examining the effectiveness of a web-based intervention for symptoms of depression and anxiety in college students: Study protocol of a randomised controlled trial.

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Examining the effectiveness of a web-based intervention for symptoms of depression and anxiety in college students: Study protocol of a randomised controlled trial.

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Abstract

Introduction The college years are a peak period for the onset of common mental disorders. Poor mental health is associated with low academic attainment, physical, interpersonal and cognitive impairments. Universities can use online approaches to screen students for mental disorders and treat those in need. The present study aims to assess the effectiveness of a guided web-based transdiagnostic individually-tailored intervention to treat students with symptoms of depression and/or anxiety.

Methods and analysis The present study is a randomised controlled trial. Participants are Dutch college students (≥ 18 years) with mild to moderate depression and/or anxiety symptoms. The intervention is a guided web-based transdiagnostic individually-tailored intervention that targets symptoms of depression and/ or anxiety. The intervention consists of 7 online sessions with a duration ranging from 4 to 7 weeks depending on individual progress. A booster session is administered four weeks after the completion of the 7th session. Primary outcome measures are the Patient Health Questionnaire (PHQ-9) for depression and the Generalised Anxiety Disorder-7 items scale (GAD-7) for anxiety. These scales are administered at screening, post-treatment and follow-up assessments (6 and 12 months post-randomisation).

Ethics and Dissemination The Medical ethics committee of the Vrije Universiteit Medical Centre has approved the protocol (registration number 2016.583, A2017.362 & A2018.421). Results of the trial will be published in a peer-reviewed journal.

Trial registration Netherlands Trial Register NTR6797 Registered on 03-11-2017

Keywords College Students; Depression; Anxiety; Web-Based Interventions; Transdiagnostic Treatment; Individually-Tailored; Cognitive Behavioural Therapy; Youth

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Article Summary

Strengths

- This study aims to advance current knowledge on the effects of web-based interventions in college students with depression and anxiety.
- A transdiagnostic and individually-tailored therapeutic approach is employed to target both symptoms of depression and anxiety.
- Both Dutch and International students will be included to increase generalizability of the findings.

Limitations

- The power calculation has been based on the primary aims of this study, thereby limiting the power to detect moderators of treatment outcome.
- The assessment of study dropout relies on self-report answers due to privacy restrictions.

Introduction

Mental health problems, such as depression and anxiety, have a significant impact on college students' functioning and are notably burdensome [1]. College years are a peak period for the first onset of common mental disorders [2] College students experience a variety of stressors (e.g., exams, living away from family, financial hardships), which make them prone to mental disorders. Research has shown that depression and anxiety are highly prevalent among college students while the majority of lifetime cases begin before 24 years of age [2]. Not surprisingly, there is a positive association between mental health and academic attainment. Mental disorders are related to physical, interpersonal and cognitive impairments, which adversely affect educational participation and exam performance [3-5]. Consequently, there is a high chance of study dropout or delay in higher education, which in turn, leads to high direct and indirect costs for both individuals and society [6 7].

Addressing student mental health might thus be effective in improving students' well-being and academic results. However, not many college students with depression or anxiety seek or can find help for their condition. Less than twenty-five per cent of college students with mental disorders utilise mental healthcare services [8]. The university can be an excellent environment for detecting students at high risk of mental disorders and for applying evidence-based treatment approaches to prevent and treat common mental disorders at an early stage. However, the limited resources of college counselling services hamper the detection of students with mental issues. In many universities, psychologists offering services to students treat only study related problems (e.g., exam anxiety, procrastination) and not symptoms of mental disorders, such as depression and anxiety[9]. In addition, the fear of stigmatisation makes students reluctant to consult university counselling services [10]. As a result, depression and anxiety are considerably underdiagnosed and typically untreated during college years with an unnecessary chance of aggravation of problems [11].

The question arises as to how universities and colleges can provide treatment, which is effective, timely, available at low cost, accessible, and that overcomes worries about stigmatisation by maintaining students' anonymity. The Internet can play a crucial role in this endeavour. Presently, internet-based approaches have a high penetration rate and are

particularly popular among youth. Many young people with mental disorders seek information on their symptoms online [10]. Universities can use electronic media to screen for students with mental disorders but also treat those in need [12]. Recently, web-based psychological interventions have been developed and examined in research and clinical settings. Several randomised controlled trials (RCTs) and meta-analyses have addressed the effectiveness of web-based and other computerised interventions in treating depression and anxiety symptoms. So far, the results have shown that web-based interventions with therapist support are superior to control groups [13-17] with similar effect sizes to conventional face-to-face treatments [18].

Furthermore, several studies that examine the effects of web-based transdiagnostic and individually tailored interventions have emerged [19-22]. Given that depression and anxiety are highly comorbid, interventions aimed at improvement of both depression and anxiety symptoms are needed. Transdiagnostic interventions target common disorder mechanisms, such as avoidance [23]. Results from a recent meta-analysis showed a medium to large effect size in favour of web-based transdiagnostic/ individually tailored interventions compared to controls in treating anxiety (g = .82) and depression (g = .79) [23].

Nevertheless, up to now, there have been relatively few studies focusing on the effectiveness of web-based interventions in treating college students with depression and/or anxiety disorders. Systematic reviews of technology-based interventions for tertiary students with mental disorders have shown mixed evidence for the effectiveness of technology interventions targeting depression and/or anxiety [10 24]. However, the focus of these reviews was broad; they included studies that employed either prevention or treatment interventions [24-28].

Similarly, few studies have specifically focused on the effectiveness of transdiagnostic web-based interventions in college students with depression and anxiety. Day and colleagues found that web-based guided transdiagnostic Cognitive Behavioural Therapy (iCBT) is more effective in treating depression (d = 0.55) and anxiety (d = 0.66) compared to a waitlist control in college students [29]. Moreover, Mullin and colleagues conducted an RCT examining the effects of transdiagnostic web-based Cognitive Behavioural Therapy in treating anxiety and

depression of college students [30]. The authors found significant results in favour of the transdiagnostic web-based intervention compared to a waiting list (anxiety: d = 1.33; depression d = 1.59) [30]. Given these encouraging findings, it is important to examine further the effects of these novel therapeutic approaches in treating college students with symptoms of depression and/or anxiety.

Objectives

Primary objectives

The present study aims to assess the effectiveness of a guided web-based transdiagnostic individually-tailored intervention in treating college students with symptoms of depression and/or anxiety.

Secondary objectives

Additionally, the present study aims to (a) explore participant characteristics as moderators of treatment outcome, (b) examine the acceptability of the treatment and (c) assess whether the investigated intervention prevents university dropout and increases educational achievement.

Hypothesis

We hypothesize that the interventions will outperform the control condition in reducing depressive and anxiety symptoms of college students.

Methods and analysis

Trial Design

The present study is a two-arm superiority RCT (1:1 allocation ratio), which compares a guided web-based transdiagnostic individually-tailored intervention to treatment as usual (TAU).

=Figure 1- Flow chart of the participant's inclusion process =

Study setting

The present study is conducted in Dutch universities and colleges. The recruitment of participants and the study procedures are managed by two main centres (the Vrije Universiteit and the Universiteit van Amsterdam).

Eligibility criteria

Participants are young adults (≥ 18 years) enrolled as bachelor or master students at a university or college in the Netherlands. Students will participate in an online survey, which is part of an epidemiological study assessing the prevalence rates of mental disorders in a college student population. This study is embedded within the WHO World Mental Health International College Student initiative (WMH-ICS). Students are invited to participate in the RCT if they: (a) experience mild to moderate depression defined as scoring above the cut-off score of 4 on the Patient health questionnaire (PHQ-9) [31] and/ or anxiety symptoms defined as scoring above the cut-off score of 4 on the Generalised Anxiety Disorder scale – 7 items (GAD – 7) [32], (b) speak Dutch or English fluently and (c) provide written informed consent before participation.

Students are excluded if they: (a) have co-morbid bipolar disorder or psychotic disorder according to the MINI International Neuropsychiatric Interview (MINI) [33], (b) experience severe depression defined as scoring above the cut-off score of 14 on the PHQ-9 and/ or anxiety symptoms defined as scoring above the cut-off score of 14 on the GAD-7 scale, (c) currently receive psychological treatment for depression and/or anxiety or have received treatment in the past 12 months and (d) have slow or no Internet connection (e.g. no broadband Internet).

Intervention

The intervention used in this study, “ICare Prevent”, is a guided web-based transdiagnostic individually-tailored intervention with mobile support and is targeted at symptoms of depression and/or anxiety. It can be used on laptops, computers, and mobile devices. This intervention has been initially developed in the German language for use in the general population and is based on adaptions of a range of evidence-based interventions [34 35]. Thus, it has been translated into Dutch and English and adapted to college student needs after a series

of focus group discussions with college students [36]. The intervention strategies have been based mainly on cognitive behavioural techniques. It uses text, homework exercises, audio-visual components, and information sheets that can be downloaded. Testimonials are used to explain homework.

The participants receive seven weekly online sessions: 1) introduction into the intervention and its technical aspects, setting goals and importance of pleasant activities, 2) tackling problems and behavioural activation, 3) psychoeducation, 4) cognitive restructuring and challenging negative thoughts, 5) choosing the most prominent complaints and accordingly for depression: problem-solving; for anxiety: exposure, 6) continuation of strategies selected from session 5, and 7) plan for the future. Four weeks after completion of the seventh sessions, participants will be invited for a booster session. The individually-tailored aspect of the intervention is applied in sessions 5 and 6. Therein, participants follow disorder-specific exercises by choosing either problem solving targeted at depressive symptoms or exposure to anxiety-provoking situations, depending on individual preference. Based on their personal needs, participants are free to choose elective modules that are integrated into sessions 2 to 7 (worry and rumination, acceptance of unfulfilled needs, relaxation, alcohol consumption as emotion regulator, self-worth, perfectionism, appreciation and gratitude and sleep hygiene). Table 1 gives an overview of the intervention.

Each session takes between 45 and 60 minutes. Participants are advised to follow one or maximum two sessions per week. Thus, the total duration of the intervention ranges from 4 to 7 weeks. The online sessions are delivered with written support given by coaches via the messaging function of the intervention platform. Participants are allowed to use the content of the intervention 24/7, as long and as often they want through the online treatment platform. In addition to the online sessions, participants have access to diaries (e.g. for tracking positive activities and monitoring sleep), mood graph, homework assignments, and the messaging system that allows participants to contact their online coach. The optional mobile app provides access to, e.g. diaries. A username and a self-generated password protect participants' access to the intervention.

=Table 1 - Intervention content =

Online treatment platform

Minddistrict is the e-health platform hosted by Minddistrict BV, which is an enterprise responsible for the provision and maintenance of the Minddistrict platform. Minddistrict provides the content management system to researchers to upload interventions/ questionnaires and to enrol participants/ e-coaches. This platform has been repeatedly used by several research projects and routine care services. Minddistrict complies with all European data safety regulations and quality standards.

Support

Trained psychology master students will deliver support to participants. The training lasts for one day and consists of three parts: (a) theory (e.g. intervention materials), (b) assignments and (c) practice. Research staff experienced in web-based interventions give the training. Coaches provide individual manualized asynchronous feedback via the messaging function of the intervention platform after the completion of each module. Moreover, coaches are available to answer additional messages about the treatment content in case they are contacted by the participants at any time point throughout the intervention. The coaches are advised to spend less than 30 minutes per individual feedback while the estimated time of feedback is 20 minutes. Thus, a coach spends in total approximately 2.5 hours per participant. A senior researcher monitors the feedback written by the coaches to ensure adherence to the treatment protocol.

Treatment as Usual

Participants in the TAU group receive information about the available regular care services in the community such as help from their general practitioner, primary and secondary mental health services from psychologists/psychiatrists. These services include mostly medications (e.g., antidepressants) and/or low intensive face-to-face psychotherapies. Students are free to decide whether they would like to seek help or not. Use of these services is recorded through self-report questionnaires at the post-treatment and follow-up assessments. This control condition has been chosen to reflect whether there is a difference between the web-based intervention and what students would normally do.

Primary outcomes

Participants who will be included in the RCT are assessed by:

Patient Health Questionnaire – 9 items (PHQ-9)

The PHQ-9 [37] is a self-report outcome measure that can be used to screen depressive symptoms. The PHQ-9 consists of 9-items. Item responses are on a 0-3 scale with total scores ranging from 0 to 27. Higher scores indicate more severe depression. PHQ-9 shows good psychometric properties with a sensitivity of .77 (.71-.84) and a specificity of .94 (.90-.97)[38]. The PHQ-9 is administered at the screening (t0), post-treatment (t2) and follow-up (t3 & t4) assessments in the intervention group.

Generalised Anxiety Disorder scale – 7 items (GAD-7)

The 7-item GAD [32] scale will be used to measure anxiety symptoms. Each of the 7 items is scored on a 0-3 scale while total score range is 0-21. Higher scores indicate more severe anxiety symptoms. The GAD-7 scale shows internal consistency with a value of Cronbach's coefficient (α) ranging from .79 to .91[39]. The GAD-7 is administered at the screening (t0), post-treatment (t2) and follow-up (t3 & t4) assessments.

Mini-International Neuropsychiatric Interview (MINI)

The diagnostic interview MINI (version 5.0) is conducted via telephone by a trained clinical psychology master student. The MINI is a short-structured interview based on the Diagnostic and Statistical Manual of Mental disorders fourth edition (DSM-IV) and the International Classification of Diseases criteria (ICD-10). The MINI is used to determine the number of participants with a current / lifetime diagnosis of Major Depressive Disorder, Panic Disorder, Agoraphobia, Social Phobia, Generalised Anxiety Disorder both at the baseline and 12-month follow-up. Moreover, during baseline the MINI will be used to estimate the number of participants with current / lifetime diagnosis of major comorbidities (Dysthymia, Suicidality, (hypo) Manic Episode, Obsessive Compulsive Disorder, Post-Traumatic Stress Disorder, Alcohol Dependence/ Abuse, Drug Dependence / Abuse, Psychotic Disorders, Anorexia Nervosa, and Bulimia Nervosa). The MINI shows good psychometric properties with good test-

retest reliability and validity [40]. The MINI is administered at baseline (t1) and 12 months follow-up (t4).

EuroQol - 5 Dimensions (EQ-5D)

Quality of life is measured with the EQ-5D [41]. The EQ-5D is a self-report questionnaire, which measures the health-related wellbeing for clinical and economic appraisal. More precisely, EQ-5D consists of five items/ dimensions: mobility, self-care, ordinary activities, discomfort, and mood state, related to anxiety or depression. Each item/ dimension consists of three categories ranging from no problems to few and finally to many problems [42]. EQ-5D construct validity is adequate, and this type of measurement can detect meaningful changes for patients with anxiety disorders. EQ-5D is generally consistent with the measure of mood state: depression/anxiety[43]. The EQ-5D is administered at baseline (t1), post-treatment (t2) and follow-up (t3 & t4) assessments.

Client satisfaction Questionnaire – 8 items (CSQ-8)

The CSQ-8[44] is used to assess client satisfaction related to the treatment. This self-report questionnaire consists of 8 items. Item responses are on a 1-4 scale with total scores ranging from 8 to 32. Higher scores of CSQ-8 indicate higher satisfaction with the treatment. The CSQ-8 shows high internal consistency with a value of Cronbach's coefficient (α) being .93 [45 46]. The CSQ-8 is administered at the post-treatment (t2)

University dropout & Educational achievement

University dropout will be monitored through self-report questions administered at post-treatment (t2) and follow-up (t3 & t4) assessments. Regarding educational achievement, the Presenteeism Scale for Students (PSS) is used to assess presenteeism [47]. The PSS is a valid and reliable measure for the college student population [47]. Moreover, the students are asked about the number of European Credit Transfer System (ECTs) achieved during a given study period. The educational achievement is measured at the baseline (t1), post-treatment (t2) and follow-up (t3 & t4) assessments.

Treatment adherence

Adherence to treatment is measured by tracking the website usage automatically. Data related to the total number of modules completed, time spent per module and number of logging into the platform are gathered.

= Table 2 - Overview of measures and assessment points =

Assessments

Table 2 presents an overview of all measures and assessment points. As mentioned above, students are recruited through an online survey, which is part of an epidemiological study. In brief, this survey consists of a broad range of short self-administered validated scales assessing mental health problems such as attention deficit hyperactivity disorder (the Adult Attention Deficit Hyperactivity Disorder Self-Report [48]), major depressive disorder, mania/ hypomania, generalized anxiety disorder, panic disorder, drug use disorder (Composite International Diagnostic Interview Screening Scales - CIDI [49]), alcohol use disorder (Alcohol Use Disorders Identification Test [50]), intermittent explosive disorder, post-traumatic stress disorder, binge-eating behavior, purging behavior, psychotic disorder (CIDI [51 52]) and suicidal thoughts and behaviours (The Self-Injurious Thoughts and Behaviours Interview [53]). Moreover, this survey assesses the self-reported quality of health, use of services for emotional or mental health problems, academic attainment and university expectations and adjustment. The e-survey will be administered at the screening (t0).

In the RCT, participants will complete online self-report questionnaires (via the Qualtrics platform) and the MINI clinical diagnostic interview, which is administered via the telephone (further details are given under Primary and Secondary outcomes). In both the intervention and control condition, participants are followed up to 12 months post-randomisation. After eligibility screening (t0), measures are administered at baseline (t1), post-treatment - 7 weeks post-randomisation (t2), six months (t3) and twelve months post-randomisation (t4). Participants are invited to complete the assessments through emails. In case a participant is not contactable on the first attempt, the research team sends up to two reminder emails within two weeks. To booster study adherence, if a participant does not respond to reminders, the research team contacts the participant via telephone. Figure 1 shows the flowchart of participants' inclusion.

Sample size calculation

The power calculation is based on a head-to-head comparison of the guided web-based transdiagnostic intervention versus treatment as usual (t-test). We have decided to calculate our sample size based on the effects of web-based interventions on depressive symptoms. We have made this choice because web-based interventions have overall higher effects on anxiety compared to depression. Thus, we anticipate a conservative estimate of Cohen's = .70 based on two recent meta-analyses on the effectiveness of psychotherapy in treating depressive symptoms in college students [54 55]. If we set the statistical power at .8 and alpha at .05, according to a two-tailed hypothesis, we need 34 participants per group to obtain a Cohen's d of .70 (total N = 68). Previous literature has shown that guided web-based interventions have a dropout rate of 28% [56]. Thus, considering the potential dropouts, the minimum sample for the RCT is 88 participants (44 participants per group).

Recruitment

Participants are recruited from Dutch universities and colleges. Recruitment for the RCT is conducted through the e-survey of the WHO WMH-ICS. Recruitment for the survey is conducted in two ways: First, we recruit participants through emails and advertisements (e.g., flyers, faculty newsletters, social media, university websites). The advertisements target all college students to inform them about the study and emphasise the importance of self-help in improving wellbeing and academic achievement. We have also created a website for this study (https://caring-universities.com), which contains information and useful links for questions. The research team sends emails to students providing information about the project and a link to the screening questionnaires. A reminder is sent to non-responders biweekly. Students can unsubscribe from the reminder emails whenever they want and their participation is voluntary. Second, study advisors, students' mentors and student ambassadors inform college students about the study.

After completing the e-survey, students eligible for the RCT are notified instantly. Those who are not eligible are sent a thank-you email for their participation in the survey. The research team approaches those who have severe symptoms of depression and/or anxiety to inform

them about the available treatment options in the community. Students who meet inclusion criteria (as described above) are informed about the RCT. Those who are interested in participating receive a more detailed information brochure about the study along with an informed consent form. After returning a signed informed consent form, students are invited by email for a telephone MINI diagnostic interview. After the diagnostic interview, students are randomised to either the web-based intervention or the TAU group. After randomisation, students are sent to a link (via email) to the online baseline questionnaires. Students who are assigned to the intervention arm are asked to create an account to follow the web-based intervention. Students in the TAU group receive information about the available regular care services in the community.

Randomisation, blinding and treatment allocation

Two independent researchers who are not involved in the study generate a random sequence using a computer random sequence generator. Randomisation takes place at an individual level, stratified by recruitment location (the Vrije Universiteit or the Universiteit van Amsterdam). Participants are randomised into two groups (web-based intervention vs TAU) with an allocation ratio of 1:1. We conduct block randomisation with randomly varied block sizes (6 to 12 allocations per block). The allocation is concealed from study's researchers since the randomisation is conducted using of a computer-generated code by an independent researcher. It is not possible to mask personnel and participants to the treatment allocation because of the nature of the intervention. However, the MINI diagnostic interview will be performed by blind interviewers with no knowledge about the allocation assignment.

Data Collection and Management

This study follows the European Union General Data Protection Regulations (GDPR). All data are driven from self-report questionnaires and are mostly collected through electronic means (Qualtrics platform). However, according to the regulations of the medical ethics committee of the VU Medical Center (VUmc), electronic informed consents are not allowed. Thus, we collect all signed informed consent forms via post. To ensure data confidentiality, participants' informed consent forms are locked in the institution allowing only authorised research staff

to have access. Electronic data are password protected in a secure environment and are accessed only by authorized personnel. The primary use of the data is anonymous.

Statistical analysis

All randomised participants will be included in all analyses according to the intention to treat (ITT) principle. Missing values will be imputed using multiple imputations. Also, we will conduct per protocol analyses including only those who completed post-treatment and follow-up assessments. All analyses will be performed using STATA version SE 13.1 [57]. The results of the M.I.N.I interview will be summarised using descriptive statistics. We will analyse the effects of the interventions on depression (PHQ-9) and anxiety severity (GAD-7) at both post-treatment and follow-up assessment using multilevel mixed models linear regression with a restricted maximum likelihood algorithm. The post-treatment depression and anxiety scores will be used as a dependent variable and trial arm condition (web-based transdiagnostic individually-tailored intervention vs TAU) as an independent variable while adjusting for baseline depression and anxiety severity. Additionally, we will calculate the effect size, Cohen's d, by subtracting the average score on primary outcome measures (PHQ-9 and GAD-7 scales) of the intervention group from the average scores of the control group at the post-treatment and dividing the results by the pooled standard deviations. To measure clinical significance, we will calculate response and symptom deterioration rates according to Reliable Change Index[58]. The reliable change will be calculated using the pre-treatment standard deviation, and the test re-test reliability coefficient of PhQ-9 (0.76)[31] and GAD-7 (0.83)[39]. Analogously, Cohen's d and clinically significant change will be calculated for follow-up assessments (6 and 12 months). Finally, at 12-month follow-up assessment, we will analyse the effects of the intervention on the current diagnosis of depression and anxiety disorders, using the data from MINI. We will use a multilevel mixed-effects logistic regression with a restricted maximum likelihood algorithm. The current diagnosis of depression or anxiety disorders will be used as a dependent variable and trial arm condition as independent while adjusting for baseline depression and anxiety severity.

Patient and Public Involvement

Student representatives and college/university stakeholders (e.g., student psychological counsellors, study advisors, deans of education, deans of the faculties, and the university

executive board members, etc.) were involved in various stages of the development of the intervention and the trial. Before the development of the protocol, the research team had several discussions with student representatives and university stakeholders regarding their views about this study. These discussions aimed at gaining a better understanding of the end-users and stakeholders' perspective, needs and preferences to inform the development of the study procedures. Moreover, we performed several focus group discussions to tailor the intervention to the college/ university student context. Finally, student representatives participated in brainstorming discussions regarding the design of the best recruitment strategy.

Possible harms

According to previous literature, internet-based interventions lead to lower symptom deterioration rates compared to controls. [59 60] Moreover, in this study participants are college students with mild to moderate symptoms of depression and/ or anxiety. This population has a high degree of functioning (e.g., attending university) and is unlikely to enter the general medical healthcare system. Nevertheless, psychological intervention might lead to unwanted outcomes. For instance, it is possible that the students experience suicidal ideation. If we detect a student who is at high suicidal risk, a specific protocol is followed: the e-coach calls the student to assess the risk by asking a series of questions. Afterwards, the e-coach contacts an experienced psychiatrist, who is involved in the study, to discuss the situation. If needed, the psychiatrist contacts the participant to advise him/ her to seek help from his/her General Practitioner (GP) or the student counselling services. The research team checks if the student sought help after a couple of days. Moreover, if the student permits us to use the contact details of his/ her GP, the research team notifies the GP to ensure that the student will get help timely.

Adverse events (e.g., increase suicidal risk, hospital admission, clinically significant symptom deterioration, study and treatment dropout rates) will be monitored and recorded throughout the trial. All adverse events will be reported per group in the outcomes of the present study.

Premature termination of the study

The research team will decide to terminate the ongoing trial in case of serious adverse events (e.g., suicide), which is directly related to the study procedures. The principal investigator (PC) will prompt the discontinuation of the trial and will inform the medical ethics committee immediately. All participants will be informed about the study termination and the reason that led to this decision. Moreover, participants will receive information about available mental health care services options

Ethics and dissemination

Research Ethics Approval, Amendments & Consent

The Medical Ethics Committee of the VUmc has approved the protocol (registration number 2016.583 & A2017.362) and all amendments will be notified this committee. The study will be conducted following the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). A signed informed consent form will be requested from all eligible subjects before participation. The Medical Ethics Committee of the VUmc monitors the progress and procedures of the trial.

Discussion

Early management of depression and anxiety may improve symptoms, increase academic performance and prevent college dropout. The present protocol describes the procedures of a randomised controlled trial conducted in Dutch universities and colleges. This study aims at examining the effects of a guided transdiagnostic individually-tailored web-based intervention in reducing symptoms of depression and/ or anxiety in college student population. It is expected that the examined intervention will outperform treatment as usual in treating college students with depression and/ or anxiety.

So far, only a few trials have examined the effectiveness of web-based transdiagnostic and individually-tailored interventions in college students. The outcomes of these trials were mixed and thus, inconclusive [10]. Moreover, to our knowledge, previous studies on college students' mental health have mostly focused on one disorder. Given that depression and

anxiety are highly comorbid [61-63], it is essential to test approaches with transdiagnostic components targeted at symptoms of both depression and anxiety. The present study aims at improving existing knowledge on the effectiveness of web-based interventions in college students suffering from depression and/or anxiety by employing a transdiagnostic and individually-tailored therapeutic approach. This study targets both Dutch and international students, thereby increasing the generalizability of our findings to different cultural backgrounds.

Nevertheless, several limitations should be expected. First, the power calculation has been based on our primary aim to examine the effectiveness of the web-based transdiagnostic individually-tailored intervention in reducing symptoms of depression and/or anxiety. Therefore, the study is underpowered to examine secondary moderator analyses, which usually require larger sample sizes. If possible, we will recruit a larger number of participants to achieve sufficient power for the secondary outcomes such as college dropout, as well as the planned moderator analysis. Second, although the intervention is delivered with therapeutic guidance, retaining students in the intervention might be a challenge. However, dropout has been considered in sample size calculation and thus, we expect that it will not influence the statistical power of our sample. Third, we cannot measure educational achievement using academic records due to ethical restrictions. Information on educational attainment will be self-reported and thus, may be less objective.

Overall, the results of this study will provide valuable information about the effectiveness of web-based interventions in improving college students' mental health and may lead to the development of the infrastructure for screening and treating mental disorders within universities.

Trial Status

The trial has started in March 2018 and is expected to be completed in August 2019.

Abbreviations

CIDI: Composite International Diagnostic Interview Screening Scales

CSQ: Client Satisfaction Questionnaire

ECTs: European Credit Transfer System

EQ-5D: EuroQol 5 Dimensions

GAD-7: Generalised Anxiety Disorder – 7 item scale

GPA: Grade Point Average

iCBT: Web-based Cognitive Behavioural Therapy

MINI: Mini International Neuropsychiatric Interview

PHQ-9: Patient Health Questionnaire – 9 item scale

PSS: Presenteeism Scale for Students

RCT: Randomised Controlled Trial

TAU: Treatment As Usual

WMH – ICS: World Mental Health Surveys International College Students Initiative

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Availability of data and materials

Not applicable

Trial Sponsor

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Role: overall responsibility for the initiation and management of the trial,

Author contributions

PC (PI), HR and RW obtained funding for this study. All authors contributed to the design of the study. EK drafted the manuscript and coordinated the recruitment of students and the data-collection at VU. AK coordinates the recruitment of students and the data-collection at UvA. RW, HR, LW, AK, EB, SB, FB, NB, CH, PV, AK, LK, DE, RB, RCK, RA, and PC were involved in revising the manuscript critically for intellectual content. All authors read and approved the final manuscript.

Consent of publication

Not applicable

Competing interests

None

Data access

Data can be accessed only after concluding a data sharing agreement in accordance with the European regulation about general data protection.

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Table 1, Intervention content

Main Intervention	
Session	Content
1. Introduction	Goal setting and importance of pleasant activities
2. Tackling problems	Identification of problems and problem solving based on behavioural activation
3. Psychoeducation	Psychoeducation focusing either on depression or anxiety depending on individual needs
4. Cognitive restructuring	Development of functional positive thinking after identifying the relationship between thoughts, wellbeing and practising strategies
5. Choosing most prominent complaints	Problem solving targeted at either depression or exposure to anxiety provoking stimuli depending on individual needs
6. Deepening of skills chosen in session 5	Problem solving and exposure in daily life
7. Plan for the future	Reflection on goal attainment and learning experiences. Implementation of intentions until the booster session
8. Booster session (4 weeks after the completions of the 7th session)	Reflection on goal attainment and learning experiences. Implementation of intentions during the upcoming months
Elective modules	
i. Worry and rumination	Information on worry and rumination, using a worry-diary and other techniques to challenge such thoughts
ii. Acceptance of unfulfilled needs	Attending to unfulfilled needs and unsolvable problems and learning to accept them
iii. Relaxation	Exercise on progressive muscle relaxation

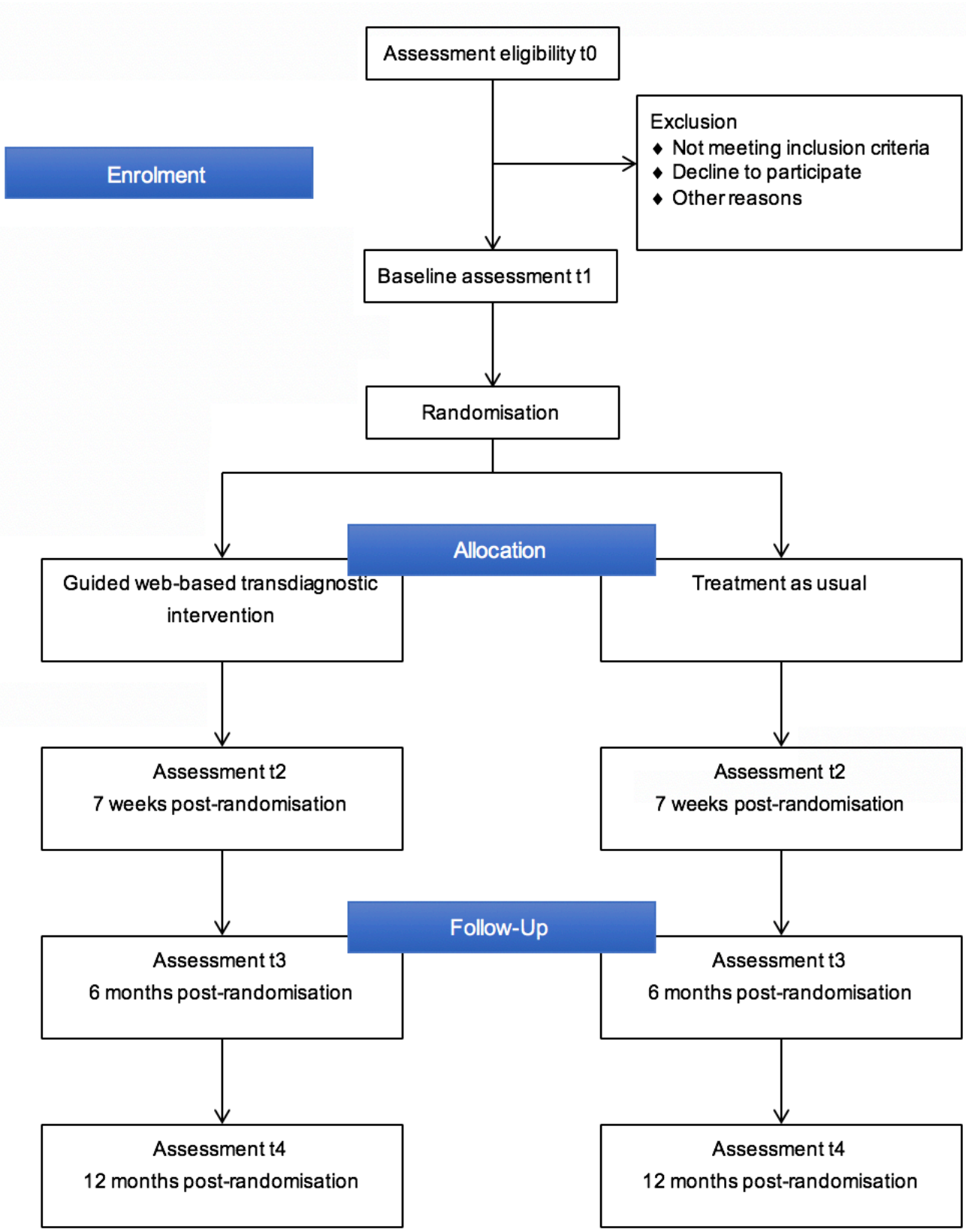
iv.	Alcohol consumption as emotion regulator	Information on the relationship between mood and alcohol, self-assessment of consumption and techniques to decrease it
v.	Self-worth	Information on the effects of low or instable self-worth and exercises to increase it
vi.	Perfectionism	Identifying personal high standards and learning techniques to exit from a vicious circle
vii.	Appreciation and gratitude	Learning how to express gratitude and how to consciously appreciate positive things in daily life
viii.	Sleep Hygiene	Sleep-limitation technique (i.e. by initially limiting sleep being able to ultimately sleep better)

Table 2. Overview of measures and assessment points

Measure (Instrument)	Assessment points				
	t0	t1	t2	t3	t4
Socio - Demographics (e-survey)	X				
DSM-IV Axis I and II disorders (e-survey)	X				
Daily functioning (e-survey)	X				
Personality traits (e-survey)	X				
Clinical measures (e-survey)	X				
Suicide plan and/or suicide attempt(s) (e-survey)	X				
Childhood maltreatment, domestic violence (e-survey)	X				
Academic experiences and functioning, participation in athletic and extra-curricular activities (e-survey)	X				
Information about lifetime and 12-month use of mental health care services (e-survey)	X				
Depressive symptoms (PHQ-9)	X		X	X	X
Anxiety symptoms (GAD-7)	X		X	X	X
The MINI International Neuropsychiatric Interview (MINI)		X			X
Quality of life (EQ-5D)		X	X	X	X
Satisfaction with treatment (CSQ-8)			X		
Presenteeism (PSS)		X	X	X	X
Educational Achievement		X	X	X	X
Study Dropout			X	X	X
Use of regular care			X	X	X

Note: t0: screening (total cohort); t1: baseline (RCT); t2: post-treatment (RCT); t3: 6 months post-randomisation (RCT); t4: 12 months post-randomisation (RCT); t5: 12 months after t0 (total cohort); t6: 24 months after t0 (total cohort)

Figure 1. Flow chart of the participants' inclusion process


Assessment eligibility t0
Exclusion
♦ Not meeting inclusion criteria
♦ Decline to participate
♦ Other reasons
Enrolment
Baseline assessment t1
Randomisation
Allocation
Guided web-based transdiagnostic intervention
Treatment as usual
Assessment t2
7 weeks post-randomisation
Assessment t2
7 weeks post-randomisation
Follow-Up
Assessment t3
6 months post-randomisation
Assessment t3
6 months post-randomisation
Assessment t4
12 months post-randomisation
Assessment t4
12 months post-randomisation

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	18
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1 & 18
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	18

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	9
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8

Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7-9
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Flow chart & p.12
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12-13
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	13-14
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14-15
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found,	14

		if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15-16
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	16
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	16
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13-14
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	19

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Submitted to the journal
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A