Skills for adolescent WELLbeing (SWELL): protocol for a preventive effectiveness randomised controlled trial for young people at high-familial risk of depression with treatment optimisation for parents with depression at study entry comparing online group Cognitive Behavioural Therapy (CBT) to treatment as usual

[Title for participants/public: Skills for adolescent WELLbeing (SWELL)]

V5.8

5th March 2025

Sponsor:	**Cardiff University** Research Governance Team Research and Innovation Services 7th Floor, McKenzie House 30-36 Newport Road Cardiff. CF24 0DE
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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and CTR's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

Trial Sponsor: Cardiff University

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Name	**Position**	**Signature**	**Date**

Director:

Dr Rachel McNamara

Name	**Signature**	**Date**

Chief Investigator:

Prof. Fran Rice

Name	**Signature**	**Date**

General Information This protocol describes the SWELL trial and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to the Centre for Trials Research.

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Trial Co-ordination:

The trial is being coordinated by the Centre for Trials Research (CTR), Cardiff University, a Clinical Research Collaboration (UKCRC) registered trials unit.
This protocol has been developed by the Trial Management Group (TMG).
For **all queries** please contact the trial team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator or a Co-Investigator.

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Randomisations:

Randomisation
Randomisation will be set up by CTR staff according to a bespoke online system (see section 14 below). Randomisation will be conducted by this system. The SWELL research team will contact participants to inform them of which study arm they have been randomised to.

Clinical queries:

Clinical queries
SWELL@cardiff.ac.uk **All clinical queries will be directed to the most appropriate clinical person.**

Serious Adverse Events:

SAE reporting
Where the adverse event meets one of the serious categories, an SAE form should be submitted to CTR within 24 hours of becoming aware of the event (See section 13 for more details). **Contact details: SWELL@cardiff.ac.uk; 02920876894**

Table of Contents

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Glossary of abbreviations

AE	Adverse Event
ART	Analysis of Resources for Trials
ARI	Affective Reactivity Index
BADS-SF	Behavioural Activation Scale for Depression (BADS-SF)
CBT	Cognitive Behaviour Therapy
CBQ	Conflict Behaviour Questionnaire
CES-D	Centre for Epidemiological Studies Depression Scale
cGAS	Children's Global Assessment Scale
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRPBI	Child's Report of Parent Behaviour Inventory
CRSI	Client Service Receipt Inventory
CRF	Case Report Form
CTR	Centre for Trials Research
CwS	Coping with Stress intervention
DAS-C	Dysfunctional Attitudes Scale for Children
DAWBA	Development and Well Being Assessment
DECIPHer	Development and Evaluation of Complex Interventions for Public Health Improvements
DH	Department of Health
DSM	Diagnostic Statistical Manual
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
GP	General Practitioner
GSE	Generalised Self Efficacy Scale
HDRS	Hamilton Depression Rating Scale
iCBT	Internet-based Cognitive Behaviour Therapy
ISRCTN	International Standard Randomised Controlled Trial Number
LEC	Life Events Checklist
LIFE	Longitudinal Interval Follow-Up Evaluation
MAR	Missing at Random
MCID	Minimum Clinically Important Difference
MDD	Major Depressive Disorder
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
NCMH	National Centre for Mental Health
NHS	National Health Service
NICE	National Institute for Clinical Excellence
PHQ-9	Patient Health Questionnaire-9
PI	Principal Investigator
PIC	Participant Identification Centre
PMH	Primary Mental Health
PSS	Perceived Stress Scale
R&D	Research and Development
RCADS	Revised Children's Anxiety and Depression Scale
RCT	Randomised Controlled Trial

REC	Research Ethics Committee
SAE	Serious Adverse Event
SAIL	Secure Anonymised Information Linkage
SCAARED	Screen for Adult Anxiety Related Disorders
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SCDC	Social Communication Disorders Checklist
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
WHODAS	World Health Organisation Disability Assessment Schedule
YP	Young Person/People

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No. *(specify substantial/non-substantial)*	**Protocol version no.**	**Date issued**	**Summary of changes made since previous version**
1 – substantial	4	09/02/23 - Sent to Sponsor prior to submission of amendment to REC	The main changes proposed in this amendment are the addition of three new sites (previously PICs) to aid with the recruitment, screening and consenting of participants, in addition to minor changes to the study design and therefore the trial documents. These include minor amendments to the proposed sample size to improve the study's power to detect differences between the intervention and treatment-as-usual groups, the removal and shortening of questionnaires to reduce burden on participants, clarification on the processes that will be followed when recruiting via primary care, and clarification on how consent will be taken remotely. Each proposed change is shown in tracked changes in the copy of this document with tracked changes (Protocol_v_4_0_with_track_changes.docx).
Non substantial-2	4.6	May 2023	Changes to the protocol include (1) changing the study title to "An effectiveness randomised controlled trial of a group Cognitive Behavioural Therapy intervention programme for young people with parental depression treatment optimisation for the prevention of depression in high-risk adolescents: Skills for adolescent WELLbeing (SWELL)". This clearly describes the study and avoids abbreviations such as CBT; (2) changing the wording of inclusion criteria (ii) from "subthreshold

			depressive symptoms" to "currently elevated depressive symptoms (not meeting threshold for a major depressive episode)" to make this definition clearer; (3) changing the wording of inclusion criteria (vi) from "they and their participating parent have a valid email address or mobile phone number" to "they and their participating parent have a valid email address and mobile phone number". Participants are required to have both an email address and phone number to take part; (4) definition of suicidal ideation as an adverse event has been changed from "suicidal ideation" to "suicidal ideation (with a plan/method considered)" which provides a clearer definition of suicidal ideation for this study; (5) updated power calculations; (6) clarification of safety reporting procedures with additional text included in section 13 of the protocol; (7) clarification of the LIFE measure and method for establishing inter-rater reliability; (8) updated source data table in section 16.3.
Non-substantial-3	4.7	July 2023	This amendment removes the questionnaire measure (“Health and habits (e.g., exercise)” from the schedule of assessments table.
Non substantial-4	4.8	August 2023	Minor changes in the wording of the protocol involve a clarification regarding the parent treatment optimisation (PTO) part of the study. Online CBT will be recommended as part of the PTO depending on the needs of the individual. In situations where the SilverCloud CBT programme cannot be accessed, alternatives will be considered.
Non-substantial-5	4.9	September 2024	Minor clarifications to the screening process, namely the process used to communicate eligibility to the potential participant following screening.

Non-substantial-6	4.10	November 2024	This amendment includes clarifying wording of the exclusion criteria, making it clearer that if the young person is currently receiving CBT or has a history of psychosis they would not be eligible to take part.
Substantial-2	5.0	December 2024	The main change proposed in this amendment is the addition of schools and well being services as a method of participant recruitment. The other protocol amendment is adding a payment of £10 voucher to all participants who complete baseline questionnaires and interviews, and clarifying the timescale within which questionnaires and interviews should be completed at each follow up period.
Non-substantial-8	5.1	Submitted to sponsor 14.02.24	This amendment includes clarifying the screening procedure in cases where parent and young person report of current depression symptoms disagree (eligibility will be decided via clinical consensus), and where the parent does not wish to / is unable to take part in the parent treatment (baseline assessments are completed and the young person randomised). Parental PTSD has been removed as an exclusion criteria in order to make our eligibility criteria more inclusive. The study definition of adverse events has been minorly amended for clarity. We have extended recruitment via schools to the UK (as opposed to in Wales only) and via GP practices to Wales (as opposed to in South Wales only).
Substantial-3	5.2	Submitted to sponsor 23.02.24	Participant voucher payment amounts have been amended, increasing from a maximum of £60 to £80 per participant.

Non-substantial 9	5.3	Submitted to sponsor 22.04.24	This amendment includes changes to the eligibility criteria to make it more inclusive. Having received CBT in the past is no longer an exclusion criteria for the young person, and the definition of young person subthreshold depression symptoms has been reduced from a CES-D score of ≥20 to a score of ≥16. Parents will also be eligible to take part if they have a history at least one depressive episode, rather than at least two episodes. Minor amendments have been made to screening procedures. Young person current depression diagnosis at screening will be assessed by asking the parent whether their child has a current diagnosis of depression diagnosed by a doctor. When assessing past depressive episodes for the parent and the young person, we will no longer ask about suicidal ideation, given ethical concerns around raising this during a screening call. Finally, if families are found to be ineligible at screening, but there is a possibility they may become eligible in the future, permission will be obtained to recontact the family in the future to check if their eligibility status has changed. Recruitment through GP practices has been extended to the whole of the UK instead of Wales only.
Non-substantial 10	5.4	Submitted to sponsor 20.05.24	This amendment involves changes to the SWELL study inclusion criteria. Firstly the age range of participants has been increased to 13-19 years (from 13-17 years). Secondly, in line with this age range increase, the inclusion criteria that states the young person should be "living with a parent...." has been changed to "living (at least some of the time) with a parent...". Also in line with the age increase, we have amended the protocol to allow us to advertise the study to young people directly. All relevant documents have been amended to

			reflect these changes, including the study protocol, participant information sheets, letter to GP cluster lead, letter informing GP of involvement, recruitment letter from GP to families, reminder letter from GP to families, Research Information sheet for Practices (RISP) and letter to schools. A new study invitation letter addressed to the young person (aged 18 and above) has also been produced. Consent forms have been amended so the most up to date versions of the information sheets are cited. Further minor amendments have been made to the protocol including introducing a timeframe by which the parent treatment optimisation (PTO) should be completed beyond the standard 12 weeks (it should be completed within 12+3 weeks of starting the PTO). The definition of Adverse Events has also been clarified, by removing a standard definition that is not relevant to this trial. Additional potential avenues for recruitment have also been included (CRIS and SAIL). Minor amendments have also been made to the letter to schools to shorten it and make it more accessible. In the recruitment letter from GP to families the word "booklet" has been changed to "leaflet" so it matches with the materials being sent out to families. Finally, an additional signposting resource for families (Melo Cymru- https://www.melo.cymru/) has been added to the information leaflets.
Non substantial amendment 12	5.5	Submitted 23.10.24	This amendment involves adding the names of the NIHR Clinical Research Network (CRN) teams, who are supporting us with advertising the study to GP surgeries in the UK, to the GP recruitment section of the study protocol. In the same section, a minor edit has been made to clarify the text/mail out process to potential participants at GP surgeries.

Non substantial amendment 13	5.6		This amendment involves some minor changes to the protocol. This includes adding the names of additional NIHR Clinical Research Network (CRN) teams (South London CRN and South London RDN) to the recruitment section of the study protocol. In the same section, the availability of a GP database search developed for SystmOne has been included, and an additional recruitment procedure for ABUHB primary CAMHS has been added. Clarifications to the protocol have also been made around adverse event (AE) reporting. Only adverse events in the young people taking part will be reported (not events that occur in the parents). These adverse events can be reported by either young person or their parent. A sentence has been added to state that where both young person and parent report the same AE, a separate reporting form will be used for each reporter. Where the same adverse event is ongoing (e.g. recurrent self-harm) it will be reported the first time it occurs, and again where there is a change (e.g. new method of self-harm or change in severity of self-harm using the same method). Additional information has also been added to the protocol to clarify the level of monitoring of questionnaire data by the research team. Online questionnaires completed by participants will be accessed at the end of the study by the research team for analysis only. Finally, more detail has been added to the qualitative analysis section on the protocol about the planned analysis (framework analysis). This amendment also includes 2 text templates (a longer and a shorter version) for GPs send to potential participants. The most recent versions of the postcards to be sent to English GP practices are also included.

Non substantial amendment 14	5.7	Submitted 14.02.25	This amendment involves a number of minor changes to the study protocol. The title has been amended so that it includes the study design, population, interventions and trial acronym (in line with SPIRIT guidance). Members of staff involved in the project have been added/updated. In the statistical considerations section of the protocol, expected loss to follow up at 9 months has been changed from 20% to 10%, in line with previous research. We have also defined the minimal clinically important difference (MCID) value "HR of at least 0.60 (equivalent to an 11% difference in MDD between intervention arms)" and added text that justifies this. Power calculations have been updated due to the change to the expected attrition rate. Minor changes to wording have been made throughout the protocol for increased clarity and accuracy of study procedure. We have added clarification that consent for linkage to routine data will be via SAIL for participants in Wales and via NHS Digital for participants in England. We have also added a reference to a new grant that will fund this linkage (Wellcome Trust 303982/Z/23/Z). Text has been removed from the protocol to avoid repetition and text that is no longer relevant has been removed. Throughout the protocol minor changes have been made to wording to make it clearer and more readable and grammatical errors have been corrected. Page numbers have been amended and the contents page updated.
Non substantial amendment 15	5.8	Submitted 21.03.25	This amendment involves minor changes to the study protocol. In section 13 (Safety reporting), the adverse event (AE) "self-harm" has been changed to "deliberate self-harm". This reflects more accurately the adverse event being reported. Wording has also been amended so that "all SAEs and AEs will be reported by the CTR and discussed as a standard agenda item by the TSC during their

			routine meetings", rather than "by the TMG and TSC". This reflects study procedures. In section 2 (synopsis) and 8 (participant selection) the inclusion criteria wording has been amended from "Living (at least some of the time) with a parent (biological or non-biological) who has a history of unipolar depression..." to "Living (at least some of the time) with a parent/carer (biological or non-biological) who has a history of unipolar depression.." so it is clear that a parent or carer can take part. In section 9 (recruitment, screening and registration) details have been added explaining the process for reconsenting participants who turn 16 during the course of the study, or when reconsenting is needed for other reasons (e.g. amendments to the consent form).

List summary of protocol amendments here whenever a new version of the protocol is produced. Ensure details are also updated in a full protocol change log.

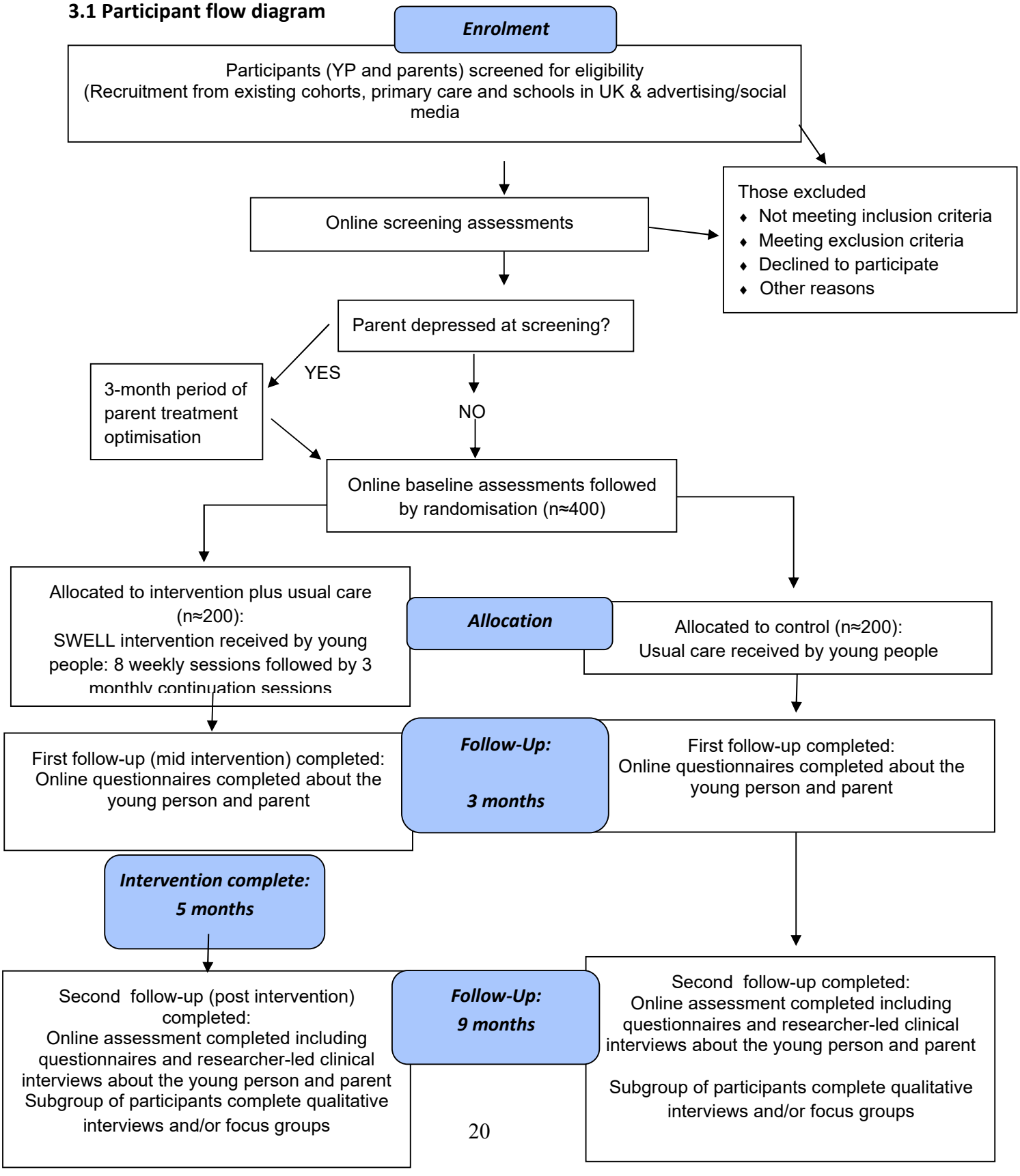
2 Synopsis

Short title	Skills for Adolescent Well-Being
Acronym	SWELL
Internal ref. no.	UID910
Funder and ref.	The Wolfson Foundation
Trial design	Randomised controlled effectiveness trial
Trial participants	Young people aged 13 to 19 years old with currently elevated depressive symptoms (not meeting threshold for a major depressive episode) and/or a history of depression, and parent/carer with a history of depression. The young person's parent with a history of depression will also be asked to participate. Professionals working on the trial will be given the opportunity to participate in qualitative interviews and/or focus groups.
Planned sample size	Up to 400 young people
Planned number of sites	5 to 6
Inclusion criteria	Adolescents will be eligible for the study if: i) they are aged 13-19 years, ii) they are currently experiencing elevated depressive symptoms and/or have a history of a major depressive episode according to DSM-5 criteria but they do not have a current diagnosis of depression (because treatment would be indicated), iii) they are living (at least some of the time) with a parent/carer (biological or non-biological) with a history of depression who is willing to consider engaging with a depression treatment plan, iv) they and their participating parent have the ability to complete trial activities as specified in the protocol, e.g., can communicate in English , v) they and their participating parent have access to the Internet, and vi) they and their participating parent have a valid email address and mobile phone number. The inclusion criteria for trial professionals participating in qualitative interviews/focus groups are: works on the trial as a therapist leading the young person CBT groups, or as a trial psychiatrist optimising parent depression treatment.
Exclusion criteria	Exclusion criteria are: i) young person is currently receiving antidepressant medication, ii) young person is currently receiving cognitive behavioural therapy (CBT), iii) young person has a current diagnosis of depression, iv) young person has generalized learning difficulties that would prevent them from completing trial activities, v) young person has current substance or alcohol abuse disorder, a diagnosis of bipolar disorder, schizophrenia, psychosis or eating disorder, vi) parent has a diagnosis of bipolar disorder, schizophrenia or personality disorder, vii) parent is receiving treatment from secondary mental health services (e.g. community mental health team or psychiatrist), viii) parent or young person is not resident in the UK
Treatment duration	8 weekly 60-minute acute sessions followed by 3 monthly continuation sessions (5 month total intervention length)
Follow-up duration	9 months post randomisation; plus consent for long-term follow-up via linkage with routine health data (e.g. the SAIL databank, NHS Digital)
Planned trial period	April 2023 – December 2026 (opening of participant recruitment until the end of follow-up and analysis)
Primary objective	To evaluate the effectiveness (defined as time to event of a major depressive episode in adolescents) of an inter-generational preventive intervention for adolescents at elevated risk of depression (defined by a history of depression in a parent and either

	current elevated depressive symptoms (≥16 CES-D) or a history of a major depressive disorder).
Secondary objectives	To examine the effect of the intervention on the secondary outcomes including depression symptoms, quality of life, anxiety, irritability and developmental competence. An embedded process evaluation will assess recruitment and reach; retention; acceptability; fidelity of intervention delivery; adherence and intervention mechanisms including hypothesised mediators (perceived stress, problem solving, cognitive change, behavioural activation and improvements in the parent-child relationship) and moderators of effect including baseline characteristics of the young people (e.g., comorbidity, age) and parents (e.g., current depression status).
Primary outcomes	Time to a DSM-5 depression episode occurring in the young person during the 9-month follow up period as defined by the Depression Symptom Rating score.
Secondary outcomes	*At 9-month follow-up:* Number of depression free weeks, length of wellness intervals, time to recovery from depressive episodes and time to recurrence of depressive episodes in the 9-month follow up period assessed with the LIFE; Depressive symptoms assessed with the CES-D; anxiety symptoms assessed with the RCADS; irritability symptoms assessed with the ARI; quality of life assessed with the EQ-5D-Y; developmental competency assessed with the Developmental Competence Scale; functional impairment associated with depression assessed with the cGAS; Individual depression risk score (an individual risk algorithm developed at Cardiff University which assesses 3 year risk of depression); service use and treatment assessed with the CSRI. *At baseline, 3-month and 9-month follow-up:* Data on potential mediators will also be collected – negative self-beliefs assessed with the DAS-C; self-efficacy and problem solving assessed with the GSE; perceived stress assessed with the PSS; behavioral activation assessed with the BADS-SF; interpersonal relationships assessed with the CBQ, CRPBI, and the child disclosure subscale from the parent monitoring measure.
Intervention	The SWELL intervention (an adapted online version of "Coping with Stress") – a psychological intervention for prevention of youth depression which is enhanced by additionally optimising treatment of parental depression when parents have high levels of depression symptoms at study entry.

3 Trial summary & schema

3.1 Participant flow diagram



3.2 Trial lay summary

Background

Depression is common in young people and can lead to long-term mental health difficulties. Young people with a depressed parent are at an especially high risk of depression themselves. Therefore, it is important to find ways to intervene early and prevent depressive episodes in this group. A previous study found that a talking intervention for small groups of young people (Coping with Stress) was effective at preventing depressive episodes in young people at risk of depression. However, the intervention was not effective when the young person's parent was currently depressed at the beginning of the study. Depression in adults is nearly always managed in primary care and is sometimes not managed optimally. Therefore, optimising treatment in line with best practice guidelines for parents who are currently depressed alongside the intervention for young people may benefit young people.

Aims

This project aims to test the effectiveness of the SWELL intervention (an adapted version of 'Coping with Stress', delivered online to fit a UK context) in preventing depression in adolescents who have a depressed parent. We will recruit adolescent-parent pairs into the study, and the project aims to optimise treatment for the parent when they are depressed at the start of the study. The project also looks at other outcomes in the young person like functioning, to see what factors might lead to improvement and how certain factors, such as the parent being depressed at the start of the study, might change how well the intervention works for the young people. We will also test how the study works both through participants completing questionnaires but also by asking those who complete and deliver the interventions what helped and what could be improved.

Design/methods

This project is a randomised controlled trial. We will recruit young people with a history of depression in a parent and who have either current elevated depressive symptoms or a past history of depression (but who do not currently have a diagnosis of depression – because treatment would be most appropriate for those young people). These young people will be recruited from existing patient cohorts/ databanks (e.g. National Centre for Mental Health, GLAD, South London and

Maudsley Clinical Record Interactive Service (CRIS), Secure Anonymised Information Linkage databank (SAIL)), from primary care centres, employee support and well- being services, schools, social media and via advertisements and study leaflets in a range of health and community settings using in-person and online methods. Before the intervention begins, the young person's parent will be assessed for current depression. When their parent is not currently depressed (as confirmed by a depression screening measure), the young person will be immediately randomised. When the parent is currently depressed, they will be offered the opportunity to enter a 12-week period during which their depression treatment is optimised. Treatment optimisation will be carried out as part of a University-led treatment programme, run by NHS psychiatrists. At the end of this 12-week parent treatment period, the young person will be randomised regardless of whether their parent's depression symptoms have improved (PHQ-9 score < 10 at baseline) or not. If the parent does remain depressed they will be directed to the usual NHS treatment pathway via their GP. If the parent is unable to complete the 12-week treatment optimization, the young person and parent will be able to continue the study and the young person will be randomised. Up to 400 young people will be assigned randomly to receive the intervention plus usual care or to continue with usual care only. The young person and their parent will participate in online assessments about their mental health at the start of the study prior to randomisation and again after 3 and 9 months post-randomisation.

4 Background

Depression is a leading cause of disability worldwide (WHO, 2008) and is associated with poor long-term outcomes including social and educational impairments, self-harm and suicide (Thapar et al, 2012; Johnson et al., 2018; Claybourne et al., 2019). The rate of depression increases during adolescence, and depression at this time can mark the beginning of long-term mental health problems (Thapar et al. 2012). Therefore, early intervention and prevention of adolescent depression is a major public health concern (Department of Health, 2009).

One of the most common, potent risk factors for depression is having a parent with depression. Those with a depressed parent are 3-4 times more likely to develop depression themselves (Rice, et al., 2002). Young people of depressed parents are a high-risk group who could benefit from prevention or early intervention. Evidence exists that interventions for depression prevention are

effective, particularly when used in targeted populations, including in young people of depressed parents (Rasing et al., 2017; Hetrick et al., 2015, Munoz et al., 2012; Havinga et al., 2021), with many of these interventions using cognitive behavioral therapy (CBT) approaches (Hetrick et al., 2015; Havinga et al., 2021).

One particular cognitive behavioral intervention that has shown promise in preventing depression in adolescents at high risk is the Coping with Stress (CwS) program (Garber et al., 2009). The CwS program is a group-based cognitive behavioral intervention for the prevention of unipolar depression. It has been found to be effective in preventing the onset of depression in young people at increased risk of depression (those with a parental history of depression and a history of depression and/or elevated subthreshold depression symptoms themselves) (Garber et al., 2009). Interestingly, the same study found that current depression in parents moderated the intervention effects. The CwS intervention was not more effective than usual care in preventing depression for young people whose parents were currently depressed (Garber et al., 2009). These results are consistent with findings of previous intervention studies that have shown that parental depression reduces effectiveness of CBT interventions for depression in young people (Brent et al., 1998; Lewinsohn et al., 1998). Therefore, identifying and treating parental depression may be important to maximize the likelihood of such interventions preventing depression in their children. Remission of depression in mothers has been associated with a decrease in psychiatric symptoms and improved functioning in offspring (Pilowsky et al., 2008; Cuijpers et al., 2015). However, research directly testing effectiveness of interventions for depression prevention in young people when concurrent parental depression is treated, is lacking.

In addition to identifying whether the intervention is effective, exploration of underlying mechanistic and contextual factors can help determine which intervention components work best, for whom, and in which circumstances. Research into the mechanisms underlying the successful prevention of depression, however, is lacking. A recent systematic review of mediators of interventions for the prevention of depression and anxiety, evaluated cognitive, behavioural, emotional, and interpersonal mediators (Moreno-Peral et al., 2020). These included negative thoughts, attributional style, self-esteem, self-efficacy, perceived stress, problem solving skills, social skills, social support, and behavioural activation. Results showed that in adults, cognitive change may be an important

mechanism for the prevention of depression, with negative thinking being the mediator with the strongest support. In children and adolescents, however, there was insufficient evidence for any of the mediators examined.

The current study

The current study was designed to test the effectiveness of the SWELL trial intervention - an adapted CwS intervention - in young people at risk of depression. Adaptations were made with input from the trial team, the trial management group (TMG), the intervention developers, clinicians, and young people. The primary adaptation is that parents who are currently depressed will receive treatment, prior to their child entering into the trial. This adaptation was intended to maximize the effectiveness of the intervention for young person. We also adapted the CwS intervention so that it could be delivered online. Online delivery of psychological interventions not only can benefit those reluctant to use face to face interventions, but it also allows interventions to be more widely available to those who may otherwise be unable to access them. There is evidence that online psychological interventions are as effective as face to face interventions especially when facilitated by a therapist (Buntrock et al., 2016). We also made minor updates to the visual and written materials that were included in the original CwS workbook. This included the use of more contemporary comic strips to illustrate key learning points. We also translated the YP workbook into Welsh to create a bilingual resource (although all intervention groups will be delivered in English during the planned trial). We called the intervention Skills for Adolescent WELLbeing (SWELL).

The study also will explore possible mechanisms through which the intervention may work. The SWELL intervention is a psycho-educational, cognitive-behavioral intervention that focuses on training adolescents in cognitive-restructuring skills and techniques for modifying negative self-statements (Clarke, 2003). It strengthens current coping techniques and teaches new coping strategies (Clarke et al., 2003). Therefore, we will examine possible mediators of the intervention such as problem-solving skills, perceived stress, self-efficacy, and unrealistic negative thinking, all of which the intervention works to improve, and thereby may protect against developing depression (Clarke et al., 2003). Improvement in the parent-child relationship is another potential mechanism through which the intervention may have beneficial effects on young people's depression, and we

will explore this in the current study.

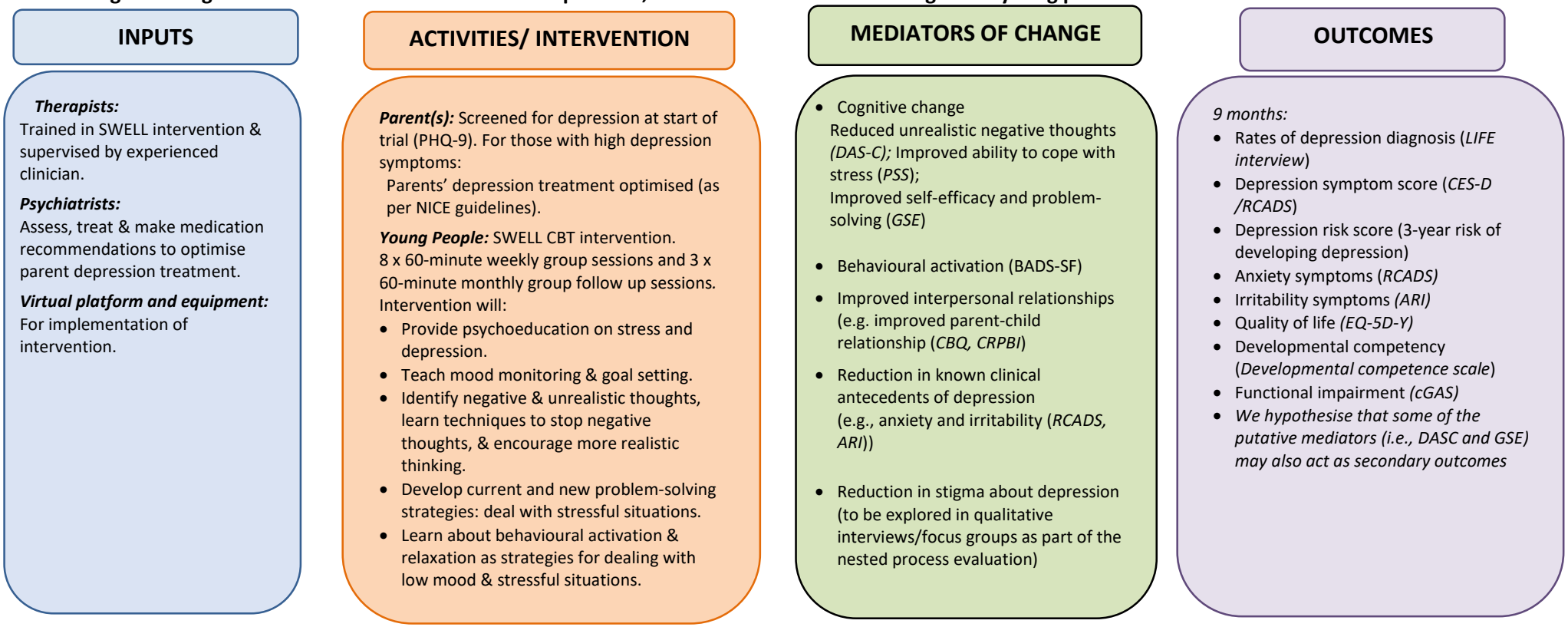
Aims

The primary aim is to test the effectiveness of the SWELL intervention which is an adapted from the 'Coping with Stress' intervention in adolescents at risk of depression and includes optimising the treatment of parental depression prior to intervention delivery. A nested process evaluation will assess recruitment and reach, retention, fidelity, adherence, acceptability, influence of potential underlying mechanisms and context (please see the logic model that has been developed for this trial in Figure 1), and will assess the impact of adaptations on effectiveness and implementation. We will also assess factors that may modify the effectiveness of the intervention including baseline characteristics of the young people (e.g., comorbidity) and parents (e.g., current depression status).

4.1 Rationale for Current Trial/Justification of Treatment Options

The rationale for the current trial is detailed in the "Background" section of this protocol. As described, the trial will be informed by the previous in-person RCT study of the Coping with Stress intervention that was conducted in the US (Garber et al., 2009), but adapted to include parent depression treatment optimisation, and to be delivered online in a UK context.

Figure 1: Logic Model of SWELL intervention on depression, mental health and functioning in the young person



Footnote to Figure 1: *PHQ-9* = Patient Health Questionnaire-9; *DAS-C* = Dysfunctional Attitudes Scale for Children; *PSS* = Perceived Stress Scale; *GSE* = Generalised Self Efficacy Scale; *BADS-SF*= Behavioural Activation for Depression Scale- short Form; *CBQ*=Conflict behaviour questionnaire; *CRPBS*= Child Report of parent's behaviour scale; *RCADS*= Revised Children's Anxiety and Depression Scale; *ARI* = Affective Reactivity Index; *LIFE* = Longitudinal Interval Follow-Up Evaluation, *CES-D* = Centre for Epidemiological Studies Depression Scale; *cGAS*= Children's Global Assessment Scale (cGAS). Family stigma in addition to the other mediators of change will be explored in the qualitative interviews/focus groups. Note: stigma about depression will be assessed in qualitative interviews only.

The research plan has been developed in consultation with the trial management group (TMG), who have clinical and research experience of adolescent depression and of evaluating mental health interventions for young people. The Wolfson Centre Young Person Advisory Group (YPAG) of 12 young people with lived experienced of depression/anxiety have also contributed feedback on our study protocol development during 3 meetings (2 online, 1 hybrid), and a smaller group meeting on 1 additional occasion. The YPAG advised on: the name SWELL, assessments used, timings of intervention and assessments, and the adaptation of the intervention (workbook content including language and visuals, online methods for delivery). One young person and a parent with experience of depression are members of the independent trial steering committee (TSC). The Chief Investigator (CI) is Professor of Developmental Psychopathology with research expertise in longitudinal studies, child and adolescent psychopathology and is a leading authority on adolescent depression. She is lead investigator on a large longitudinal study of the adolescent children of parents with depression.

This work will be conducted by a team based at the Wolfson Centre for Young People's Mental Health in collaboration with the Centre for Trials Research (CTR). We will also collaborate with the intervention development stream of the National Centre for Mental Health (NCMH). The project has been adopted by the Centre for the Development and Evaluation of Complex Interventions for Public Health Improvement (DECIPHer). The experiences of young people and parents affected by depression fed into the development of the grant that funded this project – when asked what their priorities were for research in this area, they identified prevention and early intervention as their main priority for future research.

The research team have met regularly as a TMG to discuss the planning of the trial and will continue to do so over the course of the trial. A Trial Steering Committee (TSC) will be assembled (see section 21.2), who will advise on aspects of trial design.

5 Trial Objectives/Endpoints & Outcomes

5.1 Primary objective

To evaluate the effectiveness of the SWELL intervention for prevention of depression in young people with a parent with a history of depression and a history of depression themselves or currently elevated depression symptoms.

5.2 Secondary objectives

To examine the effect of the SWELL intervention on the secondary outcomes (e.g. quality of life, anxiety, irritability, functional impairment). A process evaluation will assess recruitment and reach, retention, fidelity, adherence, acceptability, influence of potential underlying mechanisms and context. The process evaluation will also focus on assessing the impact of adaptations on effectiveness and implementation and possible intervention mechanisms. Hypothesised mediators of effectiveness of the intervention include problem solving skills and quality of the parent-child relationship. Potential moderators include baseline characteristics of the young people (e.g., comorbidity) and parents (e.g., current depression status).

5.3 Primary outcome

The primary outcome is defined as time in weeks to a probable DSM-5 depression episode in the young person during the 9-month post-randomisation follow-up period. Specifically, we will collect information on when any depressive episodes occur during the follow-up period as the primary outcome, consistent with a time-to-event analysis approach. This will be measured using at the 9-month follow-up assessment using a validated research diagnostic interview for depressive episodes similar to the life history calendar approach – the longitudinal interval follow-up evaluation (LIFE; Keller et al., 1987). The LIFE measure involves the interviewer completing at follow-up a detailed assessment that allows the interviewer to ascertain the level of depressive symptoms over the entire follow-up period by tracking the onset and offset of symptoms. This allows the derivation of a depressive symptom rating for each week of follow-up. This is used to define depressive disorder with a probable depressive episode (Garber et al., 2009) defined as a depression symptom rating scale score of 4 or more for at least 2 weeks. The LIFE provides enough detail to date individual

depressive symptoms and episodes, and allows calculation of time to recovery, length of wellness intervals and time to recurrence (Keller et al., 1987).

5.4 Secondary outcomes

The secondary outcomes measured at 9-months post-randomisation include: number of depression free weeks, length of wellness intervals, time to recovery from depressive episodes and time to recurrence of depressive episodes in the 9-month follow-up period (assessed with the LIFE); depression symptom score (assessed with the Centre for Epidemiological Studies Depression Scale; CES-D; Radloff, 1991), young person's depression risk score (a risk score tool developed by colleagues at Cardiff University that will assess individuals' 3-year risk of developing depression; Stephens et al., 2022), anxiety symptoms (assessed with RCADS), irritability symptoms (assessed with ARI), quality of life (assessed with EQ-5D-Y), developmental competence (assessed with developmental competence scale), functional impairment (assessed using cGAS), and Service use and treatment (assessed with CSRI) which may also act as a covariate.

Data on potential mediators will also be collected via online questionnaire at baseline, 3 and 9-months post-randomisation follow-up. The potential mediators to be investigated are negative self-beliefs, self-efficacy and problem solving, perceived stress, behavioral activation and interpersonal relationships. Mediator data will be collected at all three timepoints to allow for exploratory analysis of change in the mediators over time, including checking the temporal ordering of exposure, mediator and outcome, which will be important given the strong within time correlations that are likely to be observed between the mediators and the outcome. It is possible that certain hypothesized mediators, such as those relating to changes in mindset including dysfunctional attitudes and self-efficacy, may act as both mediators and secondary outcomes. Those that show evidence of change at 3 months (which is either maintained at final follow-up or not) will be included in the mediation analysis and those that show change at final follow-up but not at 3 months will be treated as secondary outcomes.

Data on potential moderators will be collected via online questionnaire at baseline. The potential moderators to be investigated are baseline characteristics of the young people (e.g., comorbidity) and parents (e.g., current depression status).

More detail on all measures that will be used is provided in section 12.

6. Trial design and setting

This is a two-arm time-to-event randomised controlled effectiveness trial comparing the SWELL intervention plus usual care to usual care only. A nested process evaluation will investigate how the intervention and its implementation work, particularly for new elements of the intervention i.e. including the treatment of currently depressed parents prior to randomisation of the young people and the delivery of the intervention in an online setting. A health economic analysis is not currently included but data will be collected on service use (via the CSRI) to allow one to be completed in the future if funding is available.

We will recruit up to 400 young people and their parent/carer. Recruitment will be via a range of routes including: existing cohorts of adults with depression (e.g. the NCMH cohort based in Wales, the GLAD cohort based in the UK), from databanks (e.g. CRIS, SAIL), from primary care centres (GPs, primary mental health care), schools and employee wellbeing services in the UK and via social media. We will advertise the study via leaflets/flyers/postcards in a range of health and community settings using in-person and online methods (e.g. waiting rooms, mental health charity groups, community centres, pharmacies, primary and secondary care settings, school in-reach services etc).

Procedure (see flow diagram, section 3.1):

After both the parent and young person have completed the online screening measures, provided consent to participate in the study and the parent has completed the PHQ-9 questionnaire, if the parent and young person meet all inclusion/exclusion criteria and the parent is not currently depressed (defined as PH-9 score <10), baseline data will be collected and then the young person will be randomised. They will be allocated to either i) the SWELL intervention plus usual care, OR ii) usual care alone. Participants will be randomised 1:1 via random permuted block randomisation stratified by site and the unit of randomisation will be the young person. For those randomised into the intervention arm of the study, the intervention will start once a minimum of 6 young people are randomised, as we aim for CBT intervention groups to have 6-8 young people each. If recruitment is slow, we will wait up to 1 month to randomise 6 young people, before we start a CBT group that is

smaller than 6. Previous research (Garber et al., 2009) shows that it is feasible to run the intervention with groups as small as 3 if recruitment is slow.

If the parent and young person meet all inclusion criteria and none of the exclusion criteria but the parent is currently depressed at the screening stage (defined as PHQ-9 score ≥10), the parent will first be offered 12-weeks of treatment optimisation, before baseline data collection and randomisation. For ethical and pragmatic reasons, if the parent does not want to/is unable to/does not adhere to the treatment optimisation, this will be noted and baseline data will be collected and the young person randomised.

Parent depression treatment optimisation

The treatment optimisation team will consist of psychiatrists and psychology assistants and will be overseen by a consultant trial psychiatrist. When a parent scores ≥10 on the PHQ-9 questionnaire at the start of the study, the treatment optimisation team will be informed. Following parent agreement to participate in treatment optimisation, one of the team will then contact the currently depressed parent for a consultation aiming to optimise their depression treatment. This will take an evidence-based approach and work within clinical guidance, including NICE clinical guideline [CG90] 'Depression in adults: recognition and management'. The steps to this screening and optimisation process are outlined below, though these may vary according to the needs of the individual as assessed by the psychiatrist:

1) Screening: PHQ-9 depression screen score is greater than or equal to 10 at screening stage
2) Assessment: Parent is assessed by the psychiatrist in a 1-hour consultation conducted either via video call, phone call or face to face in a clinic
3) Psychoeducation: Brief psychoeducation and advice will be delivered by the psychiatrist at the end of the initial consultation
4) Initiation of online CBT: psychiatrist signposts the parent to the 8-module 'Space from Depression' / 'Space from Depression and Anxiety' programme on SilverCloud platform (https://pthb.nhs.wales/services/adult-and-older-peoples-mental-health-services/silvercloud-online-cbt/). (Richards et al. 2020; Eilert et al. 2021). They will be advised by the psychiatrist to complete one module (roughly 1 hour each in length) per

week, as recommended by Richards et al.(2018). Additional support will be available from the SilverCloud support team, including technical support, fortnightly feedback on programme progress, and the ability to open additional modules that may be helpful once the 8 core modules are complete. In situations where the SilverCloud programme cannot be accessed, alternatives will be considered.

5) Medication review: psychiatrist to review the parent's medication history and make recommendations to the GP regarding the medication and other aspects of the management as required.
6) Regular follow-up: According to the needs of the individual as assessed by the psychiatrist, either the psychiatrist or a psychology assistant checks in with parent once every 2 weeks for approximately 30 minutes via video call, phone call or in person to check on their progress and provide iCBT guidance, over the 12-week period. At each check-in parents will complete a PHQ-9 questionnaire to assess their current depressive symptoms.

Whether the parent recovers (PHQ-9 score <10 at baseline assessment) by the end of the treatment optimisation period or not, baseline assessments will be completed (within 3 weeks of the end of the treatment optimisation period), followed by randomisation of the young person to the intervention plus usual care or to the usual care only group. Participants will be randomised regardless of the number of parent treatment optimisation sessions attended. Parental recovered or non-recovered status at the end of the treatment optimisation phase will be used in exploratory subgroup analyses, including whether the recovery status of the parent modifies any effects of the intervention.

Each young person in the intervention arm will be assigned to an online therapy group (6 to 8 young people led by a therapist) that will meet weekly for the first 8 weeks during the acute phase of the intervention, which will then be followed by 3 monthly group continuation sessions. Detailed information on the intervention and usual care arms of the study are provided in section 11.

Data Collection

Online questionnaire assessments completed in REDCap by both parent and young person separately will be used to assess parent current and prior mood disorders and other psychiatric

diagnoses, and young person psychiatric diagnoses, depression history and depressive symptoms at the screening stage.

For parents found to be depressed following the screening stage, who have their depression treatment optimised, PHQ-9 data will be collected every 2 weeks for the 12-week duration of the treatment optimisation. Adherence to the treatment plan will be captured at the end of the 12-week treatment optimisation phase.

Young people and parents/carers will participate in separate online assessments at baseline, 3 months and 9 months. At the 9-month follow-up, the young person's depressive symptoms and episodes will be assessed. Additional data on potential mediators (negative self-beliefs, self-efficacy and problem solving, perceived stress, behavioral activation and interpersonal relationships) will be collected via online questionnaire at baseline, 3 and 9 months post-randomisation follow-up (where assessments will be kept as short as possible) to allow for exploratory analysis of change in the mediators over time, including checking the temporal ordering of exposure, mediator and outcome. Online questionnaires will be completed as close as possible to the scheduled follow-up periods (i.e. 3 months and 9 months), but within at least 4 weeks of participants receiving them. Assessments with parents and young person (at baseline and 9 months) will be completed on the same day where possible, or as close together as is feasible. At a minimum the study team will aim to have parent and young person assessments completed within 4 weeks of each other.

Qualitative data will be collected via interview and/or focus groups with a subsample of young people, parents and professionals separately to assess their experiences of participating in the trial, which will form a part of a process evaluation assessing how the intervention works. The subsamples will be selected to be representative of different groups in the trial, for example, young people whose parents were depressed at baseline and not depressed, whose parents did and did not recover following treatment optimisation, young people from different intervention therapy groups, young people in the usual care only arm, young people in the intervention arm with differing patterns of depression over the study period (i.e. those who (1) stayed well, (2) improved and stayed well, (3) improved and then relapsed, and (4) did not improve), and participants with different levels of engagement with the study. As recruitment of participants into the study will take place over several months, the qualitative focus groups/interviews will be staggered across three different time

points in the study to allow collection of qualitative data from participants completing the trial early on in the study, in the middle stages, and in the late stages of the study period.

6.1 Risk assessment

A Trial Risk Assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment has been completed in accordance with the MRC/DH/MHRA Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

- The known and potential risks and benefits to human participants
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

This trial has been categorised as a LOW RISK, where the level of risk is no higher than the risk of standard medical care. A copy of the trial risk assessment may be requested from the CTR. The trial risk assessment is used to determine the intensity and focus of monitoring activity.

7 Site and Investigator Selection

Recruitment of participants to the trial will be carried out via the NHS and via other routes (see section 9.1). This section outlines the process by which an NHS health board will be set up as a study site (Note, not all recruitment avenues will be set up as NHS sites (e.g. GP practices will be set up as participant identification centres and non-NHS recruitment routes will also be utilised; see section 9.1). This trial will be carried out at NHS sites in the UK including, Cwm Taf Morgannwg University Health Board, Cardiff & Vale University Health Board, Aneurin Bevan University Health Board, and Swansea Bay University Health Board. Additional Health Boards will be approached as required. Staff from the Research and Development Office at each University Health Board will work alongside Cardiff University researchers to support recruitment (e.g. by liaising with GP surgeries and primary mental health practitioners)

The study will follow standard procedures in setting up NHS trusts as study sites. All interested NHS sites will be required to confirm that they have adequate resources and experience to conduct the trial.

Before any NHS site can begin recruitment a Principal Investigator (PI) at each site must be identified. The following documents would usually be in place and copies sent to the Trial email account:

- The confirmation of Capability & Capacity from the site's R&D Department following sharing of local information pack
- Favourable opinion of host care organisation/PI from Main Ethics committee
- A signed Trial Agreement
- Current Curriculum Vitae (CV) and GCP training certificate of the PI
- Completed Site Delegation Log and Roles and Responsibilities document

Full contact details for all host care organisation personnel involved, indicating preferred contactThe trial team will provide the NHS site with:

- A copy of the most recent approved version of the Participant Information Sheet(s) and Consent Form(s)
- A copy of the most recent approved GP letter

Upon receipt of all the above documents, the Trial Manager will send written confirmation to the PI detailing that the centre is now ready to recruit participants into the trial. This letter/email must be filed in each site's Site File. Along with the written confirmation, the site should receive anything relating to trial intervention and a trial pack holding all the documents required to recruit into the Trial.

Occasionally during the trial, amendments may be made to the trial documentation listed above. The CTR will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to ensure that they obtain local R&D approval for the new documents.

Site initiation will be by in-person or online meeting.

8 Participant selection

Participants are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the CI before

randomisation/registration. For more detail on how the inclusion/exclusion criteria will be measured, please see section 9.

8.1 Inclusion criteria for trial

- Adolescents aged 13-19 years.
- Experiencing current elevated depressive symptoms (CES-D score≥16), and/or has a history of depression. However, we specify that young people should not have a current diagnosis of depression (because signposting to treatment would be more appropriate for this group).
- Living (at least some of the time) with a parent/carer (biological or non-biological) who has a history of unipolar depression who is willing to consider engaging with a depression treatment plan. If the parent has two or more children aged 13-19 who are eligible and willing to participate, the eldest will be selected to participate. If both parents have a history of unipolar depression, the primary caregiver will be selected to participate, or whichever parent is willing and able to engage with a depression treatment plan.
- Both young person and parent have access to the internet via a desktop/laptop/phone/tablet and have a valid email address and mobile phone number.
- Both young person and parent have the ability to complete trial activities as specified in the protocol, e.g., ability to communicate in English, absence of learning disability that would impair ability to participate, and for the young person, ability to participate in small group therapy sessions.

8.2 Exclusion criteria for trial

- Young person already receiving specialist treatment for depression (e.g. currently on antidepressants or receiving cognitive behavioral therapy (CBT)).
- Young person has a current diagnosis of depression, made by a doctor.
- Young person has been told by a doctor or healthcare professional that they have a diagnosis of bipolar disorder, schizophrenia, psychosis, eating disorder or alcohol/drug dependence or have generalized learning difficulties, that the parent judges would prevent them from participating in trial activities.

- Parent has been told by a doctor or healthcare professional that they have a diagnosis of bipolar disorder, schizophrenia or personality disorder.
- Parent is receiving treatment from secondary mental health services (e.g. community mental health team or psychiatrist).
- Parent or young person are not resident in the UK.

8.3 Inclusion criteria for professionals working on the trial who participate in qualitative interviews and/or focus groups

- Professional works on the trial as a therapist leading the young person CBT groups, or as a trial psychiatrist optimising parent depression treatment as part of the parent treatment optimisation phase.

9 Recruitment, screening and registration

9.1 Participant identification

The recruitment process is summarised in the flow charts shown in Section 9.2. The first avenue of recruitment will be via existing cohorts of adults with depression who have agreed to receive information about research studies (e.g. the NCMH cohort). Additional recruitment will be conducted via General Practices (GPs), primary mental health (PMH) services, schools and employee support and well-being services in the UK. GP practices and PMH services will recruit from Cwm Taf Morgannwg University Health Board, Cardiff & Vale University Health Board, Aneurin Bevan University Health Board, Swansea Bay University Health Board and other health boards in the UK, if required. Participants will also be recruited through online advertising. We will also advertise the study via leaflets/flyers/postcards in a range of health and community settings using in-person and online methods (e.g. waiting rooms, mental health charity groups, community centres, pharmacies, primary and secondary care settings, school in-reach services etc).

We will receive support from NCMH and staff from the Research and Development Office at each University Health Board, who have extensive experience of recruiting young people into trials.

Recruiting through NCMH: Participants in the NCMH cohort who potentially meet study inclusion criteria (participants who have a form of contact information available, have a history of depression and a child aged 13-19) and who have consented to be contacted for future research will be identified by the NCMH team via the NCMH database. They will be contacted by NCMH researchers by email and/or letter to ask whether they would be interested in taking part in the study. Included in the email/letter will be a link to further information about the study, a link to an expression of interest form, and the contact details of the study team. Potential participants who are interested in taking part will be asked to get in touch with the study team directly via the expression of interest form or by using the study team contact details provided. We are currently seeking approval to recruit via an additional existing research cohort – the GLAD study (https://gladstudy.org.uk/) – which is an NIHR bioresource for studies about depression and anxiety. We also plan on seeking approval to recruit through the CRIS system (https://www.maudsleybrc.nihr.ac.uk/facilities/clinical-record-interactive-search-cris/) and SAIL databank (https://popdatasci.swan.ac.uk/centres-of-excellence/sail/). We will use a similar process to identify potential participants if the recruitment is approved by the appropriate governance teams.

Upon completion of the online study expression of interest form by the potential participant, the study team will email the potential participant the study information sheets and a link to allow them to book a phone/video call to discuss the study further, providing an opportunity for them to ask questions, and to complete screening questions to check for eligibility. Once the screening phone/video call with the parent is complete, the young person will also be given the opportunity to discuss the study with a researcher, before completing their own screening questionnaire (CES-D questionnaire) with the researcher over the telephone. In instances where the parent-child dyad are clearly ineligible based on the parent screening phone call, the young person will not be asked to complete the CES-D questionnaire. Following completion of the screening phone/video call, the study team will check and confirm the parent-child dyad's eligibility to participate and will send the parent an email to communicate whether or not they are eligible. Where the dyad are not currently eligible, but there is a possibility they may become eligible with time (e.g. young person has no history of depression and no current subthreshold symptoms, but may develop subthreshold depression symptoms) permission will also be obtained to recontact the family in the future to check if their eligibility status has changed.

Where the dyad are eligible, the researcher will take informed consent or assent with the parent and young person over the phone/video call. Once the parent consent has been obtained, the parent will complete the PHQ-9 questionnaire with the researcher whilst still on the telephone/videocall (all questionnaires completed whilst on the telephone will be entered online by the researcher). Assent/consent forms will also include an opportunity for participants to agree to potentially participating in qualitative interviews and/or focus groups, though only a subsample of participants will be selected during the trial to participate in this qualitative data collection. Young people who are less than 16 years of age on entry to the study (i.e have completed an assent form) will be reconsented if they turn 16 during the course of the study. The research team will aim to do this at the next planned point of contact (e.g. baseline or 9-month follow-up interviews). If amendments are made to consent forms during the course of the study, that require participants to reconsent, the research team will also aim to do this at the next planned point of contact. Only research team members will be involved in the process of screening participants and taking consent. The role of NCMH staff is to help with identification of eligible participants only.

Recruiting through general practice (GP): Health & Care Research Wales (HCRW), local NHS R&D teams and/or NIHR Clinical Research Network (CRN) teams (including Buckinghamshire, Oxfordshire and Berkshire west (BOB) integrated care board, the East Midlands CRN, North West Coast CRN, South London CRN and South London RDN) with links to primary care will support recruitment through GP practices. Where NHS R&D teams' resources are limited, with the necessary approvals in place, research staff from the study team will provide additional support with recruitment at the GP PIC site where possible. GP practices in the UK will be contacted to ask if they are willing to be involved in recruitment into the study. They will receive information about the study, and details about how to get in touch with the study team. GP practices that agree to support the study recruitment will be set up as NHS participation identification centres (PICs) following standard procedures. They will work alongside the research team and/or local R&D teams to identify eligible participants using the GP electronic records system. The study team can provide pre-developed searches for the Vision, EMIS and SystmOne GP database systems that GP practices can use to identify potentially eligible participants. Eligible participants (history of depression and a child aged 13-19) will be contacted by letter or text with further information about the study, a link to an

expression of interest form and the contact details of the study team (including email and telephone number). A reminder text will then be sent 2-4 weeks later. Those who are interested in taking part will be asked to complete the online expression of interest form or to get in touch with the study team directly. Once the study expression of interest form has been completed by a potential participant, the study team will contact them via the telephone/video-call to discuss the study further and provide an opportunity for them to ask questions. The process of screening and consent described above (under recruiting through NCMH participants) will be followed. Members of the local R&D team will be provided with study-specific training and may also be involved in the process of screening participants and taking consent.

Recruiting through primary mental health teams: Local NHS R&D Teams will work with primary mental health service (PMHS) staff to identify eligible participants attending their clinics. PMHS staff will approach potential participants about the study and give them further information, including the link to the study expression of interest form and the contact details of the study team (including email and telephone number). Once the study expression of interest form has been completed by a potential participant, the study team will contact them via the telephone/video-call to discuss the study further and provide an opportunity for them to ask questions. The process of screening and consent described above (under recruiting through NCMH participants) will be followed.
There is one exception to this process in Aneurin Bevan UHB Primary CAMHS team. They will support recruitment to the SWELL study in the following way: (1) the PCAMHS team will identify all young people on their waiting list who may be eligible for the SWELL study, (2) the PCAMHS team will phone them to discuss the SWELL study with them, (3) if the family are interested in taking part the PCAMHS team will pass their contact details to the SWELL study team (with their consent to pass on these details), (4) SWELL study team will phone potential participants to organise a screening call, (5) SWELL study researchers will let the PCAMHS team know the outcome of their involvement in the SWELL study (e.g. if they are eligible or not, or if they are allocated to the intervention or not).

Recruiting through schools / educational institutions: Young people and their parents will be recruited through secondary schools, colleges, and universities in the UK. Schools will be asked to contact parents via their usual route of communication (e.g., text message or email) to ask whether they would be interested in taking part in the study. Included in the text/email will be a link to

further information about the study and a link to an expression of interest form for parents to complete. Secondly, schools will be asked to promote the study via newsletters and social media channels. In colleges/universities, the study will be advertised to young people aged 16 and over directly. The materials used to promote the study will include a link to further information about the study and a link to an expression of interest form for potential participants to complete.
Once the expression of interest form has been completed, the study team will email the parent the study information sheets and a link to allow them to book a phone/video call for them and their child to discuss the study further, providing an opportunity for them to ask questions, and to complete screening questions to check for eligibility. The process of screening and consent described above (under recruiting through NCMH participants) will be followed.

Recruiting through employee support and wellbeing services: The study will be advertised through wellbeing services in the UK (e.g., Canopi- a service supporting NHS and social care staff across Wales). Additional employee support and wellbeing services will be contacted to ask if they may be able to support recruitment in a similar way. Staff working in these services will approach potential parent participants about the study. Those who are interested in taking part will be asked to complete the study expression of interest form or to get in touch with the study team directly. Once the study expression of interest form has been completed, the study team will contact the potential participant via the telephone/video-call to discuss the study further and provide an opportunity for them to ask questions. The process of screening and consent described above (under recruiting through NCMH participants) will be followed.

For the trial professionals participating in qualitative interviews and/or focus groups, professionals will be provided with an information sheet and consent form once they have started working on the trial, giving them the opportunity to provide consent to participate in qualitative interviews and/or focus groups with other professionals to provide feedback on their experience of running the young person CBT groups or optimising parent depression treatment.

All researchers involved in discussing the study with potential participants, completing screening questionnaires and taking consent will be trained in how to talk to families about research and how to take consent in clinical research. This training will be documented on trial and/or site-specific

training logs which the CTR trial team will monitor throughout the trial.

9.2 Recruitment flow charts

ROUTE 1: Recruiting from existing cohorts e.g. National Centre for Mental Health (NCMH)

Contact eligible participants identified through NCMH by email or letter. Eligible = history of depression, child age 13-19 years, consent to contact. Include information on the trial (e.g. information sheets) and how to get in touch if interested (including website, email address, telephone number). A link to an online form to register interest in taking part will also be included.

↓

Family gets in touch with research team (via email, telephone, reply card, online form) saying they are interested in participating.

← If no response in 2 weeks, re-contact with reminder email/letter/phone call/ text message

↓

Researcher will contact potential participant via telephone/video call, to further discuss the study and provide an opportunity for them to ask further questions. If they agree to participate, then assess eligibility using online screening questionnaires.

↓

Online screening questionnaires to be completed, to ensure inclusion criteria met.

Inclusion criteria

- Young person aged 13-19 years
- Young person is currently experiencing elevated depressive symptoms and/or has a history of depression
- Young person is living with a parent (at least some of the time) who has a history of depression
- Young person has ability to complete trial activities as specified in the protocol
- Parent and young person have access to the internet and valid email address

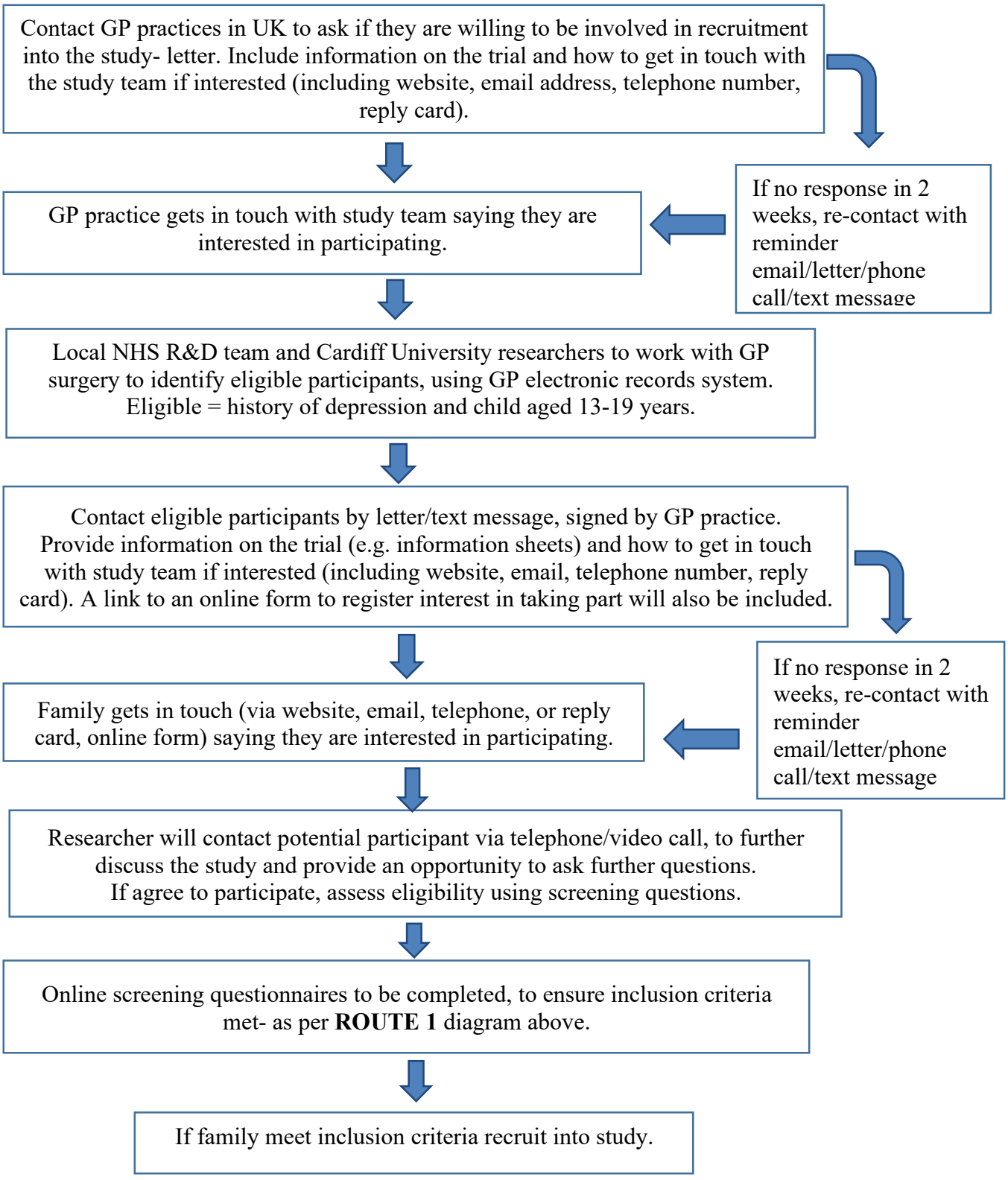
Exclusion Criteria

- Young person currently meets criteria for depression
- Young person currently receiving specialist treatment for depression (e.g., on antidepressants, receiving cognitive behavioral therapy (CBT)
- Young person has generalized learning difficulties, a diagnosis of bipolar disorder, schizophrenia, psychosis, eating disorder or alcohol/drug dependence
- Parent has a diagnosis of bipolar disorder, schizophrenia or personality disorder
- Parent is receiving treatment from secondary mental health services (e.g. community mental health team or psychiatrist)
- Parent or young person are not resident in the UK

↓

If family meet inclusion criteria recruit into study

ROUTE 2: Recruiting through General Practice/Primary Care



ROUTE 3: Recruiting through Primary Mental Health Services

Local NHS R&D team and Cardiff University Researchers to work with primary mental health service (PMHS) staff to identify eligible participants attending their clinics. Eligible = history of depression and child aged 13-19 years.

PMHS staff to approach potential participants about the study, provide information about the study (e.g. information sheets) and how to get in touch with study team if interested (including website, email, telephone number). A link to an online form to register interest in taking part will also be included. They may also ask permission for NHS R&D team or Cardiff University researchers to contact them to discuss the study further.

Family gets in touch (via website, email, telephone, or reply card, online form) saying they are interested in participating OR NHS R&D team or Cardiff University researchers contact potential participant to discuss the study, and provide information (e.g. Information sheets).

If potential participant agrees to take part, assess eligibility using screening questions.

If no response in 2 weeks, re-contact with reminder email/ letter/phone call/text message

Online screening questionnaires to be completed, to ensure inclusion criteria met- as per **ROUTE 1** diagram above.

If family meet inclusion criteria recruit into study

ROUTE 4: Recruiting through schools / educational institutions

Young people/parents will be contacted via letter/email/text message with information about the trial and how to get in touch if interested (e.g. website, email address, telephone number). A link to an online form to register interest will also be included.

Schools/colleges/universities will promote the study via newsletters/social media channels. These will include a link to further information about the study and information about how to get in touch if interested (e.g. website, email address, telephone number). A link to an online form to register interest will also be included.

↓

Family gets in touch with research team (via email, telephone, online form) saying they are interested in participating.

↓

Email sent to parent by the study team, including information sheets and a link to book a phone call/video call. Phone call/ video call to allow parent and child to discuss the study further, provide an opportunity for them to ask questions. If agree to participate, assess eligibility using screening questions.

↓

Online screening questionnaires to be completed with researcher, to ensure inclusion criteria met- as per **ROUTE 1** diagram above.

↓

If family meet inclusion criteria recruit into study

9.3 Screening logs

We will keep a record of how much information has been distributed about the study and through which source (e.g. GP, primary mental health team or NCMH). We will ask GP practices to let us know how many potentially eligible participants have been contacted. We will keep a record of the numbers of eligible and ineligible participants who complete the expression of interest form and how they heard about the study including their GP practice. For health boards where NHS R&D staff are actively involved in consenting potential study participants, we will ask practitioners at each centre to keep a screening log to monitor recruitment. When at site, these screening logs may contain identifiable information, but this must be redacted prior to being sent to the CTR (see section 22 for further detail on data monitoring/quality assurance).

9.4 Recruitment rates

Initially recruitment will be conducted primarily from NCMH. This sample includes approximately 1000 participants who appear to meet the eligibility criteria (have a history of depression and a child aged 13-19), who have agreed to be contacted to be invited to take part in research studies, and have good quality contact details (i.e., more than one form of contact available from email, post and phone number). We will additionally aim to recruit via PMH centres locally (e.g., in the Cwm Taf Morgannwg University Health Board and Cardiff and Vale University Health Board), with the possibility of extending this to other local health boards if needed in the later stages of recruitment. Participants will also be recruited through primary care, schools, employee support and wellbeing services and online and in-person (e.g. posters, leaflets) advertising. Rates of recruitment will be closely monitored so that periods of slower than expected recruitment can be identified quickly and actions be put in place to improve recruitment rates.

9.5 Informed consent

The participant's informed consent must be obtained using the trial consent forms on the basis of the information presented in the participant information sheets, which have been produced for the young people and parents/guardians. Online versions of the consent and assent forms have been developed on REDCap. These forms will be discussed in detail with potential participants following

the screening process. See section 9.1 for details on the process of screening and consenting participants. All consent/assent will be taken over the phone/video call by research team members who are trained/experienced in taking informed consent and in Good Clinical Practice.

Consent for access to routine health record data will be requested where data may be linked with routine healthcare data (e.g. for participants in Wales via the Secure Anonymised Information Linkage (SAIL) databank housed at Swansea University for longer term follow-up in a future follow-on study, on variables including depression diagnosis, use of primary and secondary mental health services for depression and prescription of depression medication.

Many young people participating in the study will be under 18 years of age. Online assent forms will be completed over the telephone with a trained researcher by young people aged < 16 years. Consent forms will be completed over the telephone by young people aged 16-19 years. Parents will complete consent forms over the telephone regarding their child's and their own participation in the study.

Only when electronic informed consent/assent has been obtained from the participant and they have been randomised/enrolled into the trial can they be considered a trial participant.

The right of the young person or their parent to refuse to participate in the trial without giving reasons must be respected. Assent/consent will be required from both the young person and their parent in order to participate. Similarly, the participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment (see section 10).

9.6 Registration and randomisation

Registration

Once a participant patient has been deemed eligible for entry into the trial, informed consent is obtained from the participant. The participant will be registered on the trial database and assigned a unique identification number.

Randomisation

The method of randomisation will be random permuted block randomisation stratified by site with a 1:1 allocation ratio and the unit of randomisation being the young person. The trial statistician has generated the allocation schedule, and this will be built into the REDCap trial database. The procedure for entering participants into the trial will consist of random allocation to either i) the SWELL intervention plus usual care, OR ii) usual care only. This will occur in two phases: 1) young people whose parent is not currently depressed will complete the baseline assessment and then be randomised immediately, and 2) young people whose parent is currently depressed will not complete baseline assessments followed by randomisation until their parent has completed a 12-week treatment optimisation period. They will undertake baseline assessments and randomisation once this is complete. Though where the parent fails to engage with the treatment optimisation (as defined by a failure to attend the initial appointment followed by two additional failed attempts at contacting/booking in an appointment for the parent), baseline assessments will be completed and the young person will be randomised. For young people allocated to the intervention arm, the intervention will begin once a therapy group is formed. We aim for therapy groups to include 6-8 participants.

10 Withdrawal & loss to follow-up

10.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the trial at any time. The participants' care will not be affected at any time by declining to participate or withdrawing from the trial. A 'withdrawal form' will be completed if a participant withdraws from the study.

If a participant initially consents but subsequently withdraws from the trial, clear distinction must be made as to what aspect of the trial the participant is withdrawing from. These aspects could be:

Withdrawal from intervention

Partial withdrawal from further data collection (e.g. questionnaires, clinical assessments)

Complete withdrawal from further data collection

Withdrawal of permission to use data already collected

We will continue to collect any safety data ongoing at the time of withdrawal, especially if the participant withdraws because of a safety event. There is specific guidance on this contained in the Participant Information Sheet.

- If a participant wishes to stop taking part in the trial completely, they may need to be seen one last time for a brief assessment about their reasons for withdrawing, to confirm their wishes and to signpost to services where needed.

In all instances participants who consent and subsequently withdraw should complete a withdrawal form (see Withdrawal Form in trial pack) or the withdrawal form should be completed on the participant's behalf by the researcher/PI based on information provided by the participant. Any queries relating to potential withdrawal of a participant should be forwarded to trial team.

10.2 Loss to follow-up

If a participant withdraws from the study, the data collected up to that point will be retained and used for the remainder of the study, if the participant does not withdraw consent for its use. We will attempt to contact those wishing to withdraw from the study to understand the reasons for withdrawing. This data might contribute to the assessment of the feasibility and acceptability of the programme and evaluation process.

11 Trial Intervention

11.1 SWELL intervention plus usual care versus usual care only

The young people will be allocated to either i) the SWELL intervention plus usual care, OR ii) usual care only.

The SWELL programme is a psycho-educational, cognitive-behavioural intervention for the prevention of unipolar depression in adolescents at an increased risk of depression. It is designed to be offered in small group settings delivered in two phases – the acute and continuation phase. The acute phase consists of eight 60-minute sessions delivered online by a trained therapist once a week, to groups of a maximum size of 8 young people across the age range of 13-19 years. The sessions are accompanied by a workbook for young people. The first few sessions give an overview of depression, its relationship to stressful situations, and introduce group members to one another. The following sessions focus on training the young people in cognitive-restructuring skills and in modifying irrational or negative thoughts, as these are hypothesized to contribute to the development and maintenance of depressive disorder. Other skills covered include assertiveness, relaxation and behavioural activation. The acute phase will then be followed by 3 monthly continuation sessions. These will be delivered to the same groups of up to 8 young people by the therapist, and will focus on reviewing and consolidating skills covered in the acute sessions.

Parents of young people receiving the intervention will be offered to attend two online parent information sessions of 60 minutes long during the weeks of the young person acute session 1 and session 4. The parent information sessions include details about the practicalities of young people attending the group, the theory underlying the intervention, how they can support their young people to engage with home practice activities between sessions and an overview of the content of each session. The first parent information session focuses on the content of young person sessions 1 to 4, and the second parent information session focuses on the content of young person sessions 5 to 8 and continuation sessions.

In this study, the intervention has been updated to identify parents who are currently depressed and to optimise their treatment before the young person is randomised to the intervention or usual care arm.

In both study arms, the young person's parent will be offered treatment optimisation as part of the study if they are currently depressed, as this will occur prior to randomisation.

The young people in the usual care arm will not receive the SWELL intervention, though they will be able to continue with any usual care that they already receive (noting that young people on antidepressants or receiving CBT will be excluded at study entry as part of exclusion criteria), and will be free to begin new treatment outside of the study. In the intervention arm, young people will also be free to continue existing treatment and begin new treatments outside of the study, alongside receiving the SWELL intervention. Young people in both the intervention arms will participate in a 3-month post-randomisation follow-up consisting of brief online questionnaires. The final 9-month follow-up assessment will consist of online questionnaires and a videocall including researcher-led clinical interviews about the young person and parent. More detail on the data collected at the 3 and 9-month follow-up assessments can be found in section 12.

11.2 Compliance

Participants will have an opportunity to discuss the study with the research team at the start via phone, video conferencing or email. When the participants are recruited, they will be asked for their contact details and how they would prefer to be contacted. The study website will also be updated regularly. Participants will receive information on the schedule of the trial including the dates of therapy sessions, and will be provided with the contact details of the research team if required during the course (or at the end) of the trial. They will continue to receive usual care (e.g. seeing school counsellor) where appropriate. Text and email reminders will be sent at regular intervals. Participants will receive voucher payments for participating after completing the baseline assessments (£10), 3-month follow-up (£20) and again after the 9-month follow-up (£30). Those participants who participate in the qualitative interviews and/or focus groups will receive an additional payment (£20).

Attendance to SWELL intervention sessions and the completion of any homework that is set will be monitored, e.g., via registers taken at each session by the therapist. The therapist will complete an adherence checklist at the end of the intervention to record young person engagement in the intervention and attendance. Adherence to the intervention will be defined as attending 6 out of 8 acute sessions and 2 out of 3 continuation sessions. Adherence will be rewarded by providing certificates following completion of the programme. Therapists will offer sessions scheduled outside the school day and one-to-one catch-up sessions on occasions when young people are unable to attend a session.

Attendance to the parent treatment optimisation phase will also be recorded in an adherence checklist completed by the psychiatrist at the end of the parent treatment optimisation phase. The opportunity to be assessed and treated by a specialist (psychiatrist) may be attractive and we will offer flexibility in how parents complete the initial assessment appointment (in person/videocall). Adherence to parent treatment optimisation will be defined as completion of the initial assessment and 4 follow-up calls.

12 Trial procedures

12.1 Overview of assessments & data collection

Data will be collected via online assessments (questionnaires and researcher-led clinical interviews) with parents and young people at baseline and follow-up assessments. Consent will be obtained to allow longer term follow-up in a separate study (funded by the Wellcome Trust grant 303982/Z/23/Z) via data linkage with routine health, education and social care data (e.g. via the SAIL databank).

All assessments and data collection will be completed remotely – via online questionnaires and video conferencing/phone call. Researchers will not look at completed questionnaires at baseline, 3 months or 9 months during the course of the study. Data collected in the questionnaires will be accessed at the end of the study for analysis only. This has been made clear to participants in the text provided with the questionnaire link.

The following domains will be assessed:

a) A rapid review of the feasibility of delivering the trial and intervention online will be assessed via qualitative interviews with the therapist/s facilitating the first two intervention groups enrolled. This will inform whether any minor adjustments to the way we conduct the trial and intervention needed before continuing the trial with the rest of the participants and therapy groups.
b) Effectiveness of the programme on primary and secondary outcomes at follow-up.

c) An embedded process evaluation of the implementation of the intervention, and participants' interactions with it, focussing on the elements of fidelity, exposure, reach and context.

d) Evaluation of the mechanisms through which the intervention brings about change (qualitative and quantitative data). (see Sections 12.2, 12.4 and Figure 1)).

e) Process evaluation to examine the impact of the main adaptations to the intervention of i) treatment for currently depressed parents at baseline and ii) delivering the SWELL intervention online (qualitative and quantitative data, see Sections 12.2 and 12.4) .

f) Description of participant characteristics to inform the representativeness of the trial (e.g. age, gender, ethnicity, language, source of recruitment (e.g. NCMH, primary care unit), details of help received where relevant (practitioner seen, form of talking/psychotherapy, prescribed medication), past history of depression, home living circumstances (e.g. lives with parent(s)/carer(s), other), education/occupation (school/college, out-of-school, university, employed), and parent characteristics including socioeconomic status.

12.2 Outcomes and measures (baseline and follow-up):

Parents and young people will complete assessments online at an initial screening stage, at baseline, and at 3 months and 9 months post-randomisation (Section 3.1: participant flow diagram). As a part of the SWELL intervention, young people will also complete regular assessments of depressive symptoms to track symptom change, which will contribute to the process evaluation of how the intervention might work and when symptoms start to improve. The full schedule of assessment measures to be used at each of these time points is shown in section 12.6.

Primary outcome

Depressive episode: The primary outcome is time (from randomisation to event in weeks) to the first DSM-5 depression episode occurring in the young people between randomisation and the 9-month follow-up period. This will be measured using the longitudinal interval follow-up evaluation (LIFE) which will be conducted via interview at the 9-month follow-up assessment (Keller et al., 1987), completed by the young people about themselves, and by the parent about the young people. The LIFE is a validated, semi-structured, research diagnostic interview designed to assess the longitudinal course of psychiatric disorder. It involves the interviewer completing a detailed assessment that

allows them to ascertain the level of depressive symptoms over the entire follow-up period. The interviewer starts by helping the participant recall the depression symptoms they described at their last interview (i.e. 9 months earlier, at baseline assessment). They then ask about change points in the participants depressive symptoms over the follow up period allowing them to track the onset and offset of symptoms. Based on this data, a depressive symptom rating (DSR) for each week of follow-up is derived. Week by week DSR scores coded by researchers during the interview at 9-month follow-up will be recorded on the study database. In this study, a score on the depression symptom rating of 4 or more for at least 2 weeks will index a depressive episode. The DSR score for depressive episodes has been shown to correlate with other standard measures of depression (Warshaw et al., 1994). The LIFE provides enough detail to date individual depressive symptoms and episodes, and allows calculation of time to recovery, length of wellness intervals and time to recurrence (Keller et al., 1987). All researchers undertaking the LIFE interview will be trained in the use of the measure. In addition, all interviews will be audio recorded, and consistency across raters will be checked (inter-rater reliability). Approximately 10% of interviews will be independently coded by a separate member of the research team and the inter-rater reliability of depressive episodes will be assessed using percentage agreement between raters.

Secondary outcomes

Number of depression free weeks, length of wellness intervals, time to recovery from depressive episodes and time to recurrence of depressive episode: The forementioned variables will be measured using the LIFE at 9-month follow-up, as described in the primary outcome section above.

Depression symptom score: Depression symptoms will be measured at screening, baseline, 3-month and 9-month follow-up to assess whether depression symptoms in young people change over the duration of the follow-up. They will be measured using the Centre for Epidemiological Studies-depression scale (CES-D) (Radloff et al., 1991), completed by the young person, and the Revised Children's Anxiety and Depression Scale (RCADS) (Chorpita et al., 2000), completed by the young person and their parent. The Center for Epidemiological Studies – depression scale (CES-D) (Radloff et al., 1991) was designed to detect depression in adults in the general population (Radloff, 1977) but is suitable for use in adolescents (Radloff et al., 1991). It is a 20-item, self-report measure of depressive symptoms; each item is scored on a scale of 0-3, with a total range of 0-60. It has good internal consistency across clinical (α = 0.83-0.84) and non-clinical samples (α = 0.81-0.93) (Stockings et al., 2015). The Revised Child Anxiety and Depression Scale (RCADS) (Chorpita et al., 2000) is a

measure of depression and anxiety in young people. It is made up of 47 items, scored on a scale of 0-4 and grouped into 6 subscales. One subscale (10 items) measures depression symptoms, and the other subscales measure symptoms of separation anxiety disorder, social phobia, generalised anxiety disorder, panic disorder and obsessive compulsive disorder. It has been shown to have excellent internal consistency (α = 0.93) (Stockings et al., 2015).

Depression risk score: a risk score tool developed at Cardiff University will be used to assess individuals' 3-year risk of developing depression (see Stephens et al., 2022). The risk score is based on age, sex, income, adolescents' symptoms of anxiety, symptoms of depression, presence of stressful life events in the past 12 months, and current parent depression symptoms. The risk score will be calculated at baseline and at the 9-month follow-up, allowing us to assess whether it changes over the course of the intervention.

Anxiety symptoms: The RCADS (Chorpita et al, 2000) (described earlier) will be used to measure anxiety symptoms at baseline, 3 and 9 months and will be completed by both the young person and their parent.

Irritability symptoms: Irritability will be measured using the Affective Reactivity Index (ARI) (Stringaris et al., 2012). The ARI is a dimensional measure of irritability containing 7 items scored on a 3-point scale. It will be completed by young people and their parents at baseline, 3 months and 9 months.

Quality of life: This will be assessed using the EQ-5D-Y. The EQ-5D-Y consists of questions about mobility, looking after self, doing usual activities, pain/discomfort, and feeling worried, sad, or unhappy (Wille et al., 2012), as well as including a vertical visual analogue scale ranging from "the best health you can imagine" to "the worst health you can imagine". It will be completed by the young people at baseline and 9-month follow-up.

Developmental competence: A questionnaire used to measure developmental competence (Brent et al., 2015), has been modified to make a 9-item measure, with each item scored 0-4 and the total ranging from 0-36. This will be completed by the young person at baseline and 9 months.

Functional impairment: The Children's Global Assessment Scale (cGAS) (Shaffer et al., 1983) will be completed by the interviewer about the young person at baseline and 9 months. The cGAS measures psychological and social functioning rated on a scale of 0-100, with a lower score indicating greater impairment.

Measures of Possible Mediators

The Logic model (Figure 1) shows hypothesized mediators of change for the SWELL intervention. Possible mediators will be measured at baseline, 3 months and 9 months to allow for exploratory analysis of change in the mediators over time, including checking the temporal ordering of exposure, mediator and outcome, which will be important given the strong within time correlations that are likely to be observed between the mediators and the outcome. It is possible that certain hypothesized mediators, such as those relating to changes in mindset including dysfunctional attitudes and self-efficacy, may act as both mediators and secondary outcomes. Those that show evidence of change at 3 months (which is either maintained at final follow-up or not) will be included in the mediation analysis and those that show change at final follow-up but not at 3 months will be treated as secondary outcomes. These include measures of negative self-beliefs, self-efficacy and problem solving, perceived stress, behavioral activation and interpersonal relationships.

Negative self-beliefs: The Dysfunctional Attitudes Scale for Children (DAS-C) (D'Alessandro and Burton, 2006) measures negative beliefs and will be completed by young people. The DAS-C is a 22-item self-report measure of dysfunctional attitudes, using a 6-point scale ranging from 1 = "strongly disagree" to 6 = "strongly agree". Scores can be summed to make a total score. It has been shown to have good internal consistency (Cronbach's α= 0 .87) (D'Alessandro and Burton, 2006).

Self-efficacy and problem solving: Young people will complete the Generalised Self-Efficacy Scale (GSE) (Schwartzer and Jerusalem, 1995) to measure self-efficacy. The GSE is a 10-item, self-report scale that assesses perceived self-efficacy. It is scored on a 5-point scale ranging from 1 = "not at all true" to 5 = "exactly true." It has good internal consistency (Cronbach's α = 0.76-0.90 across studies).

Perceived stress: Young people will complete the perceived stress scale (PSS) (Cohen et al., 1983). The PSS is a 10-item questionnaire scored on a scale from 0 to 4, measuring domains of unpredictability, lack of control, burden overload, and stressful circumstances. It has been shown to have good internal consistency (Lee et al., 2012).

Behavioural activation: Young people will complete the behavioural activation scale for depression-short form (BADS-SF) (Kanter et al., 2012). This is a 9-item, self-report scale scored on a 7-point scale from 0-6, ranging from 0 = "not at all" to 6 = "completely". It has been shown to have good internal consistency and test-re-test reliability (Kanter et al., 2012).

Family relationships: The Conflict Behaviour Questionnaire (Robin et al., 1989) will be completed by the parent. This is a 20-item measure with each item scored true or false. The Child's Report of

Parental Behaviour Inventory (CRPBI) will be completed by the young person. It is a 21-item scale that measures a child's perceptions of their parent's child-rearing behavior (Margolies et al., 1977). Finally, the child disclosure subscale from the parent monitoring measure (Stattin and Kerr, 2000) will also be completed by parents.

Measures of possible moderators

Potential moderators of intervention effectiveness to be investigated as part of exploratory analyses include characteristics of the young people (e.g., comorbidity, stressful life events and initiation of new treatments/service use) and parents (e.g., current depression status, parent's adherence to the treatment optimisation phase if they were currently depressed at screening stage).

Potential moderators - Young person

Past psychiatric history and treatment: Questions regarding previous young person mental health diagnoses and treatment history will be completed by parents about the young person as part of the initial screening for eligibility.

Measures of psychopathology: In addition to the primary and secondary outcomes described above, several other measures of psychopathology will be completed about the young person. To determine adolescents' eligibility for the trial, we will screen them for a current depressive episode, by asking their parent whether or not they have been told by a doctor that they have a diagnosis of depression. Past history of depression in the young person will also be assessed during screening. Parents will be asked if their child has ever been diagnosed with depression by a doctor. If not, they will be asked about their child's history of depression symptoms using DSM-5 criteria for a Major Depressive Episode. However, given ethical concerns around asking about suicidal thoughts at screening, the DSM-5 depression symptom "recurrent thoughts of death, suicidal ideation or suicide attempts" will not be asked about at screening and a total symptom count of 4 or more will be used to establish a history of probable depressive episode. A history of depression will be counted as present if the young person has previously been diagnosed by a doctor or if they have met DSM-5 criteria for probable depression in the past. At baseline further information about depression will be obtained using the parent reported Development and Well Being Assessment (DAWBA). The DAWBA is a structured diagnostic interview that asks about a range of psychiatric symptoms based on DSM diagnosis (Goodman et al., 2000). Symptoms of Autistic Spectrum Disorder (ASD) and Attention

Deficit Hyperactivity Disorder (ADHD) also will be assessed at baseline using the parent rated Social Communication Disorder Checklist (SCDC) (Skuse et al., 2005) for ASD symptoms and the parent rated DuPaul ADHD questionnaire (DuPaul et al., 1981) for ADHD symptoms.

Life events: Information on significant life events at baseline and at the 9-month follow-up will be obtained with the Life Events Checklist (LEC) (Johnson et al., 1980), completed by young people and parents. The LEC measures positive and negative life events in young people aged 13-18 that occurred in the last 12 months and ever. This life events measure contributes to the depression risk score (described earlier).

Service use and treatment: A modified version of the Client Service Receipt Inventory (Beecham and Knapp, 2001) will be used to measure service use and will be completed by young people and parents at baseline and at the 9-month follow-up.

Potential moderators - Parent

Family history of depression and other psychiatric disorders: Information about family history of depression will be collected at baseline from the parents. They will be asked if their parents or siblings also have a history of depression. Parents will also be asked at baseline whether any first or second degree relatives have a history of any other psychiatric disorders (e.g. anxiety, bipolar affective disorder, schizophrenia).

Measures of parental psychopathology: To determine parents' eligibility for the trial, we will screen them for a history of depression by asking whether they have ever been diagnosed with depression by a doctor. If not, they will be asked about past depression symptoms using the DSM 5 criteria for Major Depressive Episode. However, given ethical concerns around asking about suicidal thoughts at screening, the DSM-5 depression symptom "recurrent thoughts of death, suicidal ideation or suicide attempts" will not be asked about at screening and a total symptom count of 4 or more will be used to establish a history of probable depressive episode. A history of depression will be counted as present if the parent has previously been diagnosed by a doctor or if they have met DSM-5 criteria for probable depression in the past. Past psychiatric history in the parent, in particular the timing, duration, and severity of previous depressive episodes, will be recorded using a life history calendar approach (Caspi et al., 1996). Parents also will complete the Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001) at screening, baseline, 3 months, and 9 months to assess whether parents'

depressive symptoms change over the duration of the trial. The PHQ-9 measures depression symptoms and was developed to screen for depression in adults in the primary care setting. It has 9 items, each scored 0-3, with a suggested cut-off of ≥ 10 indicating mild, clinically significant symptoms (Kroenke et al., 2001). Symptoms of anxiety will be measured using the Screen for Adult Anxiety Related Disorders (SCAARED) (Angula et al., 2017). This is a 44 item questionnaire asking about anxiety symptoms in adults, with subscales including generalised anxiety disorder, separation anxiety disorder, social phobia and panic disorder or significant somatic symptoms. It will be completed by parents at baseline, 3 and 9 month follow-up.

The schedules for clinical assessment in neuropsychiatry (SCAN) (Wing et al., 1990) will assess depression diagnosis in the parent at baseline. The Parents also will be interviewed with the Longitudinal Interval Follow-Up Evaluation (LIFE) (Keller et al., 1987) at 9 months, to obtain detailed information about their depression over the follow-up period. Interviewer rated measures about the parent's depression (Hamilton Depression Rating Scale) (Hamilton, 1980) and functioning (Global Assessment of Functioning (GAF)) (American Psychiatric Association, 2000) will be completed at baseline and at the 9-month follow-up.

Parent functioning: The 12-item version of the World Health Organisation Disability Assessment Schedule (WHODAS) (WHO, 2010) will be completed by the parent at baseline and at the 9-month follow-up. The WHODAS measures health-related quality of life and asks about difficulties due to health conditions over the last 30 days. Domains covered include cognition, mobility, self-care, getting along, life activities, and participation.

Service use: A modified version of the Client Service Receipt Inventory (Beecham and Knapp, 2001) will be used to measure parent service use at baseline and at the 9-month follow-up.

Adherence to the parent treatment optimisation phase: attendance to the initial consultation and each follow-up session of the 12-week parent treatment optimisation phase will be documented by research team at the end of the 12-week period.

Baseline Demographics:

Young person characteristics: Demographic information including age, sex, gender, ethnicity, race, language, with whom the adolescent lives, geographical location, and education/occupation will be collected at baseline.

Parent characteristics: Demographic information about parents will be collected at baseline including age, sex, ethnicity, whether they have a partner/spouse, language, education level, occupation and income.

12.3 Follow-up

Participants will be followed up at 3 months and 9 months post-randomisation, which is consistent with previous studies of this intervention (Garber et al., 2009). Young people and their parents will participate in assessments separately regarding the young person's depressive symptoms (3 and 9 months), measures of potential mediators of the effectiveness of the intervention (3 and 9 months– to allow for exploratory analysis of change in the mediators over time, including checking the temporal ordering of exposure, mediator and outcome), and depressive episodes since baseline (9-month follow-up).

12.4 Process evaluation

The process evaluation will aim to investigate how the intervention worked, the parts of the intervention and trial that worked well and for whom, and to identify any aspects that could be modified to improve effectiveness prior to implementation. We will focus on the following elements: recruitment and reach, retention, fidelity, adherence and contextual factors in terms of how this might impact on intervention effectiveness. In addition, we will investigate the acceptability of the new elements introduced in this trial – the intervention being delivered online, and the addition of the parent treatment optimisation phase prior to the randomisation of the young person. The process evaluation will also help us to understand underlying mechanisms of effectiveness of the intervention, by further investigating how mediators detailed in the logic model (Section 4, Figure 1) might work. The process evaluation will employ a mixed methods approach, utilising quantitative data collected (for example, from questionnaires, registers of attendance, etc.) and qualitative data.

Questionnaires will be completed at baseline by parents in the parent depression treatment optimisation group, and at 3 months by young people and parents of young people allocated to the intervention arm. Qualitative data will be collected via interviews with parents and professionals after completion of the parent treatment optimisation, and via focus groups with young people who

were allocated to the intervention arm (approximately 16 individuals in total), parents of young people allocated to the intervention arm (approximately 8 individuals in total) and professionals involved in delivering the intervention (up to 4 individuals) as soon as possible after the 9 month follow-up. As recruitment of participants take place over an extended period of time, qualitative focus groups/interviews will be staggered across three different time points in the study to allow collection of qualitative data from participants completing the trial early on in the study period, in the middle stages, and in the late stages of the study period. These interviews and focus groups will provide more in-depth information on the acceptability of exploratory aspects of the intervention, including the treatment of current parental depression prior to the intervention for the young people, and the delivery of the intervention online. They will also provide in-depth information on the fidelity, exposure, reach and context of the intervention and trial and how this might have impacted upon intervention effectiveness. Separate interviews/focus groups will also be undertaken with young people (approximately 8 individuals) and parents of young people (approximately 8 individuals) who were allocated to the usual care only arm of the study. A process evaluation framework has been developed, following the MRC guidance on process evaluation (Moore et al. 2015) to explore in detail the different components of our process evaluation and how these will be assessed.

When sampling for the qualitative interviews and/or focus groups, we will ensure that subsamples represent as much variation in the trial participants as possible, in particular, endeavouring to include young people whose parents were depressed at baseline and not depressed, whose parents did and did not recover following treatment optimisation, young people from different intervention therapy groups, young people in the usual care only arm, young people in the intervention arm with differing patterns of depression over the study period (i.e. those who (1) stayed well, (2) improved and stayed well, (3) improved and then relapsed, and (4) did not improve), and participants with different levels of engagement with the study. In addition, we will endeavour to sample maximum variation in terms of gender, age and demographic variables such as socioeconomic status. We will ensure similar representation of all groups for the parent interviews and/or focus groups. Ongoing decisions regarding the size of these qualitative subsamples will be pragmatic based on preliminary findings.

12.5 Data linkage

We will ask participants (both parents and young people) for consent to apply for data linkage to routinely collected data on health and education, service use, symptoms/diagnosis and medication in the future. For participants in Wales such data is held anonymously in the Secure Anonymised Information Linkage (SAIL) dataset at Swansea University. For participants in England such data is held anonymously and securely in NHS Digital. Linkage in the future will require participant consent (this will be made clear in the information sheets and consent forms). We plan to analyse this data under a future funding request as part of a long term follow up of participants to explore whether earlier exposures (e.g., trauma) or use of services might modify the effectiveness of the intervention and to evaluate the impact of the intervention on longer term health outcomes such as treatment for depression.

12.6 Schedule of assessments for the trial

			Follow-up	
	Screen	**Baseline**	**Month 3**	**Month 9**
Questionnaires about Young People				
Eligibility questions (e.g., psychiatric history and treatment)	P			
Centre for Epidemiological Studies Depression Scale (CES-D)	Y	Y	Y	Y
Demographic characteristics (e.g., age, sex, ethnicity, education)		Y, P		
Revised Children's Anxiety and Depression Scale (RCADS)		Y, P	Y, P	Y, P
Affective Reactivity Index (ARI)		Y, P	Y, P	Y, P
Social Communication Disorders Checklist (SCDC)		P		
DuPaul ADHD Questionnaire		P		
Dysfunctional Attitudes Scale for Children (DAS-C)		Y	Y	Y
Generalised Self-Efficacy Scale (GSE)		Y	Y	Y
Perceived Stress Scale (PSS)		Y	Y	Y
Behavioural Activation Scale for Depression- short form (BADS-SF)		Y	Y	Y
Developmental Competence Scale (abbreviated)		Y		Y
Conflict Behaviour Questionnaire		P	P	P
Child Report of Parents Behaviour Scale		Y	Y	Y
Parental monitoring (child disclosure questions)		P	P	P
Life Events Checklist (LEC)		Y, P		Y, P
EQ-5D-Y		Y		Y
Interviews about Young People				
Development and Well Being Assessment (DAWBA)		Y, P		
Client Service Receipt Inventory (CSRI)		Y, P		Y, P
Longitudinal Interval Follow-Up Evaluation (LIFE)				Y, P
Questionnaires about Parents				
Eligibility questions (e.g., psychiatric history and treatment)	P			
Patient Health Questionnaire-9 (PHQ-9)	P	P	P	P
Demographic characteristics (incl. age, sex, ethnicity, education level, income, occupation)		P		
Screen for Adult Anxiety Related Disorders (SCAARED)		P	P	P
World Health Organisation Disability Assessment Schedule (WHODAS)		P		P
Interviews about Parents				
Schedules for clinical assessment in neuropsychiatry (SCAN)		P		
Past Psychiatric History, using life history calendar approach		P		
Client Service Receipt Inventory (CSRI)		P		P
Longitudinal Interval Follow-Up Evaluation (LIFE)				P
Other Measures				
Depression risk score (young person)		Int		Int
Children's Global Assessment Scale (cGAS)		Int		Int
Global Assessment of Functioning (GAF)		Int		Int

Hamilton Depression Rating Scale (HDRS)		Int		Int
Parent treatment optimisation adherence checklist		Res		
Young person intervention adherence checklist				Res
Young person intervention fidelity checklist			Res	

Y = Completed by young person; P = completed by parent; Int = completed by interviewer. Res = member of the research team (member of treatment optimisation team will complete parent treatment adherence checklist after the optimisation phase; therapist will complete young person adherence checklist after intervention completed; researcher observing sample of intervention group sessions will complete fidelity checklists). Where Y and P are both listed, both parent and young person complete the measure.

13 Safety reporting

The CTR are responsible for ensuring that all staff involved in this study are familiar with the content of this section.

The research team has considerable experience in working with people with mental health difficulties of all ages. Where risk to a participant is identified by the research team (e.g. suicidal thoughts/plans) an internal individual risk assessment will be completed. Following completion of the risk assessment, if required, concerns will be discussed with a clinical member of the study team and standard AE/SAE reporting should be followed (see section 13.5). A clinical member of the study team will be available to respond to concerns regarding risk to participants throughout the duration of the study.

All researchers working on this project who will be in direct contact with research participants hold adequate clearance (e.g. DBS) for working with children and young people.

The study team will record details of Adverse Events (AEs) listed in section 13.1 that are experienced by study participants (young people) and reported by either the study participants or their parents during their participation in the study (from time of signature of informed consent, throughout the duration of the study, including intervention receipt and follow-up) by completing the study specific Serious Adverse Event (SAE) form. Where both young person and parent report the same AE, a separate reporting form will be used for each. Occurrences that meet the definition of an SAE (see section 13.1) must be reported immediately (within 24 hours of knowledge of the event) to the CTR. If the SAE is reported after 24 hours when the study team was aware of this event they must provide reason as to why there was a delay in reporting. Where the same adverse event is ongoing (e.g.

recurrent self-harm) it will be reported the first time it occurs and again where there is a change (e.g. new method of self-harm or change in severity of self-harm using the same method).

13.1 Definitions

Term	Definition
Adverse Event (AE)	AEs to be recorded for the SWELL study are: • suicidal ideation (with a plan/method considered) • suicide attempt • deliberate self-harm
Serious Adverse Event (SAE)	Any adverse event that – • Results in death • Is life-threatening* • Required hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Other medically important condition***

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event or it is suspected that used or continued used of the product would result in the subjects death; it does not refer to an event which hypothetically might have caused death if it were more severe.

**** Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

***** Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

13.2 Trial Specific SAE Reporting requirements

Expected adverse events in the population under study include:

- AE1 – Act of deliberate self-harm, suicidal ideation (with a plan/method considered) or suicide attempt.

The AE listed above will follow the SAE timeframe of reporting - reported to the CTR with 24 hours of knowledge of the event - for the CI or suitably qualified delegate to assess whether they fit the protocol definition of an SAE (e.g. they require hospitalisation). Occasionally it may be appropriate for the researcher to whom the AE was reported to by a study participant to assess/comment on seriousness in their reporting of the AE to CTR. If the AE is categorised as 'serious', the CI or delegate will continue their causality assessments and standard SAE procedures will be followed.

13.3 Causality

Causal relationship will be assessed for the intervention and procedures:

Intervention: SWELL – a cognitive-behavioural group therapy for adolescents at elevated risk of depression **Procedures:** Standardised clinical interviews and questionnaires on adolescent and parent depressive symptoms and episodes (e.g. LIFE, DAWBA, CES-D)

The Chief Investigator or other appropriately trained and qualified members of the research team will assess each SAE to determine the causal relationship:

Relationship	**Description**	**Reasonable possibility that the SAE may have been caused by the intervention?**
Unrelated	There is no evidence of any causal relationship with the intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the intervention. There is another	No

	reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	
Possible	There is some evidence to suggest a causal relationship with the intervention. However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	Yes
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

13.4 Expectedness

Inherent in this study population is the risk of self-harm and suicide, and so the AEs listed in section 13.2 are expected in this population (but these AEs are not expected to be related to the intervention itself). However, the additional contact with the study team for the intervention arm may create greater opportunity for individuals in the intervention arm to report AEs.

The Chief Investigator (or another delegated appropriately qualified individual) will assess the expectedness of each SAE (i.e. events not listed in 13.2 and categorised as serious). SAEs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events. For example, an event more specific or more severe than that described in the protocol is considered unexpected.

13.5 Reporting procedures

The CTR will manage the process of reporting, tracking and follow-up of safety events throughout the duration of the study and will train the study team on how to report a safety event to the CTR. (table below covers the delegated staff for SWELL safety reporting procedures).

Procedure	Delegated Staff
Safety reporting activities e.g. AE/SAE reporting, and seriousness assessments (if required)	• Study Team (research staff, trial staff, therapists) • Principal Investigator (PI) (i.e. reporting site)
SAE processing	• CTR (Trial manager or Data Manager)
SAE assessment (seriousness, causality and expectedness)	• CI or qualified clinical reviewer • PI at reporting site

A completed SAE form for all safety events requiring timely reporting should be submitted via email to the trial-specific email address; if the event meets the definition of an expected AE or SAE, it must be reported to the CTR within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The study team member completing the SAE form should sign and date it to acknowledge that they have provided sufficient detail on the event and assessed the seriousness (if applicable) based on the protocol definitions in section 13.1. The CI or suitably qualified delegate will perform the causality and expectedness assessments within a timeframe of 24-72 hours.

The CTR will evaluate whether the seriousness criteria and other information in the SAE form are consistent and query any inconsistencies with the study team.

The participant will be identified only by trial number, partial date of birth (mm/yy) and initials. The participant's name should not be used on any correspondence. It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, the CTR may request

additional information relating to any SAEs and the site should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address:

SWELL@cardiff.ac.uk

An SAE form is not considered as complete unless the following details are provided:

- Full participant trial number
- An Adverse Event
- A completed assessment of the seriousness, and causality.

Following the initial report, all SAEs should be followed up to resolution wherever possible. Follow up information must be provided on a new SAE form.

Reports of any related and unexpected Serious Adverse Events (SAEs) will be submitted to the Research Ethics Committee (REC) and Sponsor within 15 days of the CTR becoming aware of the event. There is no requirement for Annual Safety Reports (ASRs) in addition to the information provided through the annual progress report. The CTR will report SAEs until the final follow-up assessment, or until the qualitative interviews and/or focus groups for those who participate in these, which will take place shortly after the 9-month follow-up.

All SAEs and AEs will be reported by the CTR and discussed as a standard agenda item by the TSC during their routine meetings.

13.6 Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor, CTR or CI may carry out in order to protect the participants of a trial against any immediate hazard to their health or safety. Any urgent safety measure relating to this trial must be notified to the REC and Sponsor immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken.

14 Statistical considerations

14.1 Randomisation

Participants will be randomised 1:1 using random permuted blocks stratified by site, with the unit of randomisation being the young person. The allocation schedule has been generated by the trial statistician by using ralloc (a STATA module to design randomised controlled trials) in STATA v17. The randomisation will be online to maintain allocation concealment from the trial recruiters and built into the CTR trial database. The randomisation system will be developed and tested by CTR according to their standardised procedures.

14.2 Blinding

It is not possible to blind the trial therapists or participants due to the nature of the intervention. Assessors for the follow-ups will be blind to the intervention arm. Data analysis (conducted by the trial statistician) will be carried out blinded to group allocation.

14.3 Sample size

We aim to recruit 400 adolescent participants and their parents/carers. We expect loss to follow-up of around 10% at 9 months based on previous studies of this population (Garber et al., 2009; Mars et al., 2012).

The starting point for the minimum clinically important difference (MCID) for this study is a conservative estimate of the hazard ratio (HR) of 0.63, taken from a previous study of the Coping with Stress intervention in the adolescent children of depressed parents in the US (Garber et al., 2009). However, we expect the effect of the intervention in this RCT to be greater than the one seen in the Garber et al. study (see below). We therefore define the minimum clinically important difference (MCID) for this study as an HR of at least 0.60 (equivalent to an 11% difference in MDD between intervention arms). We expect the effect size to be slightly larger than that described by Garber et al (2009) for the following reasons: 1) The study by Garber et al found that the intervention was not effective when parents were currently depressed. In this study, we will add

parent depression treatment prior to randomisation. We expect that 65% of parents will have recovered or substantially improved by the end of the optimisation period based on previous RCT studies of SilverCloud and other iCBT interventions (Richards et al 2020; Gilbody et al 2017). We anticipate that 40% of the recruited sample of parents will meet criteria for a current depressive episode based on data from our previous cohort of depressed parents where 39.3% of parents scored 10 or more on the PHQ-9 at baseline (Mars et al. 2012; 2015). We also expect the rates of parent depression at baseline to be lower in our study than observed in the Garber et al. study (45.4%). This is because our inclusion criteria (at least one parent with an episode of depression) differs slightly from the inclusion criteria used in Garber et al. (at least one parent with MDD or dysthymia in the last 3 years, or a depressive disorder with at least 3 occurrences, or a depressive episode of at least 3 years' duration during the adolescent's life). The addition of treatment optimisation to the study design and the anticipated lower rate of parental depression should create a more homogenous sample in terms of current parent depression at baseline than the previous study and therefore we expect to gain additional statistical power. 2) In the study by Garber et al (2009), parental depression at baseline was associated with a higher rate of MDD in young people in the intervention arm only suggesting that parental depression undermined the effectiveness of the intervention for the young person (rather that exhibiting an association irrespective of intervention arm). We therefore expect the inclusion of parent treatment optimisation prior to the intervention for the young person to increase the difference between study arms consistent with expecting a slightly larger effect size in this study than that observed in the Garber et al (2009) study.

With a sample size of up to 400 randomised participants, we are able to estimate the statistical power to detect a difference of at least 0.63 in the HR between the RCT arms to be 73.4% with an assumed 10% loss to follow-up at the end of a 9-month follow-up and a one sided alpha of 0.05. However for an expected greater effect, a HR of 0.6 (our specified MCID for this intervention; equivalent to an 11% difference in MDD between study arms) will achieve 79.9% power and a HR of 0.56 (equivalent to a 12% difference between study arms) will attain 87.0% power. A STATA sample

size program (ART – Analysis of Resources for Trials) was used for this estimation (Royston and Parmar, 2013; Babiker et al, 2015).

To ensure that the required sample size is achieved, the recruitment rates will be monitored by the Project Team Management group and compared to target recruitment rates which will be regularly calculated and updated. If the recruitment rates are not as expected and if the loss of follow-up rates are higher than expected, additional strategies to boost recruitment and subsequent retention will be implemented.

14.4 Missing, unused & spurious data

Missing item by item data will be handled according to the scoring algorithm for each measure individually.

14.5 Procedures for reporting deviation(s) from the original SAPC

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and Statistical Analysis Plan (SAP).

14.6 Termination of the trial

If there is evidence that the programme is having a negative effect on the participants' symptoms, if there is a significant imbalance in adverse events (e.g. suicidal ideation (with a plan/method considered), deliberate self-harm or suicide attempts) between the intervention group and usual care group (allowing for the fact that it is anticipated that more events will be reported in the intervention group, as detailed in section 13.5)., or if there are significant concerns about safety – we would need to consider stopping the trial This will be discussed with the wider research team and TSC.

14.7 Inclusion in analysis

All eligible and randomised participants will be included in the analysis – consistent with an intention to treat analysis.

15 Analysis

A detailed Statistical Analysis Plan (SAP) will be produced by the trial statistician(s) and reviewed by the Trial Management Group and oversight Steering Committee prior to database lock. Analyses are described in brief below.

15.1 Flow of participants

The flow of participants through the trial will be presented as a CONSORT flowchart (Rennie 2001; http://www.consort-statement.org/) for all participants approached in the study (see section 3.1).

15.2 Baseline data and participant characteristics

Baseline data will be presented for all consented and randomised participants. This will be summarised and tabulated using proportions and means and SDs (or median and IQRs), for the whole group and by arm. All subsequent summaries will use the complete cases and will employ the intention to treat principle (participants will remain in the groups to which they were randomised irrespective of intervention received).

15.3 Effectiveness outcomes related to the SWELL intervention:

The primary outcome is time to the first depressive episode in the young person during the 9-month follow-up period.

- Secondary outcomes include depressive symptoms, depression risk score (Stephens et al., 2023), anxiety symptoms, irritability symptoms, quality of life, developmental competence and functional impairment.

15.4 Process evaluation:

Section 12.1 defines the key questions to be assessed in the nested process evaluation. In brief, the process evaluation will assess fidelity, adherence, feasibility and acceptability of the intervention and possible intervention mechanisms. It will also assess how key adaptations made to SWELL (i.e. the addition of treatment optimisation) influence effectiveness and potential implementation of the intervention. We aim to conduct interviews and focus groups with YP, parents and professionals involved in the adolescent-focused SWELL intervention and parent treatment optimisation. We will additionally ask for feedback on trial processes which will include those allocated to both study arms ((see Sections 12.4 and 15.5 for further details).

15.5 Qualitative analysis of interviews and/or focus groups

Qualitative interviews and/or focus groups will be conducted with the participating young people, and parents separately shortly after the time of their 9-month follow-up, and with professionals (e.g. CBT therapists, psychiatrists, and trial deliverers) towards the middle to end of their participation in the trial, as a qualitative exploration of how the intervention procedure worked for them. We aim to ensure that participants in the qualitative interviews and/or focus groups represent the different groups participating in the trail, i.e., young people whose parents were depressed at baseline and not depressed, whose parents did and did not recover following treatment optimisation, young people from different intervention therapy groups, young people in the usual care arm, young people in the intervention arm with differing patterns of depression over the study period (e.g. those who (1) stayed well, (2) improved and stayed well, (3) improved and then relapsed, and (4) did not improve), and participants with different levels of engagement with the study. A small sub-set of professionals may also be interviewed earlier in the trial to provide rapid feedback to inform trial conduct. Semi-structured topic guides will be developed using a scoping literature review and input from the interdisciplinary research team. The topic guide will include overarching topics, but will be flexible and allow the interview to be guided by the interviewee and allow the interviewee to initiate

and develop topics that have not been pre-empted by researchers. This will also include open ended questions about elements that may impact upon trial effectiveness but that we have not been able to specifically measure, such as scaffolding of the parent for young person CBT, stigma, and allowing parents and children an avenue to talk about their mental health. The qualitative interview and/or focus group data will form a part of our process evaluation, focussing on the acceptability of online delivery and concurrent treatment of parent depression, potential mechanisms of change underlying intervention effectiveness (see the logic model in Section 4, Figure 1), in addition to more broadly what worked well and what did not work as well in the intervention and trial. Early interviews carried out with professionals to inform trial conduct may be analysed using rapid content analysis of audio or written transcript, to allow rapid feedback to the trial team and TMG. Recordings of qualitative interviews and/or focus groups will be transcribed and de-identified (though an identification number will be retained to allow matching across different interviews where helpful for analysis, e.g., matching parents to their child), and data analysis will proceed using a Framework analysis approach (Ritchie & Spencer, 1994). This is a process of identifying, analysing, reporting and interpreting patterns or themes and is one of the most commonly used qualitative approaches in health research (Mays et al., 2005). Framework analysis consists of two major components: creating an analytic framework and applying this analytic framework. (Ritchie & Spencer, 1994). These two major components occur through five steps: (1) Data familiarisation, (2) identifying a thematic framework, (3) indexing all data against the framework, (4) charting to summarise the indexed data and (5) mapping and interpretation of patterns found within the charts. Qualitative researchers will develop a common agreed coding framework. There will be regular review meetings and discussions to ensure consistent application of the code book between coders and to ensure the codes are interpreted consistently across the team. Framework Analysis will be supported by computer assisted qualitative analysis software (Nvivo, QSR International).

15.6 Quantitative analysis of standardised interview and baseline questionnaires

Baseline interview and questionnaire data will be scored according to the validated scoring algorithms from the relevant literature. Missing item by item data will be handled according to the scoring algorithm for each measure individually. Baseline scores will be presented descriptively, using summary statistics (means, standard deviation, and percentages with associated 95% confidence interval where appropriate) for the whole group and by arm. A comparison of baseline

data for those completing and not completing the study at 9 months will be conducted to assess drop-out bias. This comparison will not utilise hypothesis tests but will present 95% confidence intervals for differences only.

15.7 Primary outcome statistical analysis

The primary analysis will be time-to-event analysis of the primary outcome (time to the first depressive episode collected at the 9-month follow-up data point). A Cox proportional hazards regression model will be used to determine the difference between trial arms and the hazard ratio with 95% confidence intervals estimated. The Cox model will include site as a fixed factor. A further term, investigated for inclusion in the primary model, will be a random effect to account for the group delivery clustering in the intervention arm. If the effect of the clustering is determined to be negligible this term will be excluded. Assumptions of the model will be checked to ensure model validity. Pre-specified subgroups to be compared descriptively include those defined by baseline characteristics of the young people (e.g., anxiety) and parents (e.g., whether parent's treatment was optimised prior to randomisation). Such possible effect modification will be investigated via the inclusion of arm*modifier interaction term.

The primary analysis will utilise the complete case dataset, however, multiple imputation will be considered under a missing at random (MAR) framework as a sensitivity analysis, to examine possible dropout bias in the treatment effect estimate. If there is variation in intervention session attendance, a further sensitivity analysis will examine the effects of compliance with the intervention in a complier average causal effect analysis.

15.8 Secondary outcomes

Repeated measures analysis using mixed models will be used for those outcomes collected at 3 and 9 months. Linear mixed effects regression will be used to account for clustering by group delivery in the intervention arm (partial effect model) as well as baseline values as covariates where appropriate. Where the assumptions of the linear regression model are not met, transformation or categorisation will be considered. Logistic regression models will be used similarly as above for binary outcomes. Main group effects and 95% confidence intervals will be presented for all outcomes.

Exploratory mediation analyses will examine the effects of potential mediators (e.g., improved problem solving skills, improved parent-child relationship) on the primary outcome via the inclusion of the mediator predictor in the primary model. Full details will be given the statistical analysis plan.

16 Data Management

The trial's Data Management Plan (DMP) provides an overview of the data management process to be applied to the trial to assure data quality. The DMP for the SWELL trial will:

- Define the different types of data collection documents used within the SWELL trial
- Define the procedures by which data will be collected, entered, verified and cleaned in the SWELL trial
- Define the procedures to securely manage and store the data
- Define requirements for the retention of SWELL trial data
- Describe the processes and data security measures involved in data linkage as applicable

The current version of the DMP will be followed and securely stored in the trials e-TMF.

16.1 Source Data

Source Data is defined as *"All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents."* There is only one set of source data at any time for any data element, as defined in site source data agreement. Details of source data and responsible personnel are detailed within table 2.

16.2 Data collection

Data analysed and stored, including on desktop and laptop computers, will not be personally identifiable. We have developed a Risk Assessment Form, which addresses issues such as privacy and confidentiality. Please refer to section 12 for further details on data collection and section 20.2 for details on data protection. Data will be collected from source via e-CRFs completed either by; participants directly via questionnaires, on their behalf via telephone call by delegated staff, through recorded interviews and from medical note reviews (see table 2).

16.3 Completion of CRFs

Electronic CRFs

It is intended to develop data recording for this trial as a web-based system. This will be a secure encrypted system accessed by an institutional password and complies with the General Data Protection Regulation 2018. A user password will be supplied to research staff upon completion of all processes required prior to opening (informed consent training, GCP, survey training). A data management plan (DMP) will detail the process. Data quality will be assured through processes detailed in the DMP.

Qualitative Data

Qualitative data recording, storage and management will be detailed and described separately within the DMP and qualitative analysis plan.

Table 2. Source Data

Trial data		***Source data***				
	eCRF	***Audio file***	***Paper CRF***	***CSV***	***SAE form***	***Medical/Clinician Note Review***
Screening	*X*					
Consent	*X*					
Baseline Questionnaires	*X*					
DAWBA				*X*		
Outcome measures	*X*					
Treatment optimisation	*X*					*X*
Intervention delivery (Adherence & Fidelity)		*X*				*X*
Baseline and Follow Up interviews		*X*	*X*			
Qualitative interviews		*X*				
Adverse events					*X*	
Withdrawal	*X*					

Please see the trial Data Management Plan for detailed information.

17 Protocol/GCP non-compliance

Any non-compliance to the trial protocol or the conditions and principles of Good Clinical Practice should be reported to the CI or to the CTR in writing as soon as possible.

18 End of Trial definition

At the end of the trial, we will have completed the data collection from the online interviews with young people and their parents from the second follow up time point (9-months) as well as qualitative interviews and/or focus groups conducted with participants after the end of their participation in the study, as part of the process evaluation.

19 Archiving

All data will be kept for 15 years in line with Cardiff University's Research Governance Framework Regulations for clinical research and guidance from the MRC. This data will be stored confidentially on password protected servers maintained on the Cardiff University Network.

20 Regulatory Considerations

20.1 Ethical and governance approval

This protocol has received a favourable opinion from Wales NHS Research Ethics Committee (REC) 5 that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval (IRAS 305331; REC 22/WA/0254). This trial protocol will be submitted through the relevant permission system for global governance review. Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The study will be conducted in compliance with the UK Policy Framework for Health and Social Care Research, the Cardiff University Research Integrity and Governance Code of Practice and the principles of Good Clinical Practice (GCP).

20.1.1 Ethical Considerations

The main ethical considerations for this trial include obtaining consent, confidentiality, the process of randomisation, the impact of discussing sensitive information and the possibility of worrying disclosures. These are discussed below.

Consent/assent: Obtaining consent from young people needs to be considered carefully, as their age may affect their understanding of the study. Young people in this study will be aged 13-19 years old. Information sheets for participants aged 13-15 years, for older adolescents and for parents will be provided. Written consent will be obtained from all parents, and written assent/consent from all young people taking part. Both parent and young person will be made aware they can change their mind about taking part at any point.

Confidentiality: All information will be treated as confidential. We will not disclose any information that could identify participants, except where specific consent is obtained or where risk to the young

person or others is identified. All data will be stored securely and accessed only by the researchers working on the study (see section 20.2). However, as this is a trial of a group psychological intervention, it is not possible to ensure participant anonymity from the other participants taking part in the same group therapy sessions. All possible measures will be taken to stress the importance of confidentiality in the group therapy setting (see section 20.2 for details). In brief this involves the first group session focusing on participants drawing up and agreeing to a code of conduct emphasising confidentiality and treating the others in the group with dignity and respect.

Randomisation: As this is a randomised controlled trial, only around half of the participants will be randomised to receive the preventative psychological intervention which may provide benefit. However, those who do not receive the intervention will continue with their usual clinical care, so will be at no disadvantage compared to if they did not take part in the trial. All participants will be signposted to relevant resources to support their mental health which are included in the information sheets.

Obtaining sensitive information: Young people, particularly those at increased risk of mental health difficulties, are considered vulnerable. Discussing sensitive topics (e.g. via study questionnaires, interviews and group CBT sessions) have the potential to be distressing for participants. If an individual becomes distressed, the research team will assess their difficulties and provide reassurance if appropriate. If required, they will be advised to see their General Practitioner. Parents taking part, who all have a history of depression, may also become distressed when discussing sensitive topics. They will also be advised to seek help from their GP if appropriate. However, in our previous experience of undertaking studies with this vulnerable population, we have found that participants (parents and young people) usually enjoy the opportunity to think about and discuss the topics in the assessments and report that they have valued the opportunity and being listened to by the research team in a sensitive and non-judgemental way. Researchers will receive thorough training in dealing with ethical issues in a professional, safe, and respectful manner.

Worrying disclosures: When talking to a young person about their mental health and well-being it is possible that they could make worrying disclosures. For example, they may disclose a risk to themselves (e.g. self-harm/suicidal thoughts) or they may raise a child protection issue. There is a

departmental protocol in place to deal with worrying disclosures, which will be dealt with on a case by case basis through consultation with trial clinicians. If necessary, when a young person makes a worrying disclosure, action will be taken to liaise with parents, appropriate medical professionals, and/or social services. Worrying disclosures made by parents will also follow our departmental protocol. We will also measure and document suicidal thoughts and self-harm as an adverse event following the trial AE/SAE reporting procedures.

20.2 Data Protection

We will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the General Data Protection Regulation 2018. The data custodian for this trial is the CI.

It will be stressed that the participation of the young people and parents/carers would be confidential. However, it will be impossible to ensure anonymity for those allocated to take part in the online group therapy sessions. It will be made clear to those participating in the group sessions that their identity (and any other information they choose to disclose during the session) will be shared with others attending the session. During the first group therapy session, young people will be asked to agree to a group code of conduct, including respecting the confidentiality of all group members, and encouraging young people to not disclose information which may identify where they live. There will be a briefing at the start of each online session stressing the importance of confidentiality in the group therapy setting. Group therapy sessions will be audio recorded and participants will be informed that this is the case. Audio recordings will allow researchers working on the trial to monitor the quality of intervention delivery and thus aid in ensuring quality control. We will work closely with the NCMH, CTR data team and university IT team to ensure that all data in electronic format will be stored on secure password–protected computers linked to secured University servers. Data stored on networked servers will be backed up routinely (daily). Any data in paper form will be stored in secure locked storage in rooms with restricted access. Audio recording files will be uploaded into a project-dedicated study folder located on servers with restricted access to authorised researchers only, and the files will be deleted off the recording devices. Data will be

stored for up to 15 years. All data linkage (SAIL) will also be undertaken in accordance with General Data Protection Regulation (2018) and University governance.

The files will be accessed only by the researchers working on the study. No one outside of the research team or appropriate governance staff will be able to find out participant's name, or any other information which could identify them. Audio recordings from qualitative interviews and/or focus groups may be securely transferred to a professional transcription company to be transcribed. It will be made clear to the young people and their families/carers that the only time we would inform others of their participation (e.g. the family doctor or relevant authorities) would be the rare situation when there would be a risk to the young person, parent/guardian or others (e.g. a serious health risk or child protection issue). There will be no personal identifiable information included in any documents e.g. reports or publications disseminated as part of the research. Qualitative interview and/or focus group recordings will not be labelled with the participant's name or identifying information. Written quotes from qualitative interviews and/or focus groups will be used word for word in publications, reports, presentations and training, for example, but data will be de-identified. Participants will be informed about handling of their data in the Participant Information Sheet.

20.3 Indemnity

- Non-negligent harm: This trial is an academic, investigator-led and designed trial, coordinated in partnership with the CTR. The CI, local Investigators and coordinating centre do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and cannot offer any indemnity.
- Negligent harm: The Sponsor shall indemnify the site against claims arising from the negligent acts and/or omissions of the Sponsor or its employees in connection with the Clinical Trial (including the design of the Protocol to the extent that the Protocol was designed solely by the Sponsor and the Site has adhered to the approved version of the Protocol) save to the extent that any such claim is the result of negligence on the part of the Site or its employees.

20.4 Trial sponsorship

Cardiff University will act as Sponsor for the trial. Delegated responsibilities will be assigned to the sites taking part in this trial. The Sponsor has/will be delegating certain responsibilities to Cardiff University (CTR), the CI, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and trial type.

20.5 Funding

The project is funded by the Wolfson Centre for Young People's Mental Health, established with support from the Wolfson Foundation.

21 Trial management

21.1 TMG (Trial Management Group)

TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter. The TMG will meet approximately every 4-6 weeks during the course of the trial. The TMG is composed of the co-investigators, CTR team (Cardiff University) and directly employed staff (named at the beginning of this document).

21.2 TSC (Trial Steering Committee)

TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter. They will meet approximately every 12 months. The TSC will be set up ahead of the opening of trial recruitment and will include members with varying relevant experience, including a young person and a parent with a history of depression.

22 Quality Control and Assurance

22.1 Monitoring

The CI will have overall responsibility for all aspects of the project (including the training/development components) and of adhering to timelines. She will hold regular meetings with the TMG throughout, with services regarding recruitment and with the finance manager to ensure that the research is within the proposed budget.

There will be meetings every 4-6 weeks with the TMG (co-applicants, CTR and directly employed staff), and a 12 monthly TSC meeting. There will be a trials/project manager based at the Cardiff University CTR. The Project Team (CI, directly employed and CTR delivery staff) will meet more frequently (1-2 weekly) to discuss day to day management and delivery issues.

The clinical trial risk assessment will be used to determine the intensity and focus of central monitoring activity in the trial. We anticipate low risk, in which case, low monitoring levels will be employed and will be fully documented in the trial monitoring plan.

Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained.

Findings generated from central monitoring will be shared with the Sponsor, CI & local R&D.

22.2 Audits & inspections

The trial may be participant to inspection and audit by Cardiff University under their remit as Sponsor.

23 Publication policy

The protocol and the results will be written up for publication in a (health) journal and the organisations funding the research will receive a report on the findings. Personal details of the participants will not appear on any of these documents and they will not be identifiable in any way.

All publications and presentations relating to the trial will be authorised by the TMG. To maximise the value of data collected from this study for the scientific community and those affected by depression, we plan to share anonymized data and metadata (e.g. code to derive variables) outputs on Cardiff University's curated institutional research data repository. Participant consent/assent to share anonymized data for future research is contained within the participant consent and assent forms. Currently, Cardiff University's data repository is the Research Portal curated data catalogue (which assigns DOI numbers to datasets) but in 2024 this will become Fig share for Institutions.

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