Clinical Trial Protocol

Physiological, Psychological, Psychiatric, Surgical or Health Interventions

UNSW HREC Title: The MobiliseMe study: Testing different smartphone activities to help improve young people's mental health.

ANZCTR Public Title: The MobiliseMe study: Testing the effect of different smartphone activities on young people's mental health

ANZCTR Scientific Title: A randomised controlled trial evaluating the effectiveness of a CBT-based smartphone application for improving depressive symptoms and other mental health outcomes in young people

Version 5: April 2022

Dr Bridianne O'Dea

Contents

1. General Information

Protocol Title				
The MobiliseMe study: Testing different smartphone activities to help improve young people's mental health.				
Protocol identifying number	HC210889			
Version Number	V2	**Version date**	16th November 2021	
Amendment History				
Version Number	V1	**Version date**	October 2021	
Clinical Trial Sponsor				
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Personnel authorised to sign the protocol and the protocol amendment(s) for the Sponsor (ICH GCP 6.1.3)	
Name	
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Human Research Ethics Committee	
Name	UNSW Sydney Human Research Ethics Committee
Status of ethical review	☐**Approved** ☒ **In progress** ☐ **To be submitted**
Trial Sites	N/A
Funding for the Clinical Trial	
Funding Body Name	Goodman Foundation
Amount of Funding	$1.5M
Interests that the funding body has in the clinical trial	Nil
Insurance for Clinical Trial	
Insurer	UNSW Insurance
Type of Insurance	Clinical trials are not automatically covered by UNSW insurance, and confirmation must be obtained by completing the Clinical Trials Spreadsheet and sending it to the UNSW Insurance manager (peter.mccarthy@unsw.edu.au). Once insurance has been confirmed, attach a copy of the insurance certificate to the trial protocol.
Confirmation of Insurance	☐**Attached** ☐ **In progress** ☒ **To be submitted**

2. Safety and Monitoring Contacts

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Sponsors Independent Physician/Medical Expert	
Name	
Telephone	
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Telephone	
Email	
Address	

3. Delegation of Clinical Trial Duties

Responsibilities for the conduct and oversight for the trial are delegated to you as the Coordinating Principal Investigator. You may delegate trial related responsibilities to the listed

Principal Investigator(s) and any trial-related personnel. All trial-related duties delegated by the Coordinating Principal Investigator or Principal Investigator(s) and trial-related personnel must only be delegated to those that are qualified by experience and training. Delegated responsibilities must be retained in the UNSW Clinical Trial Delegation Log. The UNSW Sponsor's Delegate is to be notified of the following:

- Protocol deviation reports outlined in the UNSW Research Misconduct Procedure.
- Any serious breach of Good Clinical Practice, the clinical trial protocol, the clinical trial standard operating procedures, or the human ethics approval that is likely to affect to a significant degree the safety or rights of participants or the reliability and robustness of the data generated in the clinical trial.
- Significant safety issues that are likely to (or have the potential to) affect to a significant degree the safety or rights of participants or the reliability and robustness of the data generated in the clinical trial.
- Urgent safety measures implemented to remove or prevent a significant safety issue.
- Safety reports relating to the continuation, suspension, or discontinuation of the clinical trial for safety reasons.
- Non-compliance with the protocol, SOPs, GCP, and applicable regulatory requirement(s) significantly affects or can potentially affect human subject protection or reliability of trial results significantly.
- Participant complaints or concerns received concerning the conduct of the research.
- Significant modifications to the clinical trial are likely to affect a significant degree the safety or rights of participants or the reliability and robustness of the data generated in the clinical trial.
- Addition of participating trial sites, contractual arrangements at participating sites or modifications to legal agreements.
- The intention to conduct the trial in other countries.

4. Trial Objectives and Purpose

This clinical trial aims to investigate the effectiveness of a Cognitive Behavioural Therapy (CBT) program delivered via a smartphone application (called *ClearlyMe*) for improving mental health outcomes in Australian adolescents (aged 12 to 17 years) with mild to moderate depressive symptoms.

This trial will examine the effectiveness of a new CBT smartphone application (*ClearlyMe*) for reducing depressive symptoms in adolescents when compared to guided use and an active-attention matched control condition.

The primary outcome is depressive symptoms, measured by a change in self-report symptoms between baseline and 6-weeks post-baseline (primary endpoint). Secondary mental health outcomes include improvements in anxiety symptoms, psychological distress and emotional wellbeing between baseline and 6-weeks post-baseline as measured by validated self-report scales. Follow-up outcomes will be evaluated at 4-months post-baseline (secondary endpoint) using the same self-report scales to determine whether effects are sustained in the mid-term and whether the interventions are associated with any delayed benefits or harms.

The primary research questions that this trial seeks to address are:

1. What is the effectiveness of *ClearlyMe* (both self-directed and guided use) for reducing depressive symptoms?

Secondary research questions include:

2. What is the effectiveness of *ClearlyMe* for reducing anxiety symptoms, psychological distress, rumination, and improving emotional wellbeing, quality of life, emotion regulation, and CBT skill acquisition?
3. Does guided support lead to greater engagement with and completion of the *ClearlyMe* app when compared to self-directed use?
4. Do factors such as gender, age, baseline mental health history or symptom severity, perceived need for care or openness to digital mental health, moderate the improvements in depressive symptoms found among users of *ClearlyMe*?
5. Do factors such as rumination, emotion regulation, CBT skill acquisition, digital therapeutic alliance and program engagement/completion mediate the improvements in depressive symptoms found among users of *ClearlyMe*?

Primary and Secondary Hypotheses:

This trial will determine whether the *ClearlyMe* smartphone application is effective for lowering depressive symptoms when compared to guided use and an active attention-matched control in symptomatic adolescents. It is hypothesised that:

H1= Participants who receive *ClearlyMe* (both self-directed and guided use) will report greater reductions in depressive symptoms between baseline and primary endpoint as well as baseline and secondary endpoint when compared to participants in the control condition;

H2= Participants who receive ClearlyMe (both self-directed and guided use) will report greater improvements in secondary outcomes (anxiety, psychological distress, emotional wellbeing,

quality of life, rumination, emotion regulation and CBT skill acquisition) between baseline and primary endpoint as well as baseline and secondary endpoint when compared to participants in the control condition;

H3= Participants' engagement with and completion of *ClearlyMe* will be significantly higher among participants who receive guided support when compared to participants who receive self-directed use.

Other exploratory hypotheses:

H4= Improvements in depressive symptoms among users of *ClearlyMe* will be moderated by gender , age, history of mental health, symptom severity at baseline, greater perceived need for care and higher levels of openness to digital mental health.

H5= Improvements in depressive symptoms among users of *ClearlyMe* will be mediated by rumination, emotion regulation, CBT skill acquisition, digital therapeutic alliance, and rates of engagement/completion.

5. Background Information

Adolescence is a significant and sensitive stage of life, whereby individuals evolve physically, socially, and psychologically as they transition to adulthood (Dahl et al., 2018). Given the rapid changes in a young person's development, this period also presents important risks and opportunities for young people's mental well-being. For example, a young person's access to a supportive environment, ability to maintain healthy sleeping and exercise behaviours, learn and develop coping, problem solving, emotional and interpersonal skills can influence their mental health (WHO., 2020). Poor mental health can have detrimental consequences to a young person's quality of life and their ability to function socially and academically (McGorry et al., 2011; Patel et al., 2007). Recent research suggests the global prevalence of depressive and anxiety symptoms in children and adolescents during the COVID-19 pandemic has increased, with 1 in 4 experiencing elevated depressive symptoms and 1 in 5 experiencing elevated anxiety symptoms, highlighting the need for mental health care (Racine et al., 2021).

In a recent national survey, Australian young people reported mental health as being the most important issue and within their top three concerns (Carlisle et al., 2019). However, despite mental health being at the forefront of young people's minds, many continue to experience help-seeking barriers including stigma, negative beliefs about mental health services, preference for autonomy and accessibility factors (cost, transport, waiting times) (Aguirre Velasco et al., 2020). Interventions delivered via digital platforms have the potential to overcome many of these barriers. The COVID-19 pandemic has highlighted the demand for mental health digital interventions when accessibility factors are disrupted. Recent data showed that registration to an Australian digital CBT-based mental health program (This Way Up) during the COVID-19 period increased 500% compared to the previous year (Mahoney et al., 2021). Similarly, the use of mental health apps rose by over 200% during lockdown (ORCHA Health, 2021). However, not all digital mental health products are created equal. With approximately 20,000 mental health apps on the market, many do not incorporate evidence-based therapeutic techniques and lack

sufficient evidence to be endorsed as treatment for adolescents (Wasil et al., 2019). This is problematic as programs that are not evaluated may cause unintended adverse effects including misinformation, privacy breaches, inadequate support or worsening symptoms. Therefore, it is important that young people have direct access to evidence-based, safe, effective treatments.

Digital interventions based on Cognitive Behavioural Therapy (CBT) have been shown to be effective for children and adolescents with anxiety (Hedge's g = 0.51) and depression symptoms (Hedge's g = 0.44) when compared to passive controls (Christ et al., 2020). However, many of the credible digital interventions publicly available have been designed for adults, which means they might not be engaging or include appropriate, or relevant examples for young users. Given low adherence and engagement to digital interventions is common, it is important that products are well-matched to the needs of the individual using them to ensure they are appealing to use. Human support, guidance, or encouragement has been associated with increased adherence to digital interventions (Beatty & Binnion, 2016). However, in studies of computerised CBT with young people, the impact of support on depression and anxiety outcomes is mixed in terms of the optimal amount, or type of support provided (Ebert et al., 2015; Pennant et al., 2015; Podina et al., 2016).

The *ClearlyMe* smartphone application was developed to address the need for an adolescent-focused, evidence-based and evaluated mobile mental health intervention. *ClearlyMe* was created through an extensive, iterative co-design process with a multidisciplinary team at the Black Dog Institute in collaboration with young people, mental health professionals, and parents. The smartphone app is based on CBT and is delivered through a vibrant, youth-friendly visual identity. Therefore, this study aims to determine whether the *ClearlyMe* app reduces the severity of depressive symptoms in young people.

6. Statement of Compliance

The clinical trial will be conducted in compliance with the following guidelines and documentation:

- ICH Guidelines for Good Clinical Practice (GCP)
- National Statement on Ethical Conduct in Human Research (National Statement)
- As approved by the Human Research Ethics Committee (HREC), the clinical trial protocol is responsible for monitoring the trial's conduct.
- The responsibilities set out by the UNSW Sponsors Delegate.
  The onsite or remote monitoring standard operating procedures as put in place by the clinical trial sponsor.

7. Trial Design

This study will utilise a three-arm randomised controlled trial, conducted entirely online via the Black Dog Institute Research Engine. Data will be assessed at baseline, primary endpoint (6-weeks post-baseline) and secondary endpoint (4-months post- baseline). This methodology is appropriate to meet the research aims because RCTs are considered to provide the most reliable evidence on the effectiveness of interventions because the processes used during the conduct of this type of trial minimise the risk of confounding factors influencing the results. Because of this, the findings generated by RCTs are likely to be closer to the true effect than the findings generated by other research methods (Akobeng, 2005).

Randomisation will be carried out according to the International Council for Harmonisation (ICH) guidelines. Randomisation to one of the three trial arms will be conducted immediately after completion of the baseline assessment using a computerised randomisation procedure within the Black Dog Institute Research Engine. Stratified randomisation approach with a block size of 6 (1:1 ratio) will be used to ensure balance across the conditions in terms of age (12 to 14 years vs. 15 to 17 years), ~~gender (male vs. female),~~ and symptom severity (mild [as determined by a total score of 9 or less on the PHQ-A] vs moderate to moderately-severe [as determined by a total score of 10 or more on the PHQ-A]). Allocation will be fully automatic, with no interference from the research team.

Blinding – Participants: All study materials will refer to the interventions being examined as "smartphone activities and information for your mental health". While participants will be aware of which smartphone activity they will be required to use (due to the PICF and instructions for use provided), they will not be directly informed of their condition allocation (i.e., intervention 1 vs. intervention 2 vs. control).

Blinding – Statistician: The statistician involved in examining the effects of the conditions of primary and secondary outcomes will not be informed of participants' specific intervention allocation. Condition allocated will be marked as "Condition A, Condition B, Condition C" to ensure the statistician remains blinded to participants' intervention upon primary and secondary analysis of the results. All other potential markers of allocation will be removed from the data analysis file. Upon completion of these analyses, the statistician will be become unblinded when examining mediators and moderators as well as intervention completion rates, due to differences in the total number of modules/lessons across each condition. This data will only be reviewed by the trial statistician upon completion of the primary and secondary outcomes.

Blinding – Chief Investigators, Trial Manager and Research Officers/Assistants: The chief investigators, trial manager and research assistants will be unblinded to participants' allocation as they will have access to the Black Dog Institute Research Engine to contact participants if they experience adverse events, and to provide support to participants allocated to the "guided use" condition. They will also be responsible for downloading and cleaning the data extract. The Chief Investigators, Trial Manager, and Research Officers/Assistants will not be involved in data analysis of the primary and secondary outcomes.

For the study outputs, a CONSORT flow diagram will be provided outlining study recruitment, including *n* for each stage.

8. Sample Size

The total baseline sample size required for detecting change in the primary outcome is 489. This is based on calculations using α=0.05, power=0.8, small to medium effect sizes for psychoeducation (*d*=0.10), self-directed CBT (*d*=0.35), and guided CBT (*d*=0.65) on depressive outcomes at primary endpoint and a 20% attrition rate between baseline and primary endpoint.

Specifically, this sample size is comprised of the following sample sizes for each of the participant groups:

1. Trial Arm 1=163 participants
2. Trial Arm 2=163 participants
3. Trial Arm 3=163 participants.

This sample size is sufficient to meet the research aims and answer the research questions because the power calculation reveals that this sample size will allow for statistically significant results. As this trial will be conducted entirely online via the Black Dog Institute Research Engine, no specific trial sites will be established.

9. Selection and Withdrawal of Subjects

All inclusion and exclusion criteria will be assessed through a self-report screening assessment hosted on the study website. Excluded participants will be provided with a generic message and details on youth mental health services and other trusted mental health organisations. Participants will be provided with information on where to seek help and self-care activities. More information on the screening protocol is outlined in Section 9.4 and Appendix A.

To mitigate the potential of participants "gaming" the inclusion criteria (i.e., making multiple attempts to enter the study by various combinations of the inclusion/exclusion criteria), the Participant Information Statement and Consent Form (PISCF) will not stipulate the exact details of the inclusion and exclusion criteria for depressive scores, and will instead give generalised indications.

9.1 Inclusion Criteria

To participate in this trial, at the time of screening participants must be:

- Aged 12 to 17 years (confirmed by self-report)
- Located in Australia (confirmed by self-report)
- Experiencing mild to moderately-severe depressive symptoms (as determined by a total score of 5-19 on the self-report Patient Health Questionnaire-9- Adolescent version).
- Own or have access to a smartphone (for receipt of the study interventions)
- Have access to the Internet, an active email address and mobile phone number (for receipt of study activities, invitations, reminders)
- Comfortable with reading English at Year 7-8 level (to ensure comprehension of intervention content)
- Have a parent or guardian who can provide consent for participation.

9.2 Exclusion Criteria

At the time of screening, participants will be excluded if they are:

- Currently experiencing severe suicidal ideation (as determined by a score of ≥2 on item 9 of the self-report Patient Health Questionnaire-9-Adolescent version).
- Had serious suicidal ideation in the past month (as determined by self-report).
- A suicide attempt in the past month (as determined by self-report).
- Experiencing nil or severe depressive symptoms (as determined by a score total of ≤4 or ≥20 on the self-report Patient Health Questionnaire).
- Currently receiving OR about to start (in the next 2 weeks) any psychological treatment for feelings of low mood or depression from a psychologist, psychiatrist or other mental health professional
- Currently taking OR about to start (in the next 2 weeks) any daily prescribed medication (e.g., anti-depressants) for their mental health (low mood, depression or anxiety).

- Unable to gain parental consent to participate (as determined by failure to return parental consent form within their recruitment period).
- Located outside of Australia, not within age range or fail to satisfy any of the other inclusion criteria (as determined by the self-report screener).

9.3 Recruitment Strategy

This study will utilise an online recruitment strategy. Recruitment will take place until the desired sample size is achieved. It is estimated that the sample will be recruited within 8 months, between April to November 2022. All recruitment materials are outlined in Appendix B.

A website for the study will be established and the URL will be included in all study materials. All study adverts will direct participants to the study website, where they will access study information, undertake screening and provide consent.

Study advertisements will be published on the Black Dog Institute website and social media channels including Facebook, Twitter, and Instagram. Study advertisements will also be included in Black Dog Institute internal and external communications, via established professional newsletters to agreed subscribers.

The research team will also contact relevant mental health organisations and services independent of the research team to recruit participants to take part in the study. These organisations will be asked to share the study advertisements on their organisation's communication channels (e.g., website, social media, newsletters, mailing list, in-person clinics) using the same adverts outlined in Appendix B. Support to assist with recruitment will be assumed by the organisation's agreement to post or disseminate recruitment materials. No organisations will know whether a person agrees to participate or not as the recruitment materials will direct potential participants to the study website, which includes further instructions on how to participate, screening, and consent.

The research team will also send two email invitations via electronic direct mailout (sent one month apart) to the Black Dog Institute research database, which consists of individuals who have consented to being contacted about future research studies being conducted by the Institute. The email invitation is included in Appendix B.

The study will also utilise a paid advertising campaign on Twitter, Facebook, Instagram, and Google, for the duration of recruitment. This campaign will use the same adverts outlined in Appendix B.

As the smartphone application utilised in the current study will be released on the Apple and Google Play stores (for approved study participants to use only), a link to the study website will also be included in the description of the app. This will ensure that any young people who discover the application in a store search will be redirected to the study website.

9.4 Screening

Screening will take place via the study website. The homepage of study website will contain a brief version of the PISCF form (see Appendix A) so that participants are aware of key study requirements prior to completing the screening questions. To determine whether a participant is eligible to take part in the study, interested participants will complete a self-report screener

hosted on the study website (see Appendix A for the screening protocol). Participants will be informed that the responses to the screening assessment will be stored for reporting purposes. Consent to undergo the screening procedure will be implied based on individuals' completion of the questions. As this study is targeted at young people, parents or other individuals cannot complete the screening questions on behalf of a youth participant.

Ineligible participants will receive a short thank you message advising them that the study is not the right fit for them at this time. Participants who are ineligible because of severe depressive symptoms or suicidal ideation will be provided with additional information on where to seek help and self-care activities.

9.5 Consent

Once screening is completed, all eligible youth participants will be invited to review the full PICF and provide their personal consent via the online consent form (see Appendix C). Once this is completed, participants will then be invited to register to the study, creating a secure account on the Black Dog Research Engine. To register, participants are asked to provide their full name, email, mobile phone number and age. They are also asked to create a password to ensure account security. Registered participants will then be invited to view the online parental PISCF (Appendix C) to be completed by their parent or guardian. Participants will be asked to complete and submit the online parent consent form within 14 days. After the parental PICF is submitted by the parent, the young person will be automatically notified by the Research Engine of their confirmed involvement in the study and invited to complete the baseline assessment. A copy of the parental PICF will be emailed to the parent's email address provided. A copy of the personal PICF will also be emailed to youth participants via a URL link included in the study welcome email.

Participants will have sufficient time to consider study participation because they have 14 days to complete their parental PICF. Participants will receive three reminders to return their consent form, sent on day 3, day 5, and again on day 10. Participants who fail to complete the parental consent form will be withdrawn from the study.

Once personal and parental consent has been provided, participants will be sent an automated invitation to complete the baseline assessment. The baseline assessment will remain open for a period of 7 days, allowing participants further time to reconsider their consent after its initial provision. Participants can cease the baseline assessment at any time, which will result in their removal from the study.

The consent process used in the current study is appropriate for the study design and data collection method (i.e., online surveys) because participants are being recruited via online methods. Therefore, an online consent procedure aligns with their expectations of research participation. In addition, as this is an internet trial (i.e., all study procedures are conducted online) an online consent form is consistent with the study activities and description. Participants will not be reconsented at each timepoint due to the short duration of the study period and to reduce participant burden.

9.6 Withdrawal of Consent or Participant

Participants will be able to withdraw from the study at any time by the following:

1) *Emailing the research team*: By emailing mobiliseme@blackdog.org.au and providing their full name, date of birth, mobile number with the subject line "withdraw" or equivalent.

2) *Via the study withdrawal link provided in the initial study welcome email:* By clicking on the URL at the bottom of the welcome email, participants can withdraw at anytime and actively remove all data from the study without making direct contact with the research team.
3) *Failure to complete the baseline assessment within 7 days:* Participants who fail to complete the baseline assessment within 7 days will be automatically withdrawn from the study.

Once withdrawn from the research study, all of participants' personal identifiable data (e.g. name, email address, mobile phone number) will be removed and no further information will be collected from them. The research team will retain some information (e.g. age, gender, symptom severity) for trial reporting purposes. Withdrawn subjects will not be recontacted or followed up. However, to ensure participant safety, withdrawn subjects will be able to report whether their withdrawal from the study was associated with adverse events related or unrelated to the study activities. Participants who actively withdraw will be informed that they can, if they wish, provide feedback about any study activities but there is no obligation to do so.

Failure to complete the primary and secondary endpoint assessments will be considered lost to follow-up for that timepoint but will not withdraw participants from the study. Participants who fail to download or access the study interventions during the study period will not be withdrawn from the study. Withdrawn subjects will not be replaced as the sample size calculations accounts for study attrition.

10. Treatment of Subjects

The study flow is outlined in Appendix K. Upon the provision of full consent, participants will be invited to complete the baseline assessment via an automated email/SMS invitation generated by the Black Dog Institute Research Engine. The outcome measures assessed at baseline are outlined in Appendix D. The baseline assessment is entirely self-report. It will take approximately 20 minutes to complete, and can be completed on any Internet-enabled device. Participants will have 7 days to complete the baseline assessment (from invitation date) and will receive two reminders to complete the assessment (sent on day 3 and day 5). Participants who fail to complete the baseline assessment within 7 days will be withdrawn from the study.

Once baseline is completed, participants will be automatically randomised by the Black Dog Institute Research Engine to one of three trial arms (outlined in Section 10.1). Upon randomisation, participants will be presented with a webpage that provides them with individual instructions and installation advice on the requirements for their trial arm. Participants allocated to Trial Arms 1 and 2 who fail to download the ClearlyMe app within 7 days of randomisation will be sent an email and SMS reminder to download the app.

The study intervention period is 6-weeks, with the primary endpoint assessed at 6-weeks post-baseline. At primary endpoint, participants will be invited to complete the primary endpoint assessment via an automated email/SMS invitation generated by the Black Dog Institute Research Engine. The outcome measures assessed at primary endpoint are outlined in Appendix E. The primary endpoint assessment is entirely self-report. It will take approximately 20 minutes to complete and can be completed on any Internet-enabled device. Participants will have 7 days to complete the primary endpoint assessment (from invitation date) and will receive two reminders to complete the assessment (sent day 3 and day 5). During the intervention

period, the study will also collect data on participants' use of the interventions. This measurement is outlined in Appendix D under 'Intervention Use'.

An additional study assessment will occur at follow-up, with the secondary endpoint assessed at 4-months post-baseline. At secondary endpoint, participants will be invited to complete the primary endpoint assessment via an automated email/SMS invitation generated by the Black Dog Institute Research Engine. The outcome measures assessed at primary endpoint are outlined in Appendix D. The primary endpoint assessment is entirely self-report. It will take approximately 20 minutes to complete and can be completed on any Internet-enabled device. Participants will have 7 days to complete the primary endpoint assessment (from invitation date) and will receive two reminders to complete the assessment (sent day 3 and day 5). Upon completion of the secondary endpoint assessment, trial participation will cease. Participants will be thanked for their time and provided with additional information on mental health and help-seeking resources.

Young people will be reimbursed for the time taken to complete the study assessments. Participants will be reimbursed $10AUD (electronic gift voucher) for completion of the baseline, post-test and follow-up assessments. The total possible reimbursement will be $30AUD, which will be emailed and sent via SMS to participants within 14 days of their completion of the scheduled assessment. These amounts are aligned with the best-practice wage-payment model (Dickert & Grady 1999) such that participants are paid for time taken to participate in the study, using the current minimum wage of $19.84p/hr. In addition, participants allocated to trial arm 2 (guided use of ClearlyMe) will be reimbursed an additional 25AUD (GiftPay Voucher sent by email and SMS) upon randomisation to this group to cover the cost sending and receiving SMSs. This amount was based on the estimated costs of approximately 12 SMS sent per week at $0.30 per message. Because of this incentive, data integrity checks will be embedded into the online assessments to check for duplicate users at baseline (e.g., emails, and mobile number checks) and to ensure that standards of internet studies are met (Reips, 2002).

All study assessment data will be collected and stored on the Black Dog Institute Research Engine. This Research Engine stores data on secure servers commissioned by the University of New South Wales IT and is hosted on the GovDC Data Centres located in Silverwater, Sydney. The data is stored in a SQL Server 2016 database which is backed up daily on a drive on the server. The drive itself is backed up daily to a tertiary location. Server backups are performed daily and weekly. The daily backups are retained for 2 weeks, the weekly backups for 6 weeks, the monthly backups for 6 months and half yearly backups for 7 years. Access to the servers is strictly controlled and only authorised UNSW IT and Black Dog Institute IT staff can access the servers (VPN) using Two Factor Authentication. UNSW servers are penetration tested regularly for security vulnerabilities and UNSW IT also perform regular security patches and updates on the servers. The Research Engine itself is only accessible to authorised personnel using password protected accounts. For this project, only the Chief Investigator, researchers listed on this application, and the Black Dog Institute IT and data analytics team have access to the research data in the Research Engine. All data will be destroyed 15 years after the completion of the study by the Chief Investigator or Black Dog Institute IT.

The Research Engine automatically generates a unique participant identification code, which is included in all reports. This code enables de-identification of the dataset for analyses. For

analyses, all study assessment data will be exported, via a Microsoft Excel file, from the Research Engine to SPSS Version 26 for analysis by the research team. These files will be stored on UNSW OneDrive and only accessible to the Chief Investigators A and B, Trial Managers, Data Analyst and Senior Research Officer listed on the project. The Trial Manager and Senior Research Officer will de-identify the dataset (i.e., remove name, mobile phone number, email addresses, IP addresses, and free response data) and prepare it (i.e., cleaning and ensuring blinding) for the trial statistician to conduct the primary and secondary analyses. The de-identified and blinded file will then be transferred to the trial statistician for analyses using a password protected OneDrive file. Aggregate deidentified data in a password protected OneDrive file will be retained for future evidence synthesis.

A separate spreadsheet consisting of participants' email addresses and mobile phone numbers alongside their completion of the assessment dates, will also be stored in a password protected file in a private folder on One Drive to enable the GiftPay vouchers to be sent to participants. This file will only be accessible to the Chief Investigators, Trial Managers, Data Analyst and Research Officers/Assistants listed on the project.

As this study is collecting personal information (e.g., mobile phone numbers and email addresses), this information is protected in accordance with the Australian Privacy Act 1988. Participants have the right to access and destroy any personal information collected by this study. If participants have concerns about the way their data has been handled, they are encouraged to notify the Chief Investigator and the UNSW HREC. This information is outlined for participants in the PISCF.

Primary analyses will be conducted to determine the effect of the interventions on depressive symptoms at the primary and secondary endpoints. Analyses will be undertaken on an intention-to-treat basis, including all participants randomised, regardless of intervention received. The effectiveness of the trial interventions will be established by a change on the PHQ-9-A between baseline and 6-weeks post-baseline (primary endpoint) and 4-month follow-up (secondary endpoint), based on the interaction between time and condition, using mixed-effects linear modelling with an unadjusted p value of 0.05. Effect sizes will be calculated based on differences in change scores between baseline and 6-weeks post-baseline, using standard deviations of the change scores pooled across conditions. This modelling will account for all available data, under the missing at random assumption. However, attrition analyses will be conducted to determine whether missing data is associated with any baseline demographics (age, gender), mental health status (symptom severity) or other descriptive variables. Any baseline variables identified as substantially imbalanced between groups will be added to the models on an exploratory basis to confirm the robustness of the findings to this imbalance. Where distributional assumptions cannot be satisfied, other modelling may be used to confirm the robustness of the findings. Similar models will be used for secondary outcomes. To analyse the effects of adherence on outcomes, the mixed-effects repeated measures linear modelling will be repeated using the categorical adherence measure as a between group factor (adheres v non-adheres v control). These results will be published in the primary outcomes paper. Exploratory analyses will examine evidence for moderation, that is, whether the intervention was more effective for certain subgroups of the sample. Further, exploratory analyses will also examine evidence for mediation, that is whether the effects of the intervention were driven by other variables.

An additional file with free response data, matched with participant ID codes will be stored on UNSW OneDrive for qualitative analyses by the Chief Investigators, Trial Manager, and Research Officers/Assistants. Free-response questions will be analysed using thematic analysis to identify patterns across the responses. An inductive approach will be used to identify and group themes. The first stage of analysis will commence with familiarisation of the dataset by one researcher. Open coding will be used to summarise the data and create preliminary labels. Next, initial codes will be generated, and a coding framework will be created. A second researcher will then refine the codes and determine the final coding framework. Both researchers will recode the data using the finalised coding framework. An independent third researcher will review the data and themes to consolidate the findings. To support the validity of the analysis, analyst triangulation will be used whereby higher-order codes and final themes were determined by consensus among the researchers. The researchers coding the data will be instructed to regularly reflected on their personal reactions to ensure that they do not contaminate the data. The final themes will be presented in a separate paper on young people's perceptions of the interventions.

For participants allocated to trial arm 1 and 2, the study will also collect research data associated with their use of the intervention. This information will be used to determine which aspects of the intervention are important for improved outcomes. This trial will collect the following usage data from the *ClearlyMe* app: lessons completed, collections completed, features accessed, total time spent in app, content liked/disliked, content saved, and individual responses to lesson activities. This data will be extracted automatically from individuals' smartphones and transferred via the Internet to the Black Dog Institute Research Engine. This data will then be available for download (similar to the study assessment data) via the Black Dog Research Engine, connected to participants' study assessments using their unique participant identification code. Participants responses will be analysed to determine their compliance and engagement with the content, including linguistic analysis of their free responses. For participants allocated to trial arm 3 (i.e., the control condition), the study will also collect research data on the number of times each participant accesses each psychoeducation flyer via the URLs in the weekly SMSs. The time and date of access will be included.

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For the risk management protocol, a report will be generated from the Black Dog Institute Research Engine that contains only participants' contact details (mobile phone number, email), name and age. This file will be password protected, stored on the UNSW OneDrive and only accessible by the Trial Manager, for conduct of any of the risk management telephone calls that are required during the study.

For participants allocated to Trial Arm 2, a report will be generated from the Black Dog Institute Research Engine that contains their mobile phone number, name and age. This file will be used to conduct the weekly SMS chats. This file will be password protected, stored on the UNSW OneDrive and only accessible to the research team members conducting the weekly SMS chats.

10.1 Trial Interventions

Trial Arm 1. Intervention 1 – Self-directed CBT smartphone application *ClearlyMe*: Participants allocated to this condition will receive *ClearlyMe*. *ClearlyMe* is a free, self-directed CBT-based smartphone application that provides therapeutic content and symptom management strategies to adolescents experiencing mild to moderate depressive and anxiety symptoms. The application was specifically designed for adolescents by a multidisciplinary team of psychologists, researchers, user experience designers and software developers at the Black Dog Institute. *ClearlyMe* is delivered as an autonomous, non-sequential CBT program consisting of 37 brief lessons (i.e., therapeutic content alongside activities). Lessons include the following evidence-based treatment components: psychoeducation, cognitive restructuring, emotion awareness and acceptance, goal setting, problem solving, activity scheduling, behavioural activation, exposure, relaxation, mindfulness, and values labelling. The lessons also encourage participants to practise the psychological skills in-between lessons and return to the app to reflect or access further content as needed. The lessons vary in length, taking between 5 to 10 minutes each to complete. To help navigate the program content, users are encouraged to complete the lessons via nine curated 'collections'. A collection is defined as a structured selection of related lessons grouped together with a brief title and introduction. Each collection varies in length, taking approximately 20 minutes to complete. Users can also complete the individual lessons from a 'show all' list whereby they self-select lessons considered to be relevant to their individual needs. In this list, lessons are categorised into three groups depending on their target: 'emotions', 'thoughts', 'behaviours'. The app also includes a Moodcheck (i.e., brief mood monitoring), Mind Hacks (i.e., quick strategies that help in the moment), and Stories (i.e., short videos of young peoples' experience managing mental health symptoms and positive help-seeking experience) to provide users with additional pathways to accessing therapeutic content. For these features, specific lessons are recommended after the feature is accessed. *ClearlyMe* also includes in-app reminders, 'saving' and 'favourite' functions to support users to return to the app to reengage in content. In-app reminders include a 'revisit the app' reminder, which notifies all participants to use the app if they haven't done so in the past 7 days. This reminder is locked and cannot be turned off in the app. Users can also set an additional reminder to use the Moodcheck feature once a day for as many days as they wish. Due to the developer requirements of iOS app store and Google Play, app notifications must be able to be disabled in a user's phone settings. The app also includes a 'Get Help' section that contains information of when and where to access additional mental health support services (e.g., Kid's Helpline). Appendix E includes the full product information. To ensure compliance, participants who fail to download the *ClearlyMe* app within 7 days of randomisation will be sent an email and SMS reminder to download the app.

Participant instructions for use: In this trial, participants are provided with access to *ClearlyMe* for 6-weeks. Participants are instructed to complete the app content by undertaking at least one collection per week (approximately 20 minutes) for the intervention period; however, participants can complete the app content in any order and according to their preferences. Participants are also instructed to use the 'Get Help' section of the app if they feel they require extra mental health support during the intervention period, although this section of the app is not monitored in real-time by the research team. To further ensure compliance, all participants in this intervention arm will be sent one SMS per week from the Black Dog Institute Research Engine reminding them to use the *ClearlyMe* app. Participants allocated to this intervention arm will not receive any additional human

contact from the research team, unless technical support for the smartphone application (via email) is required.

Trial Arm 2. Intervention 2 – Guided use of CBT smartphone application *ClearlyMe*: Participants allocated to this condition will receive the same intervention provided in Trial Arm 1, with the addition of a weekly guided support session. This will take place in the form of a SMS chat provided by the research team for the duration of the intervention period. Participants will be contacted via SMS on their mobile phone number at the times provided to participants after randomisation (4pm to 7pm Monday to Friday). Contact will be made weekly, with one additional attempt made for non-response (two days apart, total of 2 contact attempts in 7 day period). In total, participants in this condition will receive 6 weekly support sessions in the intervention period. Personnel conducting the guided sessions will be research employees of the Black Dog Institute and will use a standard script, with a decision flow chart to direct the chat (see Appendix F). The SMS chat will consist primarily of technical support with some low intensity motivational coaching. Research Assistants (RAs) not clinicians, will be trained to conduct these sessions and will be supervised by a clinician. The clinician will be available during these sessions to support the RA if needed. The guided support sessions will be designed to be conducted in one sitting (i.e., within 20 minutes) but duration and script compliance will be recorded by the research assistants.

Participant instructions for use: In this trial, participants are provided with access to *ClearlyMe* for 6-weeks. Participants are instructed to complete the app content by undertaking at least one collection per week (approximately 20 minutes) for the intervention period; however, participants can complete the app content in any order and according to their preferences. Participants are also instructed to use the 'Get Help' section of the app if they feel they require extra mental health support during the intervention period, although this section of the app is not monitored in real-time by the research team. Participants will be instructed that they can expect a weekly SMS chat for the duration of the study period any time between the hours of 4pm to 7pm Monday to Friday.

Trial Arm 3. Active attention-matched control – SMS enabled, self-directed low intensity weekly psycho-education flyers with self-care:

This study will utilise an active attention matched control condition. Participants allocated to this condition will receive 6 weekly psychoeducation modules delivered via SMS with handouts that can be accessed on their mobile device. The psycho-education consists of 6 topics: What is mental health, Feeling on Edge – Understanding Anxiety, Waves of Sadness – Understanding Depression, When it's time to tell someone, When a friend needs a hand, and When friendships are complicated. Each module consists of information about mental health problems, links to credible Australian mental health organisations, and finishes with selfcare suggestions for what a young person can do right now if they are feeling worried or down. These modules were developed by the Black Dog Institute, created by mental health professionals, researchers and young people. Each module takes approximately 20 minutes to complete. A full overview of the psychoeducation content is provided as in Appendix G. Participants allocated to this intervention arm will not receive any additional human contact from the research team, unless technical support for the program (via email) is required. At the primary endpoint, participants will receive one email that contains all of the psycho-education material in one collated document for future use.

Participant instructions for use: In this trial, participants are provided with access to the digital psychoeducation content for the 6-week intervention period. Participants will be instructed to complete the content by undertaking one module per week (approximately 20 minutes) for the intervention period. Participants are also instructed to use the 'Get Help' section of the study site if they feel they require extra mental health support during the intervention period, although this is not monitored by the research team.

11. Safety and Monitoring

11.1 Assessment of Safety Event Report Forms

Safety reports will be assessed on the seriousness, causality, and expectedness of the event to the trial treatment(s), intervention(s), investigational medical product(s), investigational medical device(s). The following are known and expected adverse effects, harms, risks or discomforts associated with trial procedures, treatments or interventions.

a) Known Adverse Effects

Effect/Event	Criteria
Frequent, current suicidal ideation (i.e., thoughts of death or of harming oneself) detected through the self-report Patient Health Questionnaire-9, at baseline, primary or secondary endpoint.	A participant reports an item score of ≥ 2 ("More than half the days" to "Nearly every day") on item 9 of the PHQ-9 (i.e., "Over the last two weeks, how often have you had thoughts that you would be better off dead, or of hurting yourself in some way?")
Action	
The following actions will occur when a participant satisfies the above criteria: a) A pop-up message in the questionnaire will be displayed on participants' device. This message will provide individuals with immediate recognition of their response and recommend they tell someone they trust about how they are currently feeling. This message will read: *"Your responses have indicated that you may not be doing so well right now. Thanks for letting us know. We think it'd be great if you could tell a trusted adult about how you're feeling. If you're not up to talking to someone you know, try Kids Helpline on 1800 55 1800 or Lifeline 13 11 14. We also recommend you check out the Get Help section in the top right corner of this site"* . b) These participants will also be invited to request a call back from the research team's clinical psychologist. The following message will be displayed on the participant's screen: "*Would you like to receive a confidential call from a psychologist from the research team?"* with the option to choose 'yes' or 'no'. If the participant selects 'yes' for a call back, the Black Dog Institute Research Engine will generate an email notification to the Trial Manager that contains the participant's study ID code, first name, mobile number, and preferred call time. The Trial Manager will arrange for the Clinical Psychologist to attempt contact with the participant within two working days. The Clinical Psychologist will conduct a brief risk assessment over the phone to determine the level of suicide risk. If determined to be at risk, the participant will be advised to contact an appropriate service (e.g., a GP, the BDI Psychology Clinic, Mental Health Hotline). If the risk of harm is deemed significant enough to break confidentiality, or the participant requests it, their parents will be contacted by mobile telephone within an additional two working days. Referral suggestions will be provided. Dr Sophie Li, the	

Trial Manager and the research team's qualified clinical psychologist has significant experience in working with distressed youth both in research and clinical settings. Dr Li is well equipped to oversee and manage any issues that may arise. All participants who receive a call back will be offered an additional follow-up call, scheduled 7 days after the initial call, to check-in about the agreed safety plan. In all instances, if a participant is unable to be contacted by phone after two attempts, they will be sent an email from the study email address informing them of the attempt to make contact. This email will also contain mental health information and support services.

c) A register of these events and associated interactions (i.e., telephone call attempts, times, dates, outcomes) will be recorded in a separate risk management spreadsheet managed by the Trial Manager. These events will also be recorded in the UNSW Safety Monitoring Template.

Effect/Event	**Criteria**
Severe depressive symptoms detected at final study assessment (i.e., secondary endpoint: 4-months post-baseline) through the self-report Patient Health Questionnaire-9.	A participant reports a total score ≥ 20 on the Patient Health Questionnaire-9 at secondary endpoint assessment (i.e., 4-months post-baseline).

Action

The following actions will occur when a participant satisfies the above criteria:

a) A pop-up message in the questionnaire will be displayed on participants' device. This message will provide individuals with immediate recognition of their response and recommend they tell someone they trust about how they are currently feeling. This message will read: "*Your responses have indicated that you may not be doing so well right now. Thanks for letting us know. We think it'd be great if you could tell a trusted adult about how you're feeling. If you're not up to talking to someone you know, try Kids Helpline on 1800 55 1800 or Lifeline 13 11 14. We also recommend you check out the Get Help section in the top right corner of this site."*

b) These participants will also be invited to request a call back from the research team's clinical psychologist. The following message will be displayed on the participant's screen: "*Because you are coming to the end of the study, we'd like to offer you the opportunity to talk to a mental health professional from the Black Dog Institute about how you have been feeling lately. Would you like to receive a confidential call from a psychologist from the research team?*" with the option to choose 'yes' or 'no'. If a participant selects 'yes', the Black Dog Institute Research Engine will generate an email notification to the Trial Manager that contains the participant's study ID code, first name, mobile number, and preferred call time. The Trial Manager will arrange for the Clinical Psychologist to attempt contact with the participant within two working days. The Clinical Psychologist will conduct a brief risk assessment over the phone to determine the level of depressive symptoms and if necessary, the presence of suicidality. If determined to be at risk, the participant will be advised to contact an appropriate service (e.g., a GP, the BDI Psychology Clinic, Mental Health Hotline). If the risk of harm is deemed significant enough to break confidentiality, or the participant requests it, their parents will be contacted by mobile telephone within an additional two working days. Referral suggestions will be provided. Dr Sophie Li, the Trial Manager and the research team's qualified clinical psychologist has significant experience in working with distressed youth both in research and clinical settings. Dr Li is well equipped to oversee and manage any issues that may arise. All participants who receive a call back will be offered an additional follow-up call, scheduled 7 days after the initial call, to check-in about the agreed safety plan. In all instances, if a participant

is unable to be contacted by phone after two attempts, they will be sent an email from the study email address informing them of the attempt to make contact. This email will also contain mental health information and support services.

c) A register of these events and associated interactions (i.e., telephone call attempts, times, dates, outcomes) will be recorded in a separate risk management spreadsheet managed by the Trial Manager. These events will also be recorded in the UNSW Safety Monitoring Template.

Effect/Event	**Criteria**
Mental health related hospitalisation reported at primary or secondary endpoint or disclosed in any other study procedures (e.g. call back phone calls, participant emails).	Participants reports yes to the item *"Throughout the study, have you had any mental health problems where you had to go to a hospital emergency department, or had to stay in hospital for more than one day?"* in the primary and secondary endpoint study assessments, or, reports this event via other study procedures and activities.
Action	
All relevant study data for this event will be recorded in the UNSW Safety Monitoring Template for reporting.	

Effect/Event	**Criteria**
Self-identified deterioration in mental health due to study activities reported by participants at primary or secondary endpoints.	Participants reports yes to the item *"At any point throughout the study, did you feel that any of the study activities made your mental health or feelings of depression, anxiety or suicidality worse?"* in the primary and secondary endpoint assessments, or, reports this event via other study procedures and activities.
Action	
All relevant study data for this event will be recorded in the UNSW Safety Monitoring Template for reporting.	

b) Known Harms, Risks or Discomforts

The interventions evaluated in this trial have been designed and reviewed by mental health professionals to support young people to manage their mental health. The researchers do not anticipate significant harm or distress related to use of the interventions in the current trial, however, the following harms, risks or discomforts may occur:

a) While CBT is the gold-standard treatment for depression and anxiety, CBT-based activities undertaken in the trial interventions may require emotional effort to complete and have the potential to cause a transient increase in depressive and anxiety symptoms as well as psychological distress (e.g., exposure therapy and behavioural experiments).

b) While completion of self-report questionnaires about one's mental health have not been shown to increase distress, some participants may experience some emotional discomfort related to being asked about their mental health during the study assessments.

To minimise the potential known harms, risks or discomforts, various safety procedures will be implemented throughout the trial:

- All participants not meeting inclusion criteria at screening, including those deemed ineligible because of severe depressive symptoms and significant suicidality, will be provided with a list of referral services and information on how to access mental health crisis services. This information is provided in Appendix A.
- To mitigate potential discomfort or distress associated with the study assessments, brief youth-friendly versions have been used where possible.
- At the beginning of the study, participants will be advised that the trial interventions are not intended to replace professional medical advice, or to provide crisis support. Participants are also able to seek unlimited mental health treatment and support throughout the study period.
- A list of mental health support services will be provided to participants when completing the study assessments via the "Get Help Now" section of the study assessment websites. This list will also be shown to participants upon completion of each study assessment (see Appendix D).
- Information regarding how participants can contact the research team, how often the trial email is checked, and response time will also be provided in the study welcome email.
- All trial interventions contain emergency help information that can be accessed at any time during the intervention period.
- In addition to external support resources, participants will be informed in the PICF that they can contact the research team if they become upset or distressed because of their participation in the study. If a young person contacts the research team, a psychologist from the research team will arrange follow-up contact to assess the level of distress and direct the young person to the appropriate services. This will be provided free of charge.

How benefits outweigh potential risks of discomfort/harms:

- CBT is the gold-standard, first line treatment for depressive and anxiety symptoms in adolescents. Psychoeducation is also an evidence-based approach to reducing depressive symptoms. Therefore, all participants in the current trial will receive access to trusted mental health information and activities developed by a reputable Australian mental health organisation (The Black Dog Institute(. We expect therefore, that the benefits of interventions outweigh any potential risks of discomfort or harm associated with completing the study activities.
- The interventions in this study may also lead to increased help-seeking and greater engagement with other mental health services and support among participants.
- Participants' involvement in the trial and engagement with the program has the potential to increase their mental health literacy and self-awareness, which is important to maintain psychological wellbeing across the lifespan.

11.2 Adverse Events or Adverse Reactions

Adverse events (AE) are considered any untoward medical occurrence in a patient or clinical trial participant administered the intervention, which does not necessarily have a causal relationship with this treatment.
Adverse Reactions (AR) are considered untoward and unintended responses to the trial intervention related to any intervention procedures.

AEs and ARs are assessed using the safety monitoring flow chart. Those classified as "not serious" are assessed by the qualified physician/medical expert specified in section 2 of the protocol. The Qualified Physician cannot delegate this responsibility to other research personnel.

Adverse event reports must be reported to the Coordinating Principal Investigator within 48 hours of the research team being made aware. All adverse event reports must be recorded in the UNSW Safety Monitoring Register Template.

11.3 Serious Adverse Events

Serious Adverse Events(SAEs) that result in or lead to one or more of the following and the event is **not related** to the trial intervention:

- The death of a trial participant.
- A life-threatening illness or injury involving a trial participant.
- A participant's permanent impairment of body structure or body function.
- In-patient or prolonged hospitalisation (not for a pre-existing condition or an elective surgery) of a trial participant.
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or function of a trial participant.
- Fetal distress, fetal death or congenital abnormality or birth defect.

SAE reports are classified following the safety assessment flowchart and are assessed by Sponsors Independent Medical specified in section 2 of the protocol. The Sponsors Independent Medical cannot delegate this responsibility to other research personnel. SAR reports must be recorded in the UNSW Safety Monitoring Register Template.

11.4 Serious Adverse Reactions

A Serious Adverse Reactions (SAR) is an SAE that is **related** to the trial intervention. SAR reports are classified following the safety assessment flowchart and are assessed by Sponsors Independent Medical specified in section 2 of the protocol. The sponsors independent medical expert must determine whether the SAR was expected or unexpected. The Sponsors Independent Medical cannot delegate this responsibility to other research personnel.

a) Expected Serious Adverse Reaction

A serious adverse reaction by its nature, incidence, severity, or outcome is anticipated and identified in the current version of the intervention safety information are classified as a SAR report. SAR reports are reported to the Coordinating Principal Investigator within 72 hours for multicentre clinical trials; although this is not relevant to the current trial. Serious Adverse Reaction reports must be recorded in the UNSW Safety Monitoring Register Template.

b) Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction by its nature, incidence, severity, or outcome is unanticipated and not identified in the interventions instructions for use or safety information are classified as a SUSAR.

Fatal or life-threatening Australian SUSAR reports are reported to the Coordinating Principal Investigator, the sponsor's delegate and the approving HREC within 7 calendar days after being made aware of the case follow up information reported within a further 8 calendar days.

All other Australian SUSAR reports are to be reported to the Coordinating Principal Investigator, the sponsor's delegate and the approving HREC within 15 calendar days after being made aware of the case follow up information reported within a further 8 calendar days. SUSAR reports must be recorded in the UNSW Safety Monitoring Register Template.

11.5 Significant Safety Issue (SSI)

A safety issue that could adversely affect participants' safety or materially impact the trial's continued ethical acceptability or conduct. The Human Research Ethics Committee and Sponsor's Delegate must be notified of all significant safety issues within 15 calendar days of the sponsor instigating or being made aware of the issue**.** SSI reports must be recorded in the UNSW Safety Monitoring Register Template.

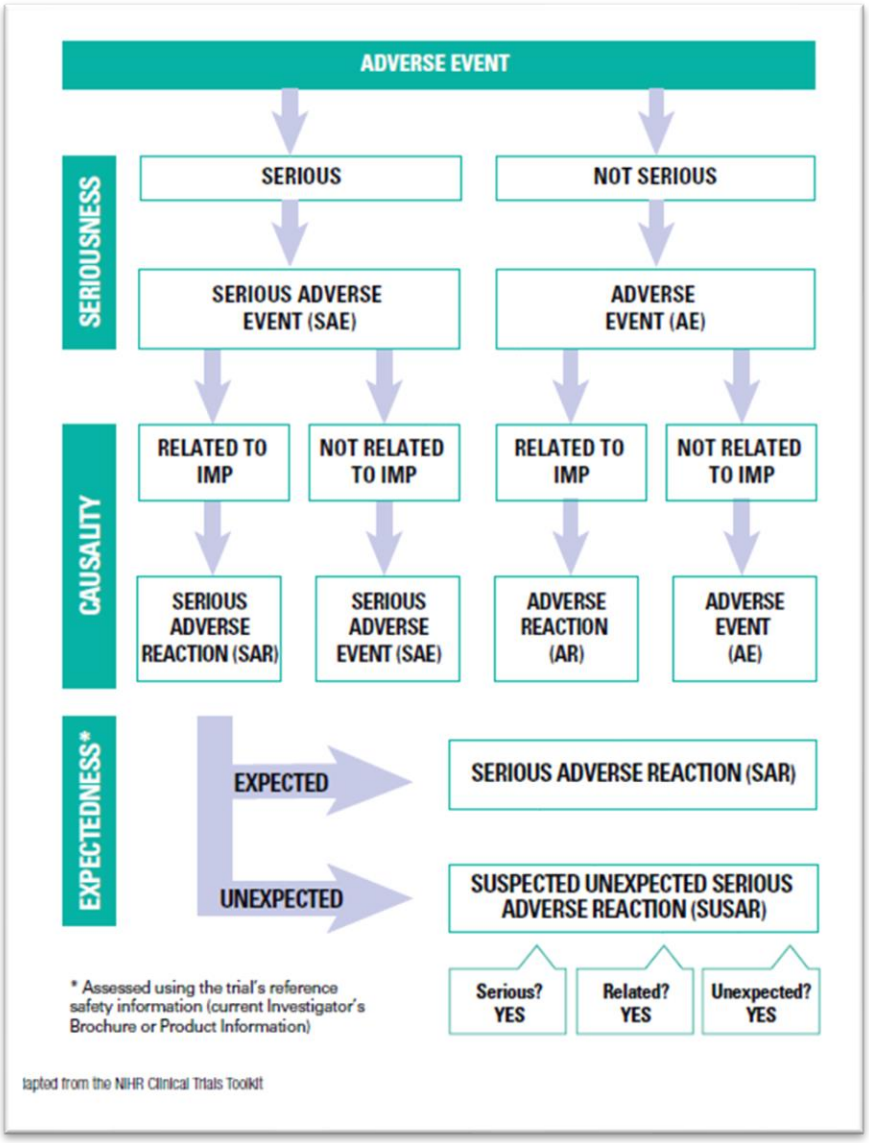
11.6 Urgent Safety Measure (USM)

A measure that is taken to eliminate an immediate hazard to a participant's health or safety. Significant safety issues where an urgent safety measure is required to be taken to eliminate an immediate hazard must be classified as a significant safety issue requiring an urgent safety measure. The Human Research Ethics Committee and the Sponsor's Delegate must be notified of any significant safety issues that meet the definition of an urgent safety measure should be notified within 72 hours. Examples include:

- a serious adverse event that could be associated with the trial procedures and that requires modification of the conduct of the trial
- a patient population hazard, such as lack of efficacy of an intervention used for the treatment of a life-threatening disease.

USM reports must be recorded in the UNSW Safety Monitoring Register Template.

11.7 Safety Assessment Flow Chart Investigational Medical Product Trials



11.8 Register of Clinical Trial Safety Monitoring Reports

A register of all event reports assessed and classified is to be retained by the Coordinating Principal Investigator and reported to the trial sponsor annually and the HREC if required.

11.9 Reporting of Clinical Trial Safety Monitoring Reports

Single case reports of Adverse Events Adverse Reactions, Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs), reports do not need to be reported to the UNSW Sponsor's Delegate or the HREC. All single case reports must be recorded in a safety monitoring register and are reported to the UNSW Sponsor's Delegate annually.

111.1 Emerging Safety Issues

The Trial Management Group (Appendix I &J) is responsible for reviewing the safety information to identify any serious emerging safety concerns. If safety concerns are

identified, this body will establish a plan to minimise the time participants may be placed at excess risk of harm. Before implementing the plan, the Trial Management Group must seek the advice of the human research ethics committee and sponsor's delegate.

112.1 Annual assessment of safety

The following information must be provided in a report to the sponsors delegate annually:

- Documented evidence that the Trial Management Group (e.g. meeting minutes) confirmed that regular safety reviews occurred.
- Analysis of the trial intervention(s) and its implications for participants considering all available safety data and relevant clinical or non-clinical studies results.
- Any reports of emerging safety issues and a description of any measures taken or proposed to minimise risks.
- A copy of the safety monitoring register.

11. Non-compliance, Protocol Deviation and Serious Breaches of Good Clinical Practice

11.1 Protocol Deviation

A protocol deviation is defined as any breach, divergence or departure from the requirements of Good Clinical Practice, the clinical trial protocol, the clinical trial standard operating procedures, or the human ethics approval that does not have a significant impact on the continued safety or rights of participants or the reliability and robustness of the data generated in the research or clinical trial. Protocol deviations are events that do not occur persistently or systematically and do not potentially result in participant harms. Examples of protocol deviations include but are not limited to:

- Deviations because of participant adherence to the protocol, including rescheduled study visits, participants refusal to complete scheduled research activities or failure to complete self-report assessments/questionnaires required by the study protocol.
- Blood samples obtained or clinical trial testing occurring at times close to, but not precisely at the time points specified in the protocol.
- The completion of consent forms, safety monitoring report, case report forms or data collection tools in a manner that is not consistent with the protocol instructions or failure to make reports within the required reporting timeframes.
- Administration of the clinical trial investigational medical product or device in a manner that is not consistent with the manufacturer's instructions for use.
- Use of an unapproved version of the participant information statement or recruitment of participants using unapproved recruitment procedures.
- Inclusion of a participant that does not meet the inclusion criteria.
- An urgent safety measure must be taken to eliminate an immediate hazard to a participant's health or safety.

11.2 Serious Breach of Good Clinical Practice

A serious breach is defined as a breach of Good Clinical Practice, the clinical trial protocol, the clinical trial standard operating procedures, or the human ethics approval that is likely to affect to a significant degree the safety or rights of participants or the reliability and robustness of the data generated in the clinical trial. Examples of serious breaches include but are not limited to:

- Persistent or systematic non-compliance with the instructions for completing consent forms, safety monitoring forms, case report forms or data collection tools that result in continued missed or incomplete data collection.

- Failure to record or report adverse events, serious adverse events, suspected unexpected serious adverse reactions, significant safety issues where urgent safety measures were implemented.
- Failure to conduct clinical trial procedures following the clinical trial delegation log.
- Widespread and uncontrolled use of protocol waivers affecting eligibility criteria, which leads to harm to trial subjects.
- Failure to report investigational medical product or device defects to the clinical trial sponsor or any relevant regulatory body.
- Failure to conduct research following the issued approvals, permits or licences by required laws, regulations, disciplinary standards, and UNSW policies relating to the responsible or safe conduct of research.
- Concealing or facilitating breaches (or potential breaches) of the Research Code by others.
- Researching without the requisite approvals, permits or licences required by laws, regulations, disciplinary standards, and UNSW policies related to the responsible or safe conduct of research.
- Failure to conduct research as approved by an ethics review body where that conduct leads to (or has the potential to) results in participant harms.
- Researching without ethics approval as required by the National Statement on Ethical Conduct in Human Research where that conduct leads to (or has the potential to) result in participant harms.
- Any breaches as outlined in the UNSW Research Misconduct Procedure or the Australian Code for responsible conduct of research that leads to (or can potentially) result in participant harms.

11.3 Reporting Protocol Deviations

- Protocol deviations occurring at a site must be documented in site files and reported by the principal site investigator to the Coordinating Principal Investigator.
- The Coordinating Principal Investigator must review the protocol deviation and the clinical trial protocol to establish the corrective actions and preventative steps to prevent the deviation from reoccurring.
- The protocol deviation and corrective action plan must be reported to the UNSW Sponsor's Delegate by the Coordinating Principal Investigator or Coordinating Research Team using the protocol deviation report form.

11.4 Reporting of a Serious Breach

- The Principal Investigator must report a serious breach occurring at a participating site to the Coordinating Principal Investigator within a specified timeframe.
- The Coordinating Principal Investigator must review the serious breach, along with the clinical trial protocol, to develop a Corrective and Preventive Action (CAPA) that defines the steps to prevent the serious breach from reoccurring.
- The serious breach report and the CAPA must be provided to the approving HREC, and the UNSW sponsors delegate for review and approval.

11.5 Reporting of Serious Breaches by Third Parties

- A Suspected Breach is a report judged by the reporter as a possible serious breach but has yet to be formally confirmed as a serious breach by the sponsor.
- A Suspected Breach form must be completed when a third party (e.g., individual/institution) wishes to report a suspected breach of Good Clinical Practice or the protocol and should be reported directly to the reviewing HREC without reporting through the sponsor.
- Recording of Protocol Deviation and Serious Breach Reports

- A register of protocol deviation and serious breach reports must be recorded. Written records and copies of documentation sent to the sponsor must be retained in the Investigator Site File.
- Copies of protocol deviation and serious breach reports must be recorded, written records and copies of documentation sent to the sponsor, referrals made to the HREC or establishing whether a breach of the Australian Code for Responsible conduct of research must be retained in the Master Site File.

12. Review of a Protocol Deviation and a Serious Breach

- The UNSW Sponsor's Delegate will review reports to establish whether the event meets the definition of a protocol deviation or serious breach, establish whether the proposed CAPA is appropriate and establish whether there is or will be ongoing impact reliability and robustness of the data generated.
- The UNSW Sponsor's Delegate will seek advice from the approving HREC on the corrective and preventive actions.
- Protocol deviation or serious breach reports where a UNSW researcher, staff or student is responsible for the protocol deviation or the serious breach will be reviewed as per the UNSW Research Misconduct Procedure to establish a breach of the UNSW Research Code of Conduct has occurred.
- Protocol deviation or serious breach reports where the UNSW Sponsor's Delegate determines that site personnel are responsible for a protocol deviation or the serious breach will be referred onto their responsible institution for review under their Research Misconduct procedures to establish whether a breach of the Australian Research Code for the Responsible Conduct of Research has occurred.

13. Statistics

This is outlined in section 10.

No interim analyses on primary or secondary outcomes is planned, unless it is warranted by safety reports and the Trial Management Group requests it.

14. Data Ownership

All research data collected during this trial is governed and handled following the Research Data Governance and Materials Handling policy. UNSW, rather than any individual or Organisational Unit, is the Custodian of data and materials and any information derived from the data. Original research data and primary materials generated in the research conducted at the University will be owned and retained by the University subject to any contractual, statutory, ethical, or funding body requirements.

15. Handling and Reporting Data

Principal Investigators are responsible for maintaining adequate and accurate source documents and trial records that include all pertinent observations on each site's trial subjects. Source data must be attributable, legible, contemporaneous, original, accurate, and complete.

Trial subjects will be assigned a participant ID, and data will be reported using the Case Report Form. Data reported on the Case Report Form, derived from source documents, should be consistent with the source documents, or the discrepancies must be explained. Any change or correction to a [case report form] should be dated, initialled, and explained (if necessary) and

should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections.

14.1 Direct Access to Source Data and Documents

Site principal investigator(s) and institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

16. Monitoring Quality Control and Quality Assurance

The Coordinating Principal Investigator and Principal Investigator(s) 'responsibility are to monitor the clinical trial. The Coordinating Principal Investigator and Principal Investigator(s) are responsible for undertaking or participating in site initiation or protocol-specific training before recruitment and data collection commences. A monitoring report demonstrating regular compliance monitoring with the clinical trial protocol, procedures, and HREC approval is provided to the UNSW Sponsor's Delegate annually.

Root, cause, analysis reports are to be completed by the Coordinating Principal Investigator for reports of non-compliance and serious breaches. A corrective and preventative action plan must be developed and actioned for any reports of non-compliance and serious breaches.

17. Clinical Trial Research Agreement

The Coordinating Principal investigators must ensure that agreements are executed at each of the following sites before site initiation, recruitment, and data collection commences.

18. Research Governance Site Authorisation

Site authorisation is to be obtained, or if a research site is added, a site authorisation letter from the delegated authority of an institution responsible for any participating site is obtained. It is to be stored as a GCP essential document before participants are recruited at a participating site.

19. Good Clinical Practice Requirements

It is recommended that the Coordinating and Principal Investigators' ensure that all investigators and trial-related staff have current Good Clinical Practice Training. Once completed, the evidence of training confirmation is to be stored as a GCP essential document.

It is the responsibility of the Coordinating and Principal Investigators to familiarise themselves with the requirements of the Guideline for Good Clinical Practice (E6, R2)

20. Essential Documents for the Conduct of a Clinical Trial

All essential documents referred to in section 8.2 of the Guideline for Good Clinical Practice (E6, R2) are to be retained by all trial investigators.

21. Clinical Trial Delegation and Responsibilities Log

Protocol / Study Number:	HC210889	**Sponsor Name:**	UNSW Sydney, Dr Ted Rohr
Principal Investigator Name:	Dr Bridianne O'Dea	**Site Number:**	NA
Site Name (if applicable)	Black Dog Institute		

***THIS FORM IS TO BE COMPLETED BY ALL PERSONNEL INVOLVED IN THE STUDY AFTER RECEIVING PROPER STUDY TRAINING AND BEFORE TAKING PART IN ANY STUDY ACTIVITIES**

Principal Investigator (PI)

By signing, I confirm/acknowledge that the tasks listed below will only be delegated to appropriately trained, skilled and qualified staff. I will remain responsible for the overall study conduct and reported data, ensuring study oversight. All associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations and have not performed any study tasks before appropriate delegation and completion of appropriate training. Mechanisms are in place to ensure that site staff receives the appropriate information and training throughout the study and that a 2-way communication channel exists between staff and self. Any changes in staff or delegation in staff will be recorded promptly.

Name	Principal Investigator's Signature	Initials	Start (dd/mmm/yyyy)	End (dd/mmm/yyyy) (complete only if prior to end of study)

Site Staff

Name	Signature	Initials	Study Role	Key Study Task(s) (choose from list below)	Start (dd/mmm/ yyyy)	End (dd/mmm/yyyy) (complete only if prior to end of study)	PI Initials & Date (dd/mmm/yyyy)
							_____ __/___/_____
							_____ __/___/_____
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							_____ __/___/_____

Name	Signature	Initials	Study Role	Key Study Task(s) (choose from list below)	Start (dd/mmm/ yyyy)	End (dd/mmm/yyyy) (complete only if prior to end of study)	PI Initials & Date (dd/mmm/yyyy)
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Name	Signature	Initials	Study Role	Key Study Task(s) (choose from list below)	Start (dd/mmm/ yyyy)	End (dd/mmm/yyyy) (complete only if prior to end of study)	PI Initials & Date (dd/mmm/yyyy)
							__/___/_____

Comments:

Electronic Signature Declaration for Principal Investigator and Site Staff

- My electronic signature as it applies to entering electronic data or signing records in sponsor-owned or sponsor -outsourced computer systems is the legally binding equivalent of my handwritten signature.
- I will not share password(s) assigned to me for this study with any other persons.

Principal Investigator's End of Study Declaration

I hereby confirm that the above information is accurate and complete, and that I authorised the delegation of study-related tasks to each individual as listed above.

Principal Investigator's Signature: _____ **Date:**

Task Key:

1. Obtain informed consent *
2. Subject selection/recruitment*
3. Confirm eligibility (review inclusion/exclusion criteria)*
4. Obtain medical history (source documents)
5. Perform physical exam*
6. Conduct study visit procedure as outlined in the protocol*
7. Make study-related medical decisions*
8. Assess AEs/SAEs*
9. Dispense study drug*
10. Perform drug accountability
11. Study drug storage and temperature monitoring
12. Sample collection
13. Sample processing and/or shipment
14. Evaluate study-related test results *
15. Use IWRS/IVRS
16. Make entries/corrections on (e)CRFs
17. Sign- off (e)CRFs*
18. Maintain essential documents
19. Perform study-related assessments as per protocol *
20. Complete company- specific log (if applicable)
21. Other (specify)_____
22. Other (specify) _____

*These tasks may only be performed by qualified individual as permitted by local law, medical or standard of care practices, or applicable required training as per job description or designation.

22. Safety Monitoring Register Template

- UNSW Safety Monitoring Register Template
- UNSW Adverse Event or Incident Event Case Report Form Example.

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Appendix I: Trial Management Group

The MobiliseMe study: Testing different smartphone activities to help improve young people's mental health

Trial Management Group

Version 1 (25th October 2021)

Administrative details

Title:	The MobiliseMe study: Testing different smartphone activities to help improve young people's mental health
Sponsor:	University of New South Wales (UNSW)
HREC:	University of New South Wales Human Research Ethics Committee
Chief Investigator:	Dr Bridianne O'Dea, Black Dog Institute, UNSW
Clinical Research Manager:	Dr Sophie Li, Black Dog Institute
Data Steward:	Dr Bridianne O'Dea, Black Dog Institute, UNSW
Funding body:	Goodman Foundation
HREC Reference number:	HC210889
ANZCTR Number:	To be confirmed
Number of Sites:	0
Number of Participants:	489

Summary
This trial aims to investigate the effectiveness of a Cognitive Behavioural Therapy (CBT) program delivered via a smartphone application (called *ClearlyMe*) for improving mental health outcomes in Australian adolescents. Participants will be randomly assigned to one of three interventions for a 6-week period. Participants will either have access to ClearlyMe, ClearlyMe with chat support, or weekly SMS with psychoeducation and self-care tips. Young people aged 12-17 years with mild to moderate depressive symptoms will be recruited online.

Design
This study will utilise a three-arm randomised controlled trial. Participants will complete outcome measures at baseline, primary endpoint (6-weeks post-baseline) and secondary endpoint (4-months post baseline. Participants will be aware of the smartphone activity they have access to after competition of baseline assessments.

Aims
This trial will examine the effectiveness of a new CBT smartphone application (*ClearlyMe*) for reducing depressive symptoms in adolescents when compared to guided use and an active-attention matched control condition.

The primary research questions that this trial seeks to address are:

6. What is the effectiveness of *ClearlyMe* (both self-directed and support use) for reducing depressive symptoms?

Secondary research questions include:

7. What is the effectiveness of *ClearlyMe* for reducing anxiety symptoms, psychological distress, rumination, and improving emotional wellbeing, quality of life, emotion regulation and CBT skill acquisition?
8. Does self-directed use of *ClearlyMe* lead to equivalent levels of program completion and engagement when compared to guided use?
9. Do factors such as gender, age, baseline mental health history or symptom severity, openness to digital mental health, digital therapeutic alliance, perceived need for care, moderate the improvements in depressive symptoms found among users of *ClearlyMe*?
10. Do factors such as CBT skill acquisition, emotion regulation, rumination, and program engagement/completion mediate the improvements in depressive symptoms found among users of *ClearlyMe*?

Data

All participants will complete self-report questionnaires, including:

- Demographics (baseline only)
- Depressive symptoms (Patient Health Questionnaire: Adolescent version; PHQ-A; baseline, primary, secondary endpoints)
- Anxiety symptoms (Generalised Anxiety Disorder-7; GAD-7; baseline, primary, secondary endpoints)
- Psychological distress (Distress Questionnaire-5; DQ-5; baseline, primary, secondary endpoints)
- Emotional wellbeing (The Short Warwick-Edinburgh Mental Well-being Scale; SWEMWBS; baseline, primary, secondary endpoints)
- Perceived need and help-seeking barriers (Perceived Need for Care Questionnaire; PNCQ; baseline, primary, secondary endpoints)
- CBT skill acquisition (Cognitive Behavioural Therapy Skills Questionnaire; CBTSQ; baseline, primary, secondary endpoints)
- Quality of life (The Child Health Utility 9D; CHU-9; baseline, primary endpoints)
- Emotion regulation (Emotion Regulation Questionnaire for Children and Adolescents; ERQ-CA; baseline, primary, secondary endpoints)
- Rumination (Ruminative Response Scale; RRS-short form; baseline, primary, secondary endpoints)
- Digital therapeutic alliance (Digital Working Alliance Inventory; D-WAI; primary endpoint)
- Digital program satisfaction (Digital program satisfaction; Satisfaction Questionnaire; primary endpoint)
- Digital program barriers (Digital program barrier; Barriers Questionnaire; primary endpoint)
- Recent mental health care (Mental Health Care Questionnaire; primary endpoint)

Intervention use will be measured automatically for each digital intervention. Participants use of the ClearlyMe app will be measured by collecting data collected including lessons completed, collections completed, features accessed, total time spent in app, content liked/disliked, content saved, and individual responses to lesson activities.

Participants use of the psychoeducational content will be measured though Google analytics tracking the number of times the URL within the SMS is clicked on.

Trial Management Group (TMG)

Overview

- The TMG will function in accordance with the principles of the following documents: Good Clinical Practice (GCP) Guidelines, Declaration of Helsinki 2000, NHMRC National Statement on Ethical Conduct in Human Research, NHMRC Guidance Safety and Monitoring of Clinical Trials involving a Therapeutic Good, and University of New South Wales HREC guidelines.
- Members will disclose conflicts of interest and will be cleared of significant conflicts of interest and potential conflicts of interest. No member should have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the TMG.
- Composition of membership will reflect expertise in clinical, statistics and the specific scientific expertise relevant to the study, in this case, severe mental health symptoms.
- A quorum group of two must be present for closed sessions and subsequent decisions and/or recommendations made by the committee.

Roles and responsibilities

The purpose of the Trial Management Group (TMG) is to supervise of the overall conduct and safety oversight of the trial, by safeguarding the interests of study participants and assessing the safety and efficacy of the trial protocol.

The TMG will provide:

- Oversight on the safety and monitoring procedures during the trial
- Provide recommendations to continue, modify, or terminate the trial
- Advice, guidance, and consultation on trial design and conduct
- Consultation on trial roadblocks and issues
- Oversight of trial processes
- Consultation on scientific quality and integrity
- Final sign-off on Trial Protocol
- Oversight of compliance with Good Clinical Practices

The investigators will:

- Assure the proper conduct of the study.
- Assure collection of accurate and timely data.
- Report relevant data to the TMG prior to scheduled meetings.
- Promptly report safety concerns to the TMG.
- Communicate with regulatory authorities (e.g., HREC) as necessary.

Composition

Internal members:

- Dr Bridianne O'Dea (Chief Investigator)
- Dr Sophie Li (Trial Manager)
- Prof Philip Batterham (Trial Statistician)

External members:

- A/Prof Jill Newby (Clinical Psychologist and Academic Researcher)
- Prof Andrew Mackinnon (Statistician)
- Dr Michelle Tye (Senior Research Fellow in Population Mental Health and Suicide Prevention)

Meetings

Prior to recruitment commencing, the TMG members will form an understanding of the protocol and study endpoints. The TMG will be provided with a monthly report on safety events and will convene a meeting after the baseline, primary endpoint (6-weeks post-baseline) and secondary endpoint (4-months post baseline) assessments have been completed to review the UNSW Safety Monitoring Template, which includes the number of call backs that were triggered, and the follow-up that was carried out. Meetings will be held face-to-face if practicable, or otherwise by video conference. Prior to each meeting, a report will be sent to the TMG outlining any recommendations and rationales.

Reporting

For this current trial, an adverse event (AE) is defined as any untoward medical or clinical occurrence in a participant without regard to the possibility of a causal relationship. A register of these events and associated interactions will be recorded in a separate risk management spreadsheet managed by the Trial Manager. These events will also be recorded in the UNSW Safety Monitoring Template.

A serious adverse event (SAE) for this trial is defined as any untoward occurrence that involves hospitalisation or death (suicide or otherwise). As per the NHMRC Safety Monitoring and Reporting Guidelines, any suspected unexpected SAEs or reactions will be reported to the TMG and the UNSW Human Research Ethics Committee within 24 hours of the research team becoming aware, using the Adverse Event Form provided by the UNSW HREC. All AEs, both solicited and spontaneous, will be reported to the TMG.

A breach of protocol is defined as something likely to affect the rights and safety of a trial participant (for example, the sharing of data to those outside those with approved access), or the reliability or robustness of the data is compromised. Any serious breaches of protocol will be reported to the TMG and UNSW HREC within 24 hours of the research team becoming aware, using the Suspected Serious Breach Report Form.

Confidentiality

All information and data provided to the TMG will be considered privileged and confidential. The TMG will agree to use these data to accomplish the responsibilities of the TMG and will not use it for any other purpose without written consent from the Chief Investigator or trial sponsor.

Safety analyses

The primary safety endpoints are:

- Frequent, current suicidal ideation (i.e., thoughts of death or of harming oneself, score greater than 2 on item 9) detected through the self-report Patient Health Questionnaire-9 at primary or secondary endpoint.
- Severe depressive symptoms detected at final study assessment (i.e., secondary endpoint: 4-months post-baseline) through the self-report Patient Health Questionnaire-9.

- Mental health related hospitalisation reported at primary or secondary endpoint or disclosed in any other study procedures (e.g. call back phone calls, participant emails).
- Self-identified deterioration in mental health due to study activities reported by participants at primary or secondary endpoints.

Stopping guidelines

The primary charge of the TMG is to monitor the study for participant safety. As such, the TMG may recommend pausing or terminating the trial if they have concerns for participant safety, based on (but not limited to) a higher than anticipated rate for one or more of the primary endpoints.

Appendix J: Standard operating procedures

The MobiliseMe study: Testing different smartphone activities to help improve young people's mental health

Trial Management Group

Version 1 (25th October 2021)

Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

Adverse Events and Serious Adverse Events

For this current trial, an adverse event (AE) is defined as any untoward medical or clinical occurrence in a participant without regard to the possibility of a causal relationship. All AEs will be collected after a participant has consented and enrolled into the trial. AEs may include severe suicidal ideation as reported on baseline, primary or secondary endpoint online self-report assessment. Severe suicidal ideation will be defined as self-reports of suicidal thoughts or thoughts of self-harm More than half the days or Nearly every day, indicated by a score of ≥ 2 on item-9 of the PHQ-9. AEs also include severe depressive symptoms reported by participants at the final assessment (secondary endpoint) before trial ends. Severe depressive symptoms are indicated by a total score ≥ 20 on the Patient Health Questionnaire-9 at secondary endpoint assessment (i.e., 4-months post-baseline). Finally, AE also include mental health related hospitalisation reported at primary or secondary endpoint or disclosed in any other study procedures (e.g. call back phone calls, participant emails).

A serious adverse event (SAE) for this trial is defined as any untoward occurrence that involves hospitalization or death (suicide or otherwise) without regard to the possibility of a casual relationship.

Adverse Reactions (AR) are considered untoward and unintended responses to the trial intervention related to any intervention procedures. AR may include self-identified deterioration in mental health due to study activities reported by participants at primary or secondary endpoints.

Reporting Adverse Events

The trial will maintain a record of any reported adverse events or serious adverse events. A summary of adverse events will be reported to the trial's qualified expert (as named in Section 1). A summary of serious adverse events will be reported annually to the UNSW sponsors delegate and UNSW ethics committee.

Due to the low-risk nature of this trial, a formal Data and Safety Monitoring Committee (DSMC) will not be convened. In lieu of the of the DMSC, a Trial Management Group (TMG) will be employed for all monitoring and reporting. Adverse events and serious adverse events will be reported to the Trial Management Group (TMG) when they meet.

Any suspected unexpected serious adverse reactions (SUSAR) will be reported immediately to the Sponsors' independent expert. If the independent expert classifies/confirms the report as an unexpected serious adverse reaction, they will report this immediately to the coordinating principal investigator (CPI). The CPI will report the SUSAR to the UNSW Sponsors' delegate as soon as possible and within 7 days of being made aware of the SUSAR.

If a significant safety issue (SSI) arises during the trial (e.g., any issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial), that requires an urgent safety measure (e.g., any action taken to eliminate an immediate hazard to a participants health), this will be documented and reported to the UNSW ethics committee and the UNSW sponsors delegate as soon as possible and within 7 days.

In accordance with UNSW requirements, the Chief Investigator will also notify the UNSW Sponsor's delegate of:

- Protocol Deviation reports outlined in the UNSW Research Misconduct Procedure.

- Any serious breach of Good Clinical Practice, the clinical trial protocol, the clinical trial standard operating procedures, or the human ethics approval that is likely to affect to a significant degree the safety or rights of participants or the reliability and robustness of the data generated in the clinical trial.
- Safety Reports relating to the continuation, suspension, or discontinuation of the clinical trial for safety reasons as they arise.
- Participant complaints or concerns received in relation to the conduct of the research.
- Any significant modifications to the clinical trial that are likely to affect to a significant degree the safety or rights of participants or the reliability and robustness of the data generated in the clinical trial.
- Amendments to clinical trial research agreements or service level agreements.
- Revisions to regulatory requirements including correspondence with the Therapeutic Goods Administration, clinical trial registries or the FDA.

Procedure for the type and duration of the follow-up of subjects after adverse events

The current trial will recruit participants from a clinical population, it's expected that feelings of anxiety and/or depression, and suicidal thoughts or thoughts of self-harm will be common. Included at the end of each mental health assessment at (baseline, primary or secondary endpoint) are suggested resources and contact details for services, should participants become distressed and need assistance. These services include Lifeline, Beyond Blue, and Kids Helpline as well as a range of resources and support from the Black Dog Institutes website. Participants that experience an AE related to severe suicide ideation or severe depressive symptom will be offered a follow-up call from a Clinical Psychologist. The Clinical Psychologist will conduct a brief risk assessment over the phone to determine the level of risk. If determined to be at risk, the participant will be advised to contact an appropriate service (e.g., a GP, the BDI Psychology Clinic, Mental Health Hotline). If the risk of harm is deemed significant enough to break confidentiality, or the participant requests it, their parents will be contacted by mobile telephone within an additional two working days. Referral suggestions will be provided.

Procedure for accounting for missing, unused, and spurious data

All data will be collected via online surveys, rather than pencil-and-paper responses, reducing the amount of missing data or errors within the data set. To maintain data integrity frequency tables of all variables (including time and date information) will be collected and checked to ensure that scale items have only legal values. These legal values will also be checked for coherency (i.e., do end times/dates occur after corresponding 'start' time/dates.

Any missing items will be flagged with a value that cannot be confused as a legal value. Additionally, a present/absent indicator variable will be created for each data collection timepoint to track missing data due to participant absence. For partially answered inventories, respondents that answer at least 50% of items on a scale and still have a valid score will be allowed (Bell &Fairclough, 2014). Respondents that have less than 50% of items on scale completed will be assigned as missing values. The research team will be guided by the trial statistician in data analysis.

Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate)

Any deviation for the original statistical plan will be submitted to the University of New South Wales HREC for approval before implementation