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Personalised app-based relapse prevention of depressive and anxiety disorders in remitted adolescents and young adults: a protocol of the StayFine RCT

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ABSTRACT

Introduction Youth in remission of depression or anxiety have high risks of relapse. Relapse prevention interventions may prevent chronicity. Aim of the study is therefore to (1) examine efficacy of the personalised StayFine app for remitted youth and (2) identify high-risk groups for relapse and resilience.

Method and analysis In this Dutch single-blind parallel-group randomised controlled trial, efficacy of app-based monitoring combined with guided app-based personalised StayFine intervention modules is assessed compared with monitoring only. In both conditions, care as usual is allowed. StayFine modules plus monitoring is hypothesised to be superior to monitoring only in preventing relapse over 36 months. Participants (N=254) are 13–21 years and in remission of depression or anxiety for >2 months. Randomisation (1:1) is stratified by previous treatment (no treatment vs treatment) and previous episodes (1, 2 or >3 episodes). Assessments include diagnostic interviews, online questionnaires and monitoring (ecological momentary assessment with optional wearable) after 0, 4, 12, 24 and 36 months. The StayFine modules are guided by certified experts by experience and based on preventive cognitive therapy and ingredients of cognitive behavioural therapy. Personalisation is based on shared decision-making informed by baseline assessments and individual symptom networks. Time to relapse (primary outcome) is assessed by the Kiddie Schedule for Affective Disorders and Schizophrenia-lifetime version diagnostic interview. Intention-to-treat survival analyses will be used to examine the data. Secondary outcomes are symptoms of depression and anxiety, number and duration of relapses, global functioning, and quality of life. Mediators and moderators will be explored. Exploratory endpoints are monitoring and wearable outcomes.

Ethics, funding and dissemination The study was approved by METC Utrecht and is funded by the Netherlands Organisation for Health Research and Development (636310007). Results will be submitted to peer-reviewed scientific journals and presented at (inter) national conferences.

Trial registration number NCT05551468; NL8237.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This marks the first study examiningrelapse prevention intervention efficacy for remitted youth, personalised based on shared decision-making, baseline diagnostic interviews, online questionnaires and individual symptom networks.
⇒ The relatively long follow-up of 36 months in this study is rare in randomised controlled trials of remitted youth.
⇒ Data collection in this study is multifaceted through self-report, semistructural interviewing and physiological measurements.
⇒ Time to relapse (primary outcome) is measured using a semistructured diagnostic interview conducted by a researcher blinded to randomisation group.
⇒ The study is single blinded, because participants are aware of their allocation to the intervention or control group.

INTRODUCTION

Depressive and anxiety disorders mostly emerge in adolescence,[1–5] are associated with functional impairment in current[6–8] as well as lifelong functioning[9–11] and have a substantial risk of relapse or recurrence.[12–16] After fully conquering a first episode of major depressive disorder in adolescence, risk of relapse increases dramatically from 20% to 60% over 1–2 years, up to 70% over 5 years.[17] Over a mean of 11 months, 8% of youth treated for anxiety disorders experienced a relapse of the primary anxiety disorder[18] and 48% over 4 years.[19] Over 7.4 years follow-up, 23–33% of treated individuals develop another disorder like depressive disorder.[20] Early onset and high risk of relapse call for interventions for remitted youth that prevent relapse and lower burden of disease including, the psychosocial consequences of these most common mental disorders.[2 6 11 21 22]

There are differences between definitions for remission, recovery, relapse and recurrence between depressive and anxiety disorders. Remission and recovery are clearly defined for depressive disorders with remission being a 2-month period or longer in which symptoms have largely normalised after meeting the criteria for a depressive disorder.[21 23 24] Recovery is defined as being in remission for a longer period (6–12 months) and signifies the end of an episode.[21 23] Regarding anxiety disorders, there is less consensus,[25–28] relapse being return of symptomatology following remission and recurrence being the onset of a new episode following recovery.[21 23] For ease of communication and unification of disorder differences we define remission, ingdenoting both remission and recovery, as no longer meeting the criteria for any depressive or anxiety disorder for at least 2 months after initially meeting the criteria for at least one depressive or anxiety disorder. Relapse, denoting both relapse and recurrence, is violation of the remission definition following remission.

Commonly used relapse prevention interventions are continuation or maintenance of antidepressant medication (ADM)[16 29–32] and psychological interventions as stand-alone or add-on to ADM continuation starting after remission.[21 33–39] Interestingly, individuals have a threefold preference for psychological interventions over ADM.[40] Meta-analyses show these psychological interventions to be a satisfactory alternative to ADM continuation in adults remitted from depressive disorders.[35 41] Effective psychological relapse prevention interventions for adults in remission of depressive disorders are mindfulness-based cognitive therapy,[42–46] well-being therapy,[47–49] continued cognitive therapy[50–52] and preventive cognitive therapy (PCT).[53–58] For anxiety disorders, the effectiveness of psychological interventions as started after remission is not yet established.[2 59 60]

In youth, scarcity of research examining relapse prevention interventions exists. A meta-analysis of only 33 ADM studies (N=164), found limited evidence that continuation ADM reduces the risk of depression relapse compared with pill placebo.[61] The few randomised controlled trial (RCTs) that examined psychological depression relapse prevention interventions in youth[62–67] include relapse prevention cognitive behavioural therapy (CBT),[68] rumination-focused CBT,[63 64] cognitive behavioural prevention[62 69] and online (relapse) prevention intervention.[66 70] To the authors' knowledge, only one study examined relapse prevention for anxiety disorders in youth, which concerns a case study describing continuation CBT for a 9 year old.[71] This CBT included psychoeducation, repetition of exercises and coping skills and making a personalised relapse prevention book with strategies to prevent relapse.

Aim of the current study is to examine the efficacy of the personalised StayFine intervention app for remitted youth including five optional modules. The intervention is app based, due to youth having easy access to smartphones, app-based psychological interventions i reducing symptoms of (mild) depressive and anxiety disorders based on systematic reviews,[72–74] and app-based interventions reducing and bypassing stigma[75] while at the same time promoting self-care and autonomy.[76 77]

The StayFine intervention app consists of two parts: (1) app-based monitoring (SF-MON) and ((2) guided app-based personalised intervention modules (SF-GAPI modules). SF-MON is used for daily ecological momentary assessments (EMA) of affect, thoughts and social company for 2 weeks. It is combined with an optional wearable to measure activity and diurnal patterns.

The SF-GAPI modules are designed as a 3-month intervention to prevent relapse of depressive and anxiety disorders in youth. These have four important features. First, the combination of modules is personalised based on individual symptom networks[78 79] and a 'psychological passport' including assessment of the previous mental health condition and baseline assessment of psychological characteristics (such as sleep, affect and flourishing). Second, they are based on a relapse prevention interventions, that is, PCT[53–58] and CBT-ingredients adapted for the relapse prevention phase[68 71 80–83] to target underlying mechanisms (rigid beliefs, negative attribution style, avoidance, low behavioural activity, low positive affect, sleep problems and low wellness) as possible working mechanisms to reduce the risk of, and extend time to relapse. Third, they do not require face-to-face therapist contact. Lastly, they are guided by a certified expert by experience to reduce stigma,[84] promote empowerment, hope and self-efficacy beliefs,[85] and improve adherence rates compared with unguided apps.[74]

Four out of eight SF-GAPI modules are based on a well-established PCT intervention, which demonstrated long-term preventive effects up to 10 years in adults in remission of depressive disorders.[53–58] In PCT individuals receive psychoeducation, evaluate rigid beliefs with help of imagination techniques and phantasy,[86] enhance the autobiographical memory of positive affect and memories using a positive diary and affect labelling and develop a personalised relapse prevention strategy.[87] Four other modules (sleep, activation, exposure and wellness) are based on cognitive behavioural therapy adapted for relapse prevention (see online supplemental file 1).

For personalisation of the SF-GAPI modules, among other data, individual symptom networks based on SF-MON are used. Symptom networks allow for better tailoring of interventions (as opposed to disorder-specific interventions) accounting for diverse symptom profiles that qualify for either depressive or anxiety disorders,[24 88 88] the high comorbidity between both (45%)[89] and multifactorial etiologies.[90] Previously, EMAs of mental functioning have been effectively used to personalise interventions for both adults with depressive and anxiety disorders (generalised anxiety disorder).[91] In lack of a current gold standard for individual symptoms networks in behavioural research,[92] personalisation is performed using an aggregation of different sources of data (see online supplemental file 2).

Study objectives

The objective of the current study is to examine the efficacy of SF-MON combined with SF-GAPI modules added to care as usual (CAU) in youth in remission of depressive or anxiety disorder(s). We hypothesise SF-MON+SF GAPI modules+CAU to be superior to SF-MON+CAU in preventing relapse over 36-month follow-up. Primary outcome is time to relapse based on a semistructured diagnostic interview. Secondary outcomes are symptoms of depressive and anxiety disorders, number of relapses, duration of relapse in days, global functioning and quality of life. In additiony, core depressive and anxiety symptoms, dysfunctional attitudes, affect, behavioural activation, sleep, stress, coping, experiential avoidance, flourishing, support, negative life events, usability and satisfaction will be examined as potential mediators to explore the working mechanisms of the modules. Furthermore, potential moderators, such as age, previous disorder and number of previous episodes, will be assessed to explore their association with sustained remission or relapse. Lastly, exploratory endpoints are daily means, fluctuations and inertia of affect, thoughts and social company, and physical activity and diurnal patterns based on the SF-MON and optional wearable.

METHODS

Trial design

This parallel-group, single-blind RCT, assesses the efficacy of SF-MON+SF GAPI modules compared with SF-MON, both added to CAU on time to relapse over 36 months (primary outcome) as assessed by a semistructured diagnostic interview: the Kiddie Schedule for Affective Disorders and Schizophrenia-lifetime version (K-SADS-PL DSM-5).[93] Participants are assessed at baseline (T0), after 4 months (T1, postintervention), 12 months (T2), 24 months (T3) and 36 months (T4) with this semistructured diagnostic interview, online self-report questionnaires and a 2-week period with SF-MON including optional use of a wearable. In addition, a four-item online questionnaire (Patient Health Questionnaire, PHQ-4)[94] for core symptoms of depressive and anxiety disorders is administered regularly for relapse detection. This study adheres to the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT)and Consolidated Standards of Reporting Trials (CONSORT) for designing and reporting on parallel-group randomised trial (protocols, see online supplemental file 3).[95 96] Table 1 depicts a schematic overview of assessments and use of the StayFine app per participant. Figure 1 shows the study flow.

Participants

Inclusion and exclusion criteria

Eligible participants are 13–21 years (N=254) and in remission of a depressive or anxiety disorders based on the K-SADS-PL DSM-5 diagnostic interview.[93 97] As previously described, we define remission as no longer meeting the criteria for any DSM-5 depressive or anxiety disorder for at least 2 months, after initially meeting the criteria for at least one DSM-5 depressive or anxiety disorder. Residual symptoms are allowed. Inclusion is open for all Dutch-speaking youth residing in the Netherlands, unrestricted to a specific organisation or previous treatment.

Exclusion criteria are, as assessed by the K-SADS-PL DSM-5, current alcohol or drug misuse, bipolar disorder, previous (hypo)mania, previous and/or current psychotic episode(s), being in remission only from post-traumatic stress disorder or obsessive–compulsive disorder or being in remission from an ineligible depressive or anxiety disorder (table 2.).Alcohol or drug use, as opposed to misuse, is not considered an exclusion criterion. Lastly, we exclude individuals currently receiving ongoing treatment (pharmacological or psychological) for anxiety or depression for more than twice per month by a psychologist, psychiatrist or other professional in an institution for mental health.

Care as usual

CAU for remitted youth represents care in daily clinical practice, its diversity including continuation of ADM, psychotherapy or—as is common in remitted individuals—no care at all. Ongoing treatment (pharmacological or psychological) that individuals currently receive for anxiety or depression may not be offered more than twice per month by a psychologist, psychiatrist or other professional in an institution for mental health. CAU is monitored throughout the study, including type and dosage of ADM, as this could have an effect on study outcome. CAU will be examined as potential confounder in the analyses.

In the trial registration, we described the primary and secondary outcomes as well as outlines of the study before inclusion of the first participant. After trial registry, we were confronted with practical issues that have led to some changes. First, the previously determined classification instrument (SCID) was changed into the K-SADS-PL DSM-5, becoming available shortly after preregistration and not requiring both child and adult versions to measure disorders between the ages encountered in the study (13–24). Every diagnosis in this study has been and will be made using this new instrument. Second, the trial registry states ‘ongoing current treatment (more than twice a month) for a mental health disorder other than the disorders listed under the inclusion criteria’ makes a participant ineligible. This should be—according to CAU for anxiety and depressive disorders—‘ongoing current treatment (more than twice a month) for a mental health disorder including those listed under the inclusion criteria’. Lastly, the DSM-5 diagnosis other specified depressive disorder, similar to other specified anxiety disorder, should be under exclusion criteria instead of inclusion criteria.

Recruitment, setting and eligibility assessment

Potential participants are informed about StayFine via (social) media, websites, schools and colleges, patient

Table 1 Schematic overview of measurements and StayFine app use per participant

		T0				T1						T2								T3								T4
Measure	**Description month**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**–**	**9**	**–**	**12**	**–**	**15**	**–**	**18**	**–**	**21**	**–**	**24**	**–**	**27**	**–**	**30**	**–**	**33**	**–**	**36**
PHQ-4	Core symptoms	x	x		x			x		x		x		x		x		x		x		x		x		x		x
K-SADS-PL DSM-5	Diagnostic interview	x				x						x								x								x
BDI-NL	Depressive symptoms	x				x						x								x								x
RCADS (adapted)	Anxiety symptoms	x				x						x								x								x
DAS-17	Dysfunctional attitudes	x				x						x								x								x
EQ-5D-Y	Quality of life	x				x						x								x								x
PANAS-NL	Affect	x				x						x								x								x
BADS-SF	Behavioural activation	x				x						x								x								x
SRSQ	Sleep	x				x						x								x								x
PSS-10	Stress	x				x						x								x								x
UCL	Coping	x				x						x								x								x
BEAQ	Experiential avoidance	x				x						x								x								x
MHC-SF	Flourishing	x				x						x								x								x
MSPSS-N	Support	x				x						x								x								x
Open end question	Negative life event					x						x								x								x
SUS	Usability					x						x								x								x
SSS*	Satisfaction					x																						
SF-MON	Affect, activities, social company	x				x						x								x								x
Wearable	Activity and diurnal pattern	x				x						x								x								x
SF-GAPI modules*	Guided app-based personalised intervention modules		x	x	x																							

*Only for participants in the SF-MON+SF-GAPI+CAU group.
BADS-SF, Behavioural Activation for Depression Scale Short Form; BDI-NL, Beck Depression Inventory-NL; BEAQ, Brief Experiential Avoidance Questionnaire; CAU, care as usual; DAS-17, Dysfunctional Attitude Scale; EQ-5D, EuroQol Questionnaire five dimensions; K-SADS-PL DSM-5, Kiddie Schedule for Affective Disorders and Schizophrenia – lifetime version; MHC-SF, mental health Continuum-Short Form; MSPSS-N, Multidimensional Scale of Perceived Social Support; PANAS-NL, Positive and Negative Affect; PHQ-4, Patient Health Questionnaire 4; PSS-10, perceived stress scale; RCADS, Revised Children's Anxiety and Depression Scale; SF-GAPI, guided app-based personalised intervention modules; SF-MON, app-based monitoring; SRSQ, Sleep Reduction Screening Questionnaire; SSS, service satisfaction scale; SUS, system usability scale; T0, study entry; T1, post-relapse prevention intervention; T2, 12 months follow-up; T3, 24 month follow-up; T4, 36 month follow-up; UCL, Utrechtse Coping Lijst.

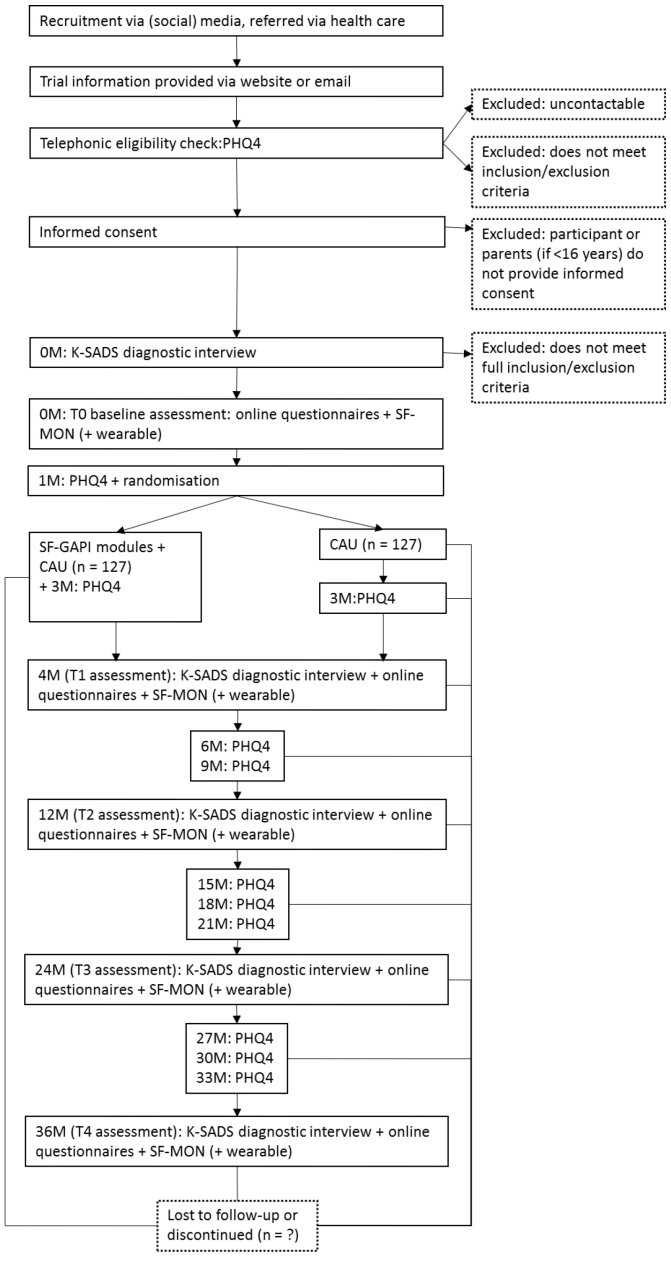

Figure 1 Flow of participants in the StayFine study. CAU, care as usual; K-SADS, Kiddie Schedule for Affective Disorders and Schizophrenia; PHQ-4, Patient Health Questionnaire-4; SF-GAPI, guided app-based personalised intervention modules.

organisations and national mental health platforms. Individuals can request more information via contact-form on the website, email or through professionals. A subsequent 15 min call provides verbal information and assesses eligibility using a standardised form (table 3). Eligible participants (and parents of eligible participants if under 16 years) are provided with written information about the study via email and are contacted for written and verbal informed consent after 2 weeks (see online supplemental file 4) for informed consent materials). The diagnostic interview allows for a final check of eligibility at T0, during which the items posed in table 3 are explored in more elaborate detail. All assessments occur online, eliminating the need to visit research centres.

Sample size

The current study was powered to detect a difference in relative risk-reduction (HR=0.60) of 40% between randomisation groups, with 80% power and a two-sided 5% alpha level, assuming the relapse rate for depressive and anxiety disorders is 60% (50%–70%) over 3 years. Taking into account a 20% attrition rate, this resulted in a required total sample size of 254 (with 80%*254=203.2, thus resulting in 101 participants per condition) to detect a clinically relevant effect between randomisation groups to reduce the relative risk on relapse/recurrence of 40% in favour of the intervention group during the follow-up period, based on previous studies in adolescents[19 20 98–100] and adults[37 101] comparing similar groups.

Randomisation and blinding

Randomisation (1:1) occurs after completion of the T0 assessment in Castor Electronic Data Capture (EDC)[102] using variable block randomisation (6, 8 or 10). Randomisation is stratified (2*3) by previous treatment (no treatment vs treatment) and number of previous episodes (1, 2 or >3 episodes). Treatment is defined as guidance by a general practitioner or treatment provided by a psychologist or psychiatrist in (specialised) mental healthcare. An independent colleague not involved in the study has access to Castor EDC[102] solely to randomise participants. Researchers share treatment allocation with each participant via email. Interviewers performing diagnostic interviews are blinded to randomisation allocation.

Table 2 Eligible and ineligible anxiety and depressive disorders

Eligible/ineligible	Type
Depressive disorders eligible	Major depressive, persistent depressive, disruptive mood dysregulation disorder.
Anxiety disorders eligible	Separation-, social or generalised anxiety disorder, specific phobia, panic disorder, agoraphobia.
Depressive disorders ineligible	Premenstrual dysphoric disorder, depressive disorder due to another medical condition, substance/medication-induced depressive disorder, other specified depressive disorder, unspecified depressive disorder.
Anxiety disorders ineligible	Selective mutism, substance/medication-induced anxiety disorder or anxiety disorder due to another medical condition, other specified anxiety disorder, unspecified anxiety disorder.

Table 3 Items of eligibility check

Question	Answer option eligible	Answer option illegible
Date eligibility check	dd-mm-yyyy	n.a.
Age (years)	13–21 years	<13 years or >21 years
Age (months)	0–11 months	n.a.
Currently receiving treatment	No, yes for depressive, anxiety disorders or another psychological problem	n.a.
Frequency of current professional treatment for depression or anxiety*	≤2 times per month	3 or more times per month
Past-treatment	Yes, no.	n.a.
Formulated a relapse prevention plan in the past	Yes, no.	n.a.
Current medication use	Yes, no.	n.a.
Number of days of current non-episode (feeling okay or good for at least half of the time))†	≥ 60 days before date of eligibility check	59 days or less before the eligibility check
Previous depressive, or anxiety disorder or complaints?	Yes, but I do not know which disorder; yes, I know which disorder	No, I did not have a disorder or complaints
Previous disorder(s)?	See inclusion/exclusion criteria	See inclusion/exclusion criteria
Previous other mental disorders or complaints?	See inclusion/exclusion criteria	See inclusion/exclusion criteria
Difficulty understanding Dutch language?	No	Yes
Current participation in another scientific mental health study?‡	No	Yes
Do you have daily access to a smartphone?		
PHQ-4: 4-item questionnaire for depressive and anxiety core symptoms§	Score on both subscales <3	A score of >3 on one or both subscale of depressive or anxiety symptoms

*Treatment frequency can change over time.
†Feeling good for more than half of the time for at least 2 months is used as precursor for at least 2 months of remission.
‡Participation in other mental health scientific research usually involves multiple assessments in-between assessments of the current study. This could interfere with the effect of the intervention. Therefore, potential participants are asked to check when the last assessment of the other study is performed and to contact StayFine to discuss eligibility.
§A subscale score of three or higher on the PHQ-4 is considered elevated, not resembling remission.
PHQ-4, Patient Health Questionnaire-4.

Participants are asked not to share their allocation before and during diagnostic interviews. To assess whether the blinding procedure is successful, interviewers guess the condition group postinterview at T1–4 assessments. Unblinding is permissible only in case of an SAE (eg, resulting in death).

Withdrawal and non-adherence

Participants who relapse are allowed and encouraged to continue in the study. Participants who drop out of the SF-GAPI modules or assessments are not replaced. Disclosed reasons for withdrawal, non-adherence or loss to follow-up are reported.

Relapse prevention interventions

SF-MON

All participants, regardless of randomisation, receive app-based monitoring with optional wearable (SF-MON) as part of the T0–4 assessments. SF-MON includes a 16-item questionnaire about affect, thoughts and social company, administered six times a day for 2 weeks. Example items are: 'on a scale of 0 (totally disagree) to 100 (totally agree), how (1) anxious, (2) energetic, (3) tired, (4) relaxed, do you feel at the moment?'. Prior to starting, an instruction regarding the SF-MON is provided by phone. Reminders are set at personalised times (typically between 8.00 and 22.00 hours and 2–3 hours apart), and electronic positive feedback about monitoring completion is provided during each assessment promoting adherence.

Use of a wearable, Axivity AX3,[103] is advised, but optional. The wearable continuously measures acceleration (ie, movement, vibration and orientation changes in all 3-axes (x,y,z),converted to score physical activity), diurnal patterns and sleep data. The wearable and instructions for use are sent through package delivery prior to starting each monitoring, to be returned via return envelope afterwards. Sensitivity analyses postdata collection

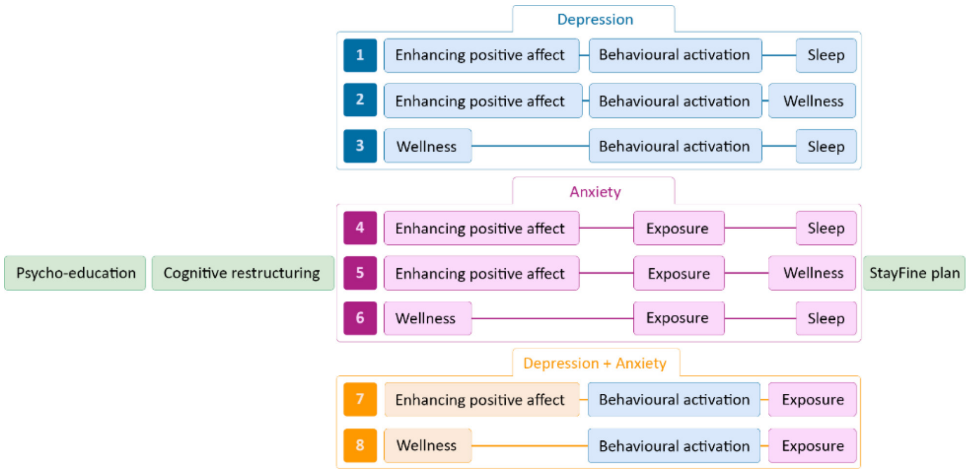

Figure 2 Combination of modules.

will show whether wearing the AX3 itself had an effect on other measurement outcomes.

The regular assessments and use of the wearable are considered to be additional to CAU as they could in itself have an effect on relapse.

SF-GAPI modules

Participants randomised to the experimental group receive SF-GAPI modules over the course of 3 months. There are eight advised combinations that include six out of eight modules (figure 2). All participants start with psychoeducation, followed by cognitive restructuring to evaluate rigid beliefs. Then, depending on the personalisation, participants continue with a combination of: enhancing positive affect, behavioural activation, exposure, sleep and Wellness. All participants conclude with the StayFine plan in which a personalised relapse prevention plan is made. Online supplemental file 1 provides a more detailed description of the modules and online supplemental file 2 provides a description of the personalisation procedure.

Measurements

Assessments with a semistructured diagnostic interview, online self-report questionnaires and SF-MON occur at baseline (T0), after 4 months (T1, postintervention), 12 months (T2), 24 months (T3) and 36 months (T4). Researchers and research assistants with at least a bachelor's degree in psychology or similar major are trained in administering the diagnostic interview. The training comprises of DSM-5 disorder theory, role playing in pairs and in front of the group, discussion about scoring, use of a timeline to map (duration of) episodes and supervision of at least two interviews. Inter-rater reliability will be established.

The PHQ-4 questionnaire is administered online after completion of the baseline SF-MON and 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33 and 36 months after the baseline diagnostic interview to monitor core symptoms of depressive and anxiety disorders throughout the study. All serious adverse events (SAE) reported spontaneously by the subject or observed by researchers are recorded, together with those reported through the online questionnaires and semistructural interviews.

Relapse detection: stepped detection by PHQ-4, BDI, Revised Children's Anxiety and Depression Scale and K-SADS

A score of 3 or higher on the depression or anxiety subscale of the PHQ-4 is used as cut-off score to initiate further testing for relapse.[94 104] The PHQ-4 is repeated approximately 7 days after the first, to monitor symptom levels. A repeated subscale score >3 is followed by the Beck Depression Inventory (BDI) and the Revised Children's Anxiety and Depression Scale (RCADS). An elevated score (ie, BDI>14 or BDI item 9 (suicidality) >2 or RCADS>30 (women) or RCADS >21 (men)) means the participant is contacted within 48 hours to plan a diagnostic interview (K-SADS) to assess depressive and anxiety disorders. If a current disorder is detected, the participant is advised to contact the general practitioner or previous therapist to discuss treatment options. A licensed psychologist of the research team is contacted as soon as possible in case of any signs of acute suicidality (eg, ongoing thoughts or plans) or other severe psychiatric symptoms (eg, psychotic thoughts or behaviours).

Primary outcome

Time to relapse of a DSM-5 depressive or anxiety disorder over 36 months is the primary outcome as assessed by a diagnostic interview (K-SADS-PL DSM-5).[93] Each classification of depressive and anxiety disorders is dichotomously coded.

Secondary outcomes

Secondary outcomes are: number of relapses (based on K-SADS), duration of relapse in days (based on K-SADS), global functioning (Global Assessment of Functioning Scale),[105] depressive symptoms (BDI-NL),[106 107] anxiety symptoms (RCADS; 31 item-version with anxiety items only)[108 109] and quality of life (Dutch version of the EuroQol Questionnaire five dimensions).[110 111]

Other parameters

Potential moderators are age, ethnicity, education level, living situation, previous episodes, previous care, comorbidity, SAEs and negative life events. Potential mediators are core symptoms of depressive and anxiety disorders (PHQ-4),[94] affect (Positive and Negative Affect),[112 113] dysfunctional beliefs (Dysfunctional Attitude Scale),[114] behavioural activation (Behavioural Activation for Depression Scale Short Form),[115 116] coping (UCL),[117] sleep (SRSQ),[118] stress (perceived stress scale),[119 120] experiential avoidance (Brief Experiential Avoidance Questionnaire),[121] flourishing (mental health Continuum-Short Form),[122] support (Multidimensional Scale of Perceived Social Support)[123] and usability (SUS).[124 125] In addition, app-based data on usage will be explored. Exploratory endpoints are daily means, fluctuations and inertia of affect, thoughts, and social company (SF-MON) and wearable-based activity and diurnal patters (Axivity AX3)[103] during T0–4. These can possibly be predictors or mediators of the intervention effect and are stand-alone exploratory outcomes as well.

Satisfaction with the SF-GAPI modules is assessed using an online questionnaire (SSS)[126] and three questions at the end of each module: ((1) 'how new is the content of this module for you?', (2) 'how often do you use the information and exercises' and (3) 'we are interested in your feedback. Please describe what you think of the module'.

Statistical analysis

Primary study parameter

Intention-to-treat analysis in all and sensitivity analysis in completers

Data will be primarily analysed according to the intention-to-treat principle. In addition, the data will be analysed exploratory for the completers only (sensitivity analyses). Completers are defined as participants who complete the T4 36-month follow-up assessment, with at least the diagnostic interview, and, if in the experimental group, who completed more than half of the assignments in the modules chosen. Interim analyses are not planned. Baseline characteristics of the participants between the randomisation groups will be compared.

The primary analysis will be a Cox regression proportional hazards model with time to relapse over 36 months as dependent variable and randomisation group as independent variable. Effect size in this analysis is the HR. To see whether the proportional hazards assumption holds, we will create and evaluate log minus log plots first. Drop-out during follow-up and no relapse up to the end of the study will be defined as censored. Kaplan-Meier curves will be used to visualise the difference in relapse risk between the randomised groups over the follow-up period.

Secondary study parameters

The secondary outcomes are repeatedly measured, continuous variables that will be analysed in terms of change over time using linear mixed effect models with a random intercept and, if significantly improving the model, also a random slope for participants. These models use all available data (ie, they do not exclude persons with missing values) and account for within-subject correlation over time. They can also be used to adequately deal with possible baseline imbalances. Intervention effects in these models will be quantified by entering group*time interaction terms. The remainder of the secondary outcomes are difference in the number of relapses during follow-up between the randomised groups that will be analysed using Poisson regression.

The possible mediating effect of the candidate mediator variables on relapse risk (as indicated by the HR) will exploratory be assessed by adding the candidate mediator as an independent variable into the Cox regression model.

In addition, moderators in the effect analyses are added to explore subgroups of participants with a particularly strong or weak relative response. Differential intervention effects in subgroups will be evaluated by testing the statistical significance of randomisation*moderator variable interaction terms. Subgroup (of response) specific effects will be reported if statistically significant.

For secondary outcomes, multiple imputation will be used for incomplete predictor data under the missing at random or missing completely at random assumption. All effect parameters will be supplied with a 95% CI. Statistical significance will be set at $p<0.05$, two sided.

Data handling

Data collection primarily occurs online via EDC systems Castor EDC (data.castoredc.com), online K-SADS server (www.nimhksads.net/) and Minddistrict (stayfine.minddistrict.com). Additional data are collected on paper and is entered in Castor EDC afterwards. All study-related information is stored securely (with coded ID numbers) in locked file cabinets in areas with limited access to maintain participant confidentiality. All records that contain names or other personal identifiers, such as informed consent forms are stored separately from study records identified by code number. All local databases are secured with password-protected access systems. Every 6 months, data back-ups are made for the EDC systems.

Ethics and dissemination

This study protocol was first approved by the Dutch Medical Research Ethics Committee Utrecht on 19 June 2019 (NL67637.041.19; an update with minor changes in details was approved on 28 September 2021). Freely given, written informed consent will be obtained in accordance with regulatory requirements. Random allocation of participants to randomisation groups is considered reasonable as no adverse effects are expected in any of the groups. Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, is agreed on by the METC Utrecht. A data monitoring committee was not deemed necessary as participants are healthy, remitted

youth and no adverse effects are expected in any of the randomisation groups. Results will be submitted to peer-reviewed journals and presented at (inter)national conferences.

Trial status

Enrolment started in December 2019. The trial was registered on 15 December 2019 in the Netherlands Trial Register: NL8237 (https://trialsearch.who.int/Trial2.aspx?TrialID=NL8237). The trial registration was updated in September 2022 via a new registration on ClinicalTrials.gov: NCT05551468, because the Netherlands Trial Register was taken offline and it is impossible to update the registration at the time of writing. Data collection started December 2019 and is planned to end December 2025.

Patient and public involvement

Focus groups with experts by experience, remitted youth and youth without a history of depressive or anxiety disorders were used as input for conception of the research question, outcome measures and recruitment strategy, and a pilot study to assess feasibility and acceptability with study measures and the StayFine app. Results will be shared online with participants via newsletters.

DISCUSSION

It seems paramount to direct prevention interventions at remitted youth who are at high risk of relapse. This study is the first to establish feasibility of SF-GAPI modules in remitted youth. The relatively long follow-up of 3 years will provide a unique insight in the course of depressiveand anxiety disorders and on daily life functioning of remitted youth.

Moreover, this study incorporates app-based monitoring with EMA (SF-MON) in remitted youth. A unique feature of the study is the combining of individual symptom networks with diagnostic and symptom level outcomes from diagnostic interviews and self-report questionnaires and shared decision-making to personalise the choice of modules (regardless of DSM-5 classification). Therefore, this study will establish feasibility of app-based monitoring and use of personalisation in remitted youth and examines the potential of early warning signs of depressive or anxiety relapse.[127 128] Data gathered can contribute to defining the golden standard in individual symptom networks for personalisation of relapse prevention interventions.

The multitude of outcomes provides several opportunities to examine working mechanisms of the modules to advance our understanding of indicators of relapse and generates hypotheses of pathways that lead to relapse. Moreover, examination of moderators will advance our knowledge about which individuals benefit most from relapse prevention and who need additional interventions. Exploratory wearable outcomes may further add to our understanding of how activity and diurnal patterns are associated with depressive and anxiety disorders.

If the SF-GAPI modules reduce the risk of relapse, it can have several advantages for remitted youth since the remission phase provides a window of opportunity to develop cognitive, social and behavioural skills.[129] With prolonged time in remission, individuals may achieve better overall functioning and strengthen oneself against relapse. This could reduce high personal and societal costs. If the StayFine app is found to be effective, it will be the first personalised app-based relapse prevention intervention for youth that contributes to breaking the cycle of relapse.

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Contributors MHN, CB and YS conceived the study. SJR, BEAMK, MHN, CB and YS, developed and finalised the study design. CJA provided statistical expertise in the clinical trial design and in the personalisation procedure including individual networks. All authors contributed to refinement of the study protocol. SJR drafted the manuscript. MHN, CB and YS supervised drafting of the manuscript. All authors provided critical revisions to the manuscript and approved the final manuscript. YS is grant holder. SJR, BEAMK, MHN, CB and YS will have access to the final trial dataset. The authors intend to share deidentified individual clinical trial participant-level data after publication of results with researchers who provide a methodologically sound proposal. Requests can be sent to Y.Stikkelbroek@uu.nl.

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Competing interests CB is codeveloper of the Dutch multidisciplinary clinical guideline depression, for which she receives no remuneration; is a member of the scientific advisory board of the National Health Care Institute, the Netherlands, for which she receives an honorarium, although this role has no direct relation to this study; she has presented keynote addresses at conferences, such as the Association for Psychological Science, for which she sometimes receives an honorarium; she receives royalties from her books and coedited books, and she developed PCT based on the cognitive model of A. T. Beck. MHN developed and translated cognitive behavioural therapy treatment manuals, including blended internet-based treatment programs unrelated to the current project, for which she receives no direct payments. MHN also reports travel expenses, some subsistence, and speaker honoraria for lectures or clinical training workshops paid for by mental health centres. She is a member of the workgroup of the Dutch multidisciplinary

guideline for anxiety (non-remunerated). YS is codeveloper of the national guidelines on youth affective disorders, for which she receives no remuneration. YS has presented at conferences, for which she sometimes receive an honorarium. She receives royalties from her books and manuals, and she developed the D(o) epressie (blended) intervention for youth based on the social learning theory of Lewinsohn and colleagues, for which she receives no direct payments. CB, MHN and YS have presented clinical training workshops, some of which include a fee. SJR, BEAMK, MHN, CB, YS have developed the modules of the current Stayfine app (monitoring and intervention) and receive no payments from that.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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