**Clinical Trial Protocol**

**Investigational Medical Device**

“Courage Quest” - A Digital Exposure-Focused Intervention for Children with Anxiety: A Pilot Case Series Intervention Study and Randomised Controlled Trial

Version 5: 6th October 2023

Professor Jennie Hudson

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# **General Information**

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| --- |
| **Protocol Title**  |
| “Courage Quest” - A Digital Exposure-Focused Intervention for Children with Anxiety: A Pilot Case Series Intervention Study and Randomised Controlled Trial |
| **Protocol identifying number** | HC230097 |
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| **ANZCTR** | Study 1: ACTRN12623000779673Study 2: ACTRN12623000828628 |
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| **Name** | UNSW |
| **Status of ethical review** | [x]  **Approved**[ ]  **In progress** [ ]  **To be submitted** |
| **Trial Sites** | The trial will be conducted online; the research team will be working from Black Dog Institute |
| **Funding for the Clinical Trial** |
| **Funding Body Name** | 1. Perpetual Impact Philanthropy Program on behalf of the Bendix Family Charitable Endowment ($117, 894)2. Commonwealth Bank ($10,000)3. Black Dog Institute ($585,382) |
| **Amount of Funding** | $713,276 |
| **Regulatory Requirements**  |
| **Therapeutic Goods Administration Clinical Trial Notification**  | [ ]  **Yes**[x]  **No**  |
| **Insurance for Clinical Trial**  |
| **Insurer** | UNSW  |
| **Type of Insurance**  | Clinical trials are not automatically covered by UNSW insurance, and confirmation must be obtained by completing the [Clinical Trials Spreadsheet](https://www.fin.unsw.edu.au/sites/default/files/content/clinicaltrials.xlsx) 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**  | [x] **Attached** [ ]  **In progress** [ ]  **To be submitted** |

# **Safety and Monitoring Contacts**

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# **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](https://research.unsw.edu.au/document/Clinical%20Trial%20Delegations%20Log.docx). 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 has the potential to 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 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.
* Addition of participating trial sites, contractual arrangements at participating sites or modifications to legal agreements.
* The intention to conduct the trial in other countries.

# **Trial Objectives and Purpose**

The overarching goal of this research is to develop and evaluate a digital exposure-focused intervention (the Courage Quest intervention) for children aged 8 to 12 years with one or more anxiety disorders. We are aiming to answer the following research question:

Does the Courage Quest intervention reduce anxiety symptoms and result in greater remission of anxiety and related disorders for children aged 8 to 12 years compared to children participating in an active control intervention?

We aim to evaluate this through two studies: 1) a pilot case series intervention study and 2) a randomised controlled trial. This protocol is for both Studies 1 and 2.

# **Background Information**

This project has the potential to decrease anxiety disorders and symptoms in Australian children. Prior to the COVID-19 pandemic, anxiety disorders were on the rise, with a dramatic increase - nearly double – the number of Australian children diagnosed with anxiety from 2008 to 2013 (4.4% vs 7.6%) (Danchin et al., 2019; Sadler et al., 2018).

Cognitive Behavioural Therapy (CBT) is the current recommended first line of treatment for paediatric anxiety disorders (Creswell et al., 2020; Hudson et al., 2019). CBT involves anxiety management strategies (e.g., cognitive restructuring, relaxation) followed by exposure therapy. Exposure therapy involves facing one’s fears and includes a range of repeated tasks (like speaking in class, reducing reassurance-seeking questions, or sleeping in their own bed), typically arranged in increasing difficulty (i.e., graded exposure). Exposure therapy is believed to be successful because it establishes new memories about the feared situation that compete with existing ‘anxious’ memories (Craske et al., 2014).

Research has found that psychological treatment for anxiety via specialist clinics achieve 50% remission, resulting in many children remaining symptomatic (James et al., 2020). Treatment success is hindered by an absence of research on which key components of CBT (e.g., cognitive restructuring, relaxation, graded exposure) and other evidence-based treatments are optimal for treating anxiety (National Institute for Health Research, 2021). Increasing treatment efficacy is critical to solving this issue.

Currently, there is an absence of research systematically evaluating exposure therapy (Teunisse et al., 2022). A recent meta-analysis identified weaker effect sizes when relaxation was used, and stronger effect sizes when exposures were conducted (Whiteside et al., 2020). Thus, outcomes could be improved by increasing exposures and excluding relaxation. Yet no research examines this experimentally. A systematic research program is needed to optimise exposure to increase efficacy. Workshops for youth with lived experience of anxiety as well as carers and clinicians identified that exposure is not often implemented in practice (Teunisse et al., 2022). Indeed, clinicians reported feeling anxious about creating distress, often resulting in exposure being omitted in favour of non-evidence-based strategies. Thus, parents and youth felt they were not given adequate support. Further, clinicians reported there is no digital platform to help youth conduct exposure and no tool to deliver blended care treatment. Although e-treatments are available (e.g., Brave, Cool Kids), exposure is introduced mid-treatment after other strategies, and it is not prioritised as the key ingredient. Online treatments are completed as an alternative rather than a complement to seeing a practitioner.

Supporting parents to provide exposure-focused therapy for their children with anxiety is one solution, particularly in cases where people do not have access to formal treatment (e.g., if they are on a waitlist). A randomised controlled trial by Creswell et al. (2017) examined parent-delivered CBT, including graded exposure, for children aged 5-12 years referred for anxiety difficulties. The trial found that parent-delivered CBT was feasible and safe, with no treatment- or trial-related adverse events reported. Creswell et al. (2017) recommended parent-delivered CBT as a cost-effective first-line treatment approach for children with anxiety.

Indeed, parent-facilitated CBT (including graded exposure) appears a promising first-line approach for children with anxiety with no access to formal treatment. Rapee et al.’s (2006) randomised controlled trial examined differences in standard group treatment, waitlist control, or bibliotherapy treatment. Bibliotherapy involved parents receiving printed information on treatment for anxiety (with a significant graded exposure component) and conducting the treatment with their child using the printed information as a guide. Parents conducted bibliotherapy for 3 months without therapist support. The study found that bibliotherapy treatment led to 15% more children being anxiety-free after 12 and 24 weeks, compared to waitlist control (Rapee et al., 2006).

Similarly, a randomised clinical trial by Rapee et al. (2017) examined a stepped care model of treatment for children with anxiety disorders where the first intervention step involved a low intensity bibliotherapy including graded exposure techniques. Parents of children under 13 years old received a workbook with guided exercises while their parents received a book detailing strategies (including graded exposure) to help manage their child’s anxiety, as well as 4 x 30-minute telephone support sessions. The second and third steps involved therapist-led cognitive behavioural interventions also including graded exposure techniques. This study found that bibliotherapy and the standard therapist treatment had strong treatment gains. Lastly, participants receiving stepped care did not differ significantly to participants receiving standard care for remission of primary anxiety disorder or remission of all diagnoses.

In this study, we aim to extend the field by developing a digitised exposure-focused intervention for parents and children. The “Courage Quest” intervention will be developed as a parent guided intervention with therapist support. The intervention will be pilot tested using a case series intervention design, the outcomes from which will refine the intervention. The hypothesis of Study 1 is that there will be clinically significant reductions in children’s anxiety symptoms and disorders (parent and child reported) after completion of the intervention. We then plan to evaluate the refined intervention in a pilot RCT comparing the efficacy of the "Courage Quest” intervention to an active control condition. The control condition will use the Raising Healthy Minds intervention before being given access to the “Courage Quest” intervention. Hypotheses of Study 2 are that both groups will show reduction in anxiety symptoms and disorders at post-treatment and delayed follow-up. Further, we hypothesise that children in the intervention group completing the Courage Quest intervention will show significantly greater reduction in children’s anxiety symptoms and disorders (parent and child reported) than children in the control condition at post-treatment. Lastly, due to the control group’s access to the “Courage Quest” intervention, we hypothesise that children in the control group’s will have similar reduction in children’s anxiety symptoms and disorders at delayed follow-up will be similar comparative to that of children in the intervention group.

**References:**

Craske, M.G., et al., Maximizing exposure therapy: An inhibitory learning approach. 2014. 58: p. 10-23.

Cresswell, C., et al., Clinical outcomes and cost-effectiveness of brief guided parent-delivered cognitive behavioural therapy and solution-focused brief therapy for treatment of childhood anxiety disorders: A randomised controlled trial. Lancet Psychiatry, 2017. 4: 529-539.

Creswell, C., P. Waite, and J. Hudson, Practitioner Review: Anxiety disorders in children and young people – assessment and treatment. Journal of Child Psychology and Psychiatry and Allied Disciplines, 2020. 61(6): p. 628-643.

Danchin, M., et al., Trends in Prevalence and Management of Childhood Anxiety by Australian Pediatricians. Academic Pediatrics, 2019. 19(1): p. 35-43.

Hudson, J.L., J. Anagnos, and V. Ingram, Phenomenology and standard evidence-based care of anxiety disorders in children and adolescents, in Innovations in CBT for Childhood Anxiety, OCD, and PTSD: Improving Access and Outcomes. 2019. p. 3-27.

James, A.C., et al., Cognitive behavioural therapy for anxiety disorders in children and adolescents. The Cochrane database of systematic reviews, 2020. 11: p. CD013162.

National Institute for Health Research, Involve (www.invo.org.uk). 2021.

Rapee, R. M., et al., Bibliotherapy for children with anxiety disorders using written materials for parents: A randomized controlled trial. Journal of Consulting and Clinical Psychology. 2006. 74(3): 436-444.

Rapee, R. M., et al., Comparison of Stepped Care Delivery Against a Single, Empirically Validated Cognitive-Behavioral Therapy Program for Youth With Anxiety: A Randomized Clinical Trial. Journal of the American Academy of Child & Adolescent Psychiatry, 2017. 56(10): 841-848.

Sadler, K., et al., Mental health of children and young people in England, 2017. 2018.

Teunisse, A., et al., A scoping review investigating the use of exposure for the treatment and targeted prevention of anxiety disorders in young people. Revise and Resubmit, Journal of Child Psychology & Psychiatry Advances, February 2022

Whiteside, S.P., et al., A meta-analysis to guide the enhancement of CBT for childhood anxiety: exposure over anxiety management. 2020. 23(1): p. 102-121.

# **Statement of Compliance**

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

* [ICH Guidelines for Good Clinical Practice (GCP)](https://www.tga.gov.au/publication/note-guidance-good-clinical-practice)
* [National Statement on Ethical Conduct in Human Research (National Statement)](https://nhmrc.gov.au/about-us/publications/national-statement-ethical-conduct-human-research-2007-updated-2018)
* 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.

# **Conflicts and Interests**

The investigators have no conflicts or competing interests to declare.

# **Methodology**

## Study Design

Study 1: Pilot case series of the Courage Quest intervention

A pilot evaluation using a case series intervention design will recruit 7 children with clinical anxiety and their parents to pilot test the Courage Quest intervention. We will evaluate remission in anxiety disorders and symptom reduction pre- and post- intervention. Thus, participants will be asked to complete the questionnaires on *two occasions* (baseline and post-intervention).

Following the intervention and post-intervention assessment, researchers will conduct semi-structured qualitative interviews with participants to understand experiences with the intervention. Study 1 will help us to refine the Courage Quest intervention that will be evaluated in Study 2.

The flowchart below summarises the study design and procedure (n’s to be added at completion of study):



Study 2: RCT to evaluate the Courage Quest intervention

We will evaluate the refined Courage Quest intervention in a randomised controlled trial to compare the efficacy of the intervention on anxiety remission rates and symptom reduction compared to an active control condition called the Raising Healthy Minds intervention. A sample of 250 children (8-12 years) with an anxiety disorder (as defined in the inclusion and exclusion criteria of Section 10) will be randomised to either the intervention (Courage Quest) or control (Raising Healthy Minds) condition for 10 weeks. Following these 10 weeks, the control condition will gain access to the Courage Quest intervention.

The primary outcome will be remission of anxiety disorders. Secondary outcomes will include symptom reduction of child anxiety based on parent and child report. These outcomes will be measured and reported in accordance with international consensus reporting guidelines (Creswell, 2021). Secondary outcome measures will include user engagement and usage data. Participants will be asked to complete the questionnaires on *three occasions* (baseline, immediately post-intervention, and 10-week delayed follow-up assessment).

The flowchart below summarises the study design and procedure (n’s to be added at completion of study):



Reference:

Cresswell, C., et al., Research Review: Recommendations for reporting on treatment trials for child and adolescent anxiety disorders - an international consensus statement. Journal of Child Psychology and Psychiatry, 2021. 62(3): 255-269.

## Description of the interventions

Intervention - Courage Quest.

The Courage Quest intervention is a 10-week digital intervention that aims to equip children and their parents with strategies to overcome child anxiety. It will take the form of a web- and mobile-based app. Parents will complete a training module within the Courage Quest intervention to familiarise themselves with the app and activities. The training module comprises information about the following topics: program overview, what anxiety is, what causes anxiety, how avoidance makes it harder to reduce anxiety, signs, and symptoms of anxiety, using rewards to motivate children to continue/finish the intervention, and the importance of practising graded exposure activities.

Both parents and children will then access the intervention content which includes the core strategies of psychoeducation (e.g., learning about anxiety) and graded exposure (e.g., Courage Quest gradually). The content will be delivered through weekly modules over a 10-week period ( 20 minutes to 1 hour per week). The parent and child complete the content together on a device (e.g., laptop or tablet – device to be decided through stakeholder engagement and IT requirements). The content will be delivered in the form of videos, brief text with auditory explanations, and examples. The child and parent will be presented with activities and “digital worksheets” to complete online. Participants will have 1 week to complete weekly modules. See Appendix A for example content from the app.

Therapist support will also be provided to parents for 3 x 20-minute telephone/telehealth conversations to problem solve any difficulties they may be experiencing with the program. This includes helping parents to guide their children in setting up rewards, entering worries and goals, creating activities for their graded exposure practices, and doing the graded exposure practice activities. These support sessions will be scheduled in at a time convenient to the parent, roughly after the first, fifth, and eighth weeks. See Appendix B for therapist support guide. These therapist support sessions will be completed over Zoom and video- and audio-recorded and transcribed so that the research team can ensure the integrity and consistency of the therapist support sessions. For more details on the data storage of recordings, please see Section 11a “Data Storage”.

Control – Raising Healthy Minds.

Raising Healthy Minds is a free mobile app created by the Raising Children Network (Australia) and funded by the Australian Federal Department of Health. We have permission from the Director of the Raising Children Network to include this app in our study. The app provides information and resources to parents about their child’s mental health.

As an equivalent to the Courage Quest training module, participants in the control group will be required to complete a training module which will contain information about how to navigate the Raising Healthy Minds intervention (e.g., screen recordings of how to access the app, how to find their weekly content etc.).

As an equivalent to the Courage Quest intervention content, the research team have selected Raising Healthy Minds intervention content to be delivered in 10 weekly reading lists to be sent to parents weekly using a push notification. The content will include mental health information, and provide strategies for parents to try either themselves, or with their child, and will take approximately 20 minutes to 1 hour (see Appendix C for more information on content and timing per week). Parents may also choose to spend additional time on the content, e.g., implementing Raising Healthy Mind’s suggested strategies with themselves or their child outside of the app. The Raising Healthy Minds intervention content will contain information about anxiety, so this information is not required in the training module. Importantly, the Raising Healthy Minds intervention content will not include information about graded exposure, to ensure that the effects of graded exposure is only being tested in the Courage Quest intervention.

Participants in this group will also receive 3 x 20-minute telephone/telehealth conversations regarding their experience with the Raising Healthy Minds intervention. The therapist will not provide any CBT support, as the content in the Raising Healthy Minds intervention is more general in nature and does not specifically explore CBT or graded exposure techniques. Instead, the therapist can provide psychological support using counselling skills such as active listening, asking parents to recount any challenges their child had during the week, clarifying the meaning behind the topics of the app, and problem solving. The therapist can also provide problem solving for technical difficulties and accessing the app. These support sessions will be scheduled in at a time convenient to the parent, roughly after the first, fifth, and eighth weeks. See Appendix D for therapist support guide. As per the intervention group, these therapist support sessions will be completed over Zoom and video- and audio-recorded and transcribed so that the research team can ensure the integrity and consistency of the therapist support sessions. For more details on the data storage of recordings, please see Section 11a “Data Storage”.

See the below table on the comparison between the control group and intervention group therapist support sessions:

|  |  |  |
| --- | --- | --- |
| **Content** | **When using Courage Quest** | **When using Raising Healthy Minds** |
| Timing and frequency | Number of sessions | 3 | 3 |
| Length per session | 20 minutes | 20 minutes |
| Support provided  | Support for child’s mental health | CBT-based focusing on graded exposure, to reflect the content of the app | Counselling-based, to reflect the general content of the app |
| Problem solving technical difficulties | **✓** | **✓** |

Please note that when participants in the control group gain access to the Courage Quest intervention, they will receive another 3 x 20-minute therapist support sessions during this time. These therapist sessions will follow Appendix B and thus the therapist will provide the same support that the intervention group received.

## Data Collection

Studies 1 and 2

Data for both Studies 1 and 2 will be collected using standardised questionnaires and semi-structured telephone interviews as outlined below.

The following questionnaires will be administered online through Qualtrics:

* Screening questions for parents (see Appendix E)
* Demographic questionnaire (see Appendix F)
* Revised Child Anxiety and Depression Scale 25 items for Child and Parent (RCADS-25-C/P; Ebesutani et al., 2017) for children and parents (see Appendix G)
* Child Anxiety and Depression Life Interference Scale – Parent and Child versions (CADLIS-P and CADLIS-C) (see Appendix H)
* The Kiddie Schedule for Affective Disorders and Schizophrenia Child Psychiatric Diagnostic Interview (KSADS-COMP; Townsend et al., 2020) self-report completed by parents (see Appendix I)
* Post-intervention activity tracker and acceptability rating scale (see Appendix J)

The following app usage data will also be collected through direct export from the Courage Quest intervention and Raising Healthy Minds intervention (control condition).

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose** | **Data collected** | **Courage Quest** | **Raising Healthy Minds** |
| To understand participants’ engagement with the app | Login frequency (total and per day) | **✓** | **✓** |
| App usage (minutes and days) | **✓** | **✓** |
| Pages visited and minutes spent on page | **✓** | **✓** |
| Number of visits to each page | **✓** | **✓** |
| To understand how participants engage with graded exposure in the Courage Quest intervention  | Modules completed and time spent to complete | **✓** | N/A |
| Number of worries, goals, and activities that are added, edited, or reviewed and how often | **✓** | N/A |
| Number of goals added, edited, or reviewed and how often | **✓** | N/A |
| Number of graded exposure activities per goal added, edited, or reviewed | **✓** | N/A |
| Number of graded exposure activities completed, re-attempted, or abandoned | **✓** | N/A |
| Number of goals completed | **✓** | N/A |
| Free text data (e.g., participant’s worries, goals, and level activities) | **✓** | N/A |
| To monitor the safety of participants while they conduct the graded exposure (see more information regarding severity alerts in section 12.2) | Feelings ratings | **✓** | N/A |
| Compilation of all participants who have triggered severity alerts, and feelings ratings that triggered the alerts | **✓** | N/A |
| To understand which gamification and incentive features participants utilised in the Courage Quest intervention | Rewards that are added, edited, reviewed, or redeemed | **✓** | N/A |
| Profile avatar selected, and if edited, or reviewed | **✓** | N/A |
| Date/timestamp if completion certificate was downloaded after completion of intervention | **✓** | N/A |

Study 1 only

For Study 1 only, qualitative data will be obtained through one-on-one semi-structured telephone interviews approximately 1 hour long each. Interviews will ask participants about their experience with the Courage Quest intervention, including barriers of use and any modifications they believe the intervention would benefit from (see Appendix K for interview guide). Findings from these interviews will guide any modifications we make to the intervention for its evaluation in Study 2. With participant consent, telephone interviews will be audio-recorded on voice recorders connected to the telephone and transcribed verbatim. Files from the voice recorder will be transferred to UNSW storage as outlined in Section 11a. The data collected from these interviews will aid in the refinement of the Courage Quest intervention prior to Study 2.

## Procedure

Study 1:

Consent and Screening

1. Participants will first complete screening questions (approximately 10 minutes) to determine eligibility (see eligibility criteria in section 10). These questions will ask parents about their child’s age, grade, previous diagnoses, anxiety, and willingness to participate in the study. No identifiable information will be collected at this stage.
2. Participants who are eligible will be directed to the Participant Information Statement and Consent Forms. This ensures that people who are not eligible do not have to read the lengthy information about the study.
3. Following consent, participants will proceed to one last screening question assessing suicidal ideation (see Appendix E). Asking this question after consent ensures we have contact details to conduct a risk assessment follow-up with any parents of children who have suicidal ideation. Details of the risk assessment follow-up will be recorded in a register (see Appendix V).
4. If no suicidal ideation is indicated, researchers will contact participants by phone to provide information about the KSADS-COMP and to ask participants to schedule in a time to complete it (see Appendix L for telephone script).
5. Participants will then receive an email to complete the KSADS-COMP (approximately 1 hour), a standardised and validated assessment of childhood mental illness (see Appendix I for a description of the assessment, items, psychometric properties, and scoring information).
6. Researchers will email a report to participants with feedback from the KSADS-COMP. While this does not provide any diagnoses, it allows parents to better understand their child’s mental health (see Appendix M for template of this report).

Outcome Assessments and Intervention

1. Researchers will contact all participants who completed the KSADS-COMP by phone to discuss next steps (i.e., if they are eligible to continue, that they need to do the baseline assessment before downloading the app, what emails/surveys they will receive) (see Appendix N for telephone script).
2. Participants will then be able to complete the baseline assessment (approximately 10-15 minutes), which starts with the demographic questionnaire, which has been developed by the research team to gain insight to key socioeconomic indicators (such as gender, ethnicity, location, education, household income, and history of mental health) used to better understand the study sample. The baseline assessment also includes the RCADS-25-C/P (Appendix F), CADLIS-P and -C (Appendix H). These are standardised and validated measures to identify childhood anxiety. Please refer to the Appendices for a description of the tests, their psychometric properties, and scoring information.
3. Participants will receive information on how to download the app (Courage Quest intervention).
4. Participants will complete the 10 week Courage Quest intervention.
5. Participants will then be able to complete the post-intervention assessment (approximately 15-20 minutes). This will include demographic questions to link participants’ responses over time, and to determine if the child has received treatment for psychology since the previous survey. The survey also includes the KSADS-COMP, the RCADS-25-C/P, CADLIS-P and -C, and the post-intervention activity tracker and acceptability rating scale. The latter has been developed for this research based on existing measures and will obtain parent- and child- reported data on how often participants engaged with the strategies in the apps, and how usable and acceptable the intervention and control apps are. Please see Appendix J for items and scoring information.
	1. For the KSADS-COMP, a similar procedure to Steps 4 and 5 above will occur, i.e., researchers will contact participants by phone to ask participants to schedule in a time to complete it. Following this, participants will then receive an email to complete the KSADS-COMP

Qualitative interviews

1. For Study 1, researchers will contact participants after the post-intervention assessment to schedule in the semi-structured qualitative interview.

Study 2:

The procedure for Study 2 is the same as the Study 1 procedure except for the following points:

* Following the baseline assessment (step 8 above), all participants in Study 2 will be randomised into the intervention or control groups. Participants will be individually randomised using stratification to ensure balance across the conditions (i.e., Intervention or Control) on the following variables: 1) parent-reported anxiety symptoms, based on RCADS-P t-scores of <70 vs ≥70), 2) location (metropolitan vs rural/remote), and 3) gender identity of child (boy, girl, non-binary/other). Randomisation will be completed through the randomizer feature of Qualtrics.
* Participants of Study 2 will not partake in the semi-structured qualitative interview (step 12 above)
* Participants of Study 2 will additionally complete a delayed follow-up assessment 10 weeks after completing the intervention (step 10 above). This will include demographic questions to link participants’ responses over time, and to determine if the child has received treatment for psychology since the previous survey. The survey also includes the RCADS-25-C/P, CADLIS-P and -C, the post-intervention activity tracker and acceptability rating scale (approximately 10-15 minutes), and the KSADS-COMP (approximately 1 hour).
	+ For the KSADS-COMP, a similar procedure to Step 11a (above in Study 1’s procedure) will occur, i.e., researchers will contact participants by phone to ask participants to schedule in a time to complete it. Following this, participants will then receive an email to complete the KSADS-COMP

## Data Analysis

Study 1: Pilot case series of the Courage Quest intervention

A number of data integrity checks and processes will be in place to ensure we collect legitimate responses. These include: adding attention checks (e.g., “please select the *italic* option”) for parent participants, preventing participants from submitting multiple responses (via Qualtrics security features), inserting a re-CAPTCHA code to prevent bot submissions, preventing responses from IP addresses outside of Australia, and analysing the internal reliability between timepoints, average time to complete the survey, and timestamps of completion. The research team will contact any parent participants whose data appear fraudulent. If participants are uncontactable or are found to be fraudulent, their data will be removed from the final analysis and they will not receive reimbursement for the survey.

We will evaluate the efficacy of the Courage Quest intervention on anxiety outcomes using repeated-measures ANOVAs to compare anxiety outcomes at baseline and post-intervention. Paired samples *t-*tests will be used to identify if there are any significant reductions in anxiety from pre to post intervention compared to baseline to pre-intervention. Data is unlikely to be normally distributed and appropriate non-parametric tests will be used as required.

Subjective data through the post-intervention activity tracker and acceptability rating scale will be analysed alongside objective exported app usage data (as described above) to provide a comprehensive understanding of user engagement.

Qualitative free text data from the Courage Quest intervention (e.g., worries, goals, activity levels) will be analysed through content analysis.

Qualitative interview data will be analysed through thematic analysis.

Study 2: RCT to evaluate the Courage Quest intervention

Note: T1 = baseline, T2 = immediate post-treatment, T3 = delayed 10 week follow up

Sensitivity and dropout analyses will be conducted on the final data set. In cases where participants received additional treatment after being enrolled into the study, we will use the sensitivity analyses to determine if this has influenced the findings, and whether these participants’ data will be included in the final dataset.

We will also include a number of data integrity checks and processes to ensure we collect legitimate responses. These include: adding attention checks (e.g., “please select the *italic* option”) for parent participants, preventing participants from submitting multiple responses (via Qualtrics security features), inserting a re-CAPTCHA code to prevent bot submissions, preventing responses from IP addresses outside of Australia, and analysing the internal reliability between timepoints, average time to complete the survey, and timestamps of completion. The research team will contact any parent participants whose data appear fraudulent. If participants are uncontactable or are found to be fraudulent, their data will be removed from the final analysis and they will not receive reimbursement for the survey. Participants will only be randomised following these data integrity checks.

To assess the primary outcome of anxiety remission, we will analyse the proportion of participants meeting the clinical threshold for caseness on the diagnostic measures (KSADS-COMP, which provides diagnoses based on the DSM-V) at post-T1 using mixed effects logistic regression model including participant as a random intercept effect. We will examine the differences between the intervention and control groups at T2, and also the differences in the control group between T2 and T3.

To assess the secondary outcome of parent- and child- reported child anxiety, we will be using mixed-model repeated measures (MMRM), with time as the within-groups factor (T1, T2, and T3) and condition as the between-group factor (intervention vs. control). This approach handles missing data by including all available data from each subject into the analysis and assumes missing data are missing at random. The maintenance of training effects will be evaluated by testing within-group change from T1 to T3. This will be compared to change from T1 to T2. Response to training in the waitlist control group will be evaluated by testing within-group change from T2 to T3 vs change from T1 to T2. The extent of change and outcomes at follow-up will be compared to that observed in the intervention group.

Subjective data through the post-intervention activity tracker and acceptability rating scale will be analysed alongside objective exported app usage data (as described above) to provide a comprehensive understanding of user engagement.

Qualitative free text data from the Courage Quest intervention (e.g., worries, goals, activity levels, notes/comments after activity practises) will be analysed through content analysis to understand participants’ engagement with the app, and their understanding of graded exposure (e.g., if the goals and activities were appropriate to their worries, if they created multiple activities per goal, if they worked on multiple goals).

# **Sample Size**

Study 1: Pilot case series of the Courage Quest intervention

To develop and refine the Courage Quest intervention, we will recruit 7 children aged 8 to 12 years and their parents (allowing for 25% drop out due to small sample size). Five children would be deemed sufficient to gain insight into the practicalities of the Courage Quest intervention, obtain feedback from children and parents to refine the intervention in preparation for the RCT. Once we reach the minimum target of 7 children, we will cease recruitment. In cases where we recruit 7 children but do not achieve the minimum of N = 5 children completing the entire pilot case series, we will re-open recruitment.

Study 2: RCT to evaluate the Courage Quest intervention

To evaluate the Courage Quest intervention, we will recruit 250 participants aged 8 to 12 years and their parents (allowing for 20% drop out). Two hundred children would provide 80% power and alpha of .05 to detect a difference between groups of d=.40 – a medium sized effect. Once we reach the minimum target of 250 children, we will cease recruitment.

# **Selection and Withdrawal of Subjects**

## **Inclusion Criteria**

Research Participants for Study 1 & 2:

Children and their parent/carer will be included based on the following criteria:

* Child aged 8 to 12 years
* Child diagnosed with one or more anxiety disorders and/or obsessive-compulsive disorder (as determined on the KSADS-Comp)
* Capacity to answer questions independently or with assistance if needed
* Participants require access to a device (e.g., laptop, tablet, desktop) and internet to use the Courage Quest intervention and the Raising Healthy Minds intervention (control condition). A question in the demographic questionnaire (Appendix F) will ask if participants have access to a device and internet. If they select “No”, then a subsequent question will ask if we can contact the participant to discuss lending them a tablet device, on loan at no cost, to use for the study. If they select “No, I would like to withdraw from the study as I will not have regular access to a device and internet and do not want to be contacted regarding the loan of a device”, they will be withdrawn from the study. If they select “Yes”, a research team member will contact them to provide the option to participants for them to be mailed the tablet, with a replied-paid return package included for them to return the tablet at the end of the study. We will inform them that they are to return the tablet before receiving their gift cards. We will also inform them that if participants withdraw from the study, we will ask them to return the tablet as soon as possible.

## **Exclusion Criteria**

Research Participants for Study 1 & 2:

Exclusion criteria

* Child has a diagnosis of major depression (as determined by the KSADS-COMP)
* Child has a primary oppositional defiant disorder, or conduct disorder diagnosis that is equal to or greater than their anxiety disorder severity (as determined by the KSADS-COMP)
* Child has a primary attention deficit hyperactivity disorder diagnosis that is greater than their anxiety disorder severity (as determined by the KSADS-COMP)
* Child has a diagnosed intellectual disability (as determined through parent self-report)
* Child is currently receiving CBT-based psychological therapy for anxiety (other than school counsellor support), i.e., seeing a psychologist for anxiety or using a CBT-based program (e.g., Cool Kids or BRAVE) for anxiety (as determined through parent self-report)
	+ Note: child will be eligible if they are receiving other types of (i.e., non-CBT-based) psychological treatment
* Child is currently prescribed medication for anxiety (as determined through parent self-report).
* Child is reported to have life-threating suicidal ideation and/or had serious suicidal ideation in the last month (as determined through parent self-report). A clinician (Dr Francis, Dr Sicouri, Dr Aji, Dr Chen, or Prof Hudson) will complete a risk assessment follow-up with parents. This follow-up will occur via telephone within 72 hours of the self-report.
* For Study 2, child must not have participated in Study 1

## **Recruitment Strategy**

Participants for Studies 1 & 2 will be recruited through the following channels:

* BDI networks (Psychology Clinic, Lived Experience Advisors, School Advisory Committee, Social Media Campaign via Facebook, Instagram, and Twitter)
* UNSW networks (e.g., staff Yammer, Adminnet)
* Australian parenting networks (e.g., raising children’s network)
* Parenting networks via social media (e.g., Facebook, Instagram, Twitter)
* School counsellors (at independent and private schools in Australia)
* Psychology clinics (advertising study to waitlist clients)
* Conference presentations
* Word of mouth discussions
* Social media

The research team will ask the network or organisation to advertise the study to their organisation or networks, e.g., by posting a study advertisement (Appendix O), or sharing information about the study, e.g., a link to the BDI website (Appendix P & Q) or a video the research team will develop based on the content of Appendix O and the recruitment materials (see below).

Support to assist with recruitment will be assumed by the organisation’s agreement to post or disseminate recruitment materials. An organisation or network will not know whether a person agrees to participate or not as the recruitment materials (see Appendices O-Q) will direct potential participants to the online consent, which includes the participant information statements and consent forms (see Appendices R-U).

**Reminders**

During screening and the three data collection time-points, in the absence of a response to the initial contact, reminder/follow-up contact with potential participants will be undertaken via:

* One initial reminder and two follow up reminders to complete the questionnaires will be sent to the parent via email and SMS before being considered lost to follow up. Each reminder will include instructions for participants to withdraw their consent to participate in future rounds of surveys or from further contact.

During attempts to call participants to provide instructions for completing the KSADS-COMP (Step 3 in Section 8 “Methodology” subsection “8.4 Procedure”):

* Researchers will speak with participants via phone call a maximum of 3 times to provide instructions for the KSADS-COMP and/or to schedule in a time for the participant to complete the KSADS-COMP. If the participant is not responding after 3 weeks, a final email will be sent to the participant before being considered lost to follow up.

During completion of the KSADS-COMP:

* If participant has not completed the KSADS-COMP within the same day as scheduled, researchers will contact them by phone the day after their scheduled date. Participants will be contacted by phone a maximum of 3 times by researchers during this period. Researchers will send a final follow-up email to participants after 1 week from their scheduled date.
* If participants have not completed the KSADS-COMP within 2 weeks as scheduled, participant will be considered lost to follow up.

During attempts to call participants to provide instructions for on next steps following completion of KSADS-COMP (Step 7 in Section 8 “Methodology” subsection “8.4 Procedure”):

* Researchers will speak with participants via phone call a maximum of 3 times to provide next steps. This phone call is to help participants understand the next stage of the research study, but is not a mandatory process. Thus, if the participant is not responding after 1 week, we will email them the study questionnaire link, together with a written version of the Next Steps Phone Script (Appendix N) and proceed with the study as usual.

During intervention:

* Participants will receive weekly email and SMS notifications on Mondays for when new modules can be accessed. The email notification will also remind them to log in (if they haven’t the last week), complete any previous Modules, and will contain information about their scheduled practices.
* Participants will also receive weekly email and SMS notifications on Thursdays to remind participants to start modules (if they haven’t already), add their goals/worries/activities, and practise their scheduled activities.

During scheduling/completion of 3 x therapist support sessions:

* Researchers will speak with participants via phone call a maximum of 3 times to schedule in the support session.
* If participant is uncontactable during the time of the scheduled interview, researchers will contact participant through 1 email and 1 SMS.
* These support sessions are to provide additional support to parents if needed, but they are not a mandatory process. Thus, if participant does not complete the therapist support session, they can still continue the trial and will therefore **NOT** be withdrawn. If participant does not complete the therapist support session, they can still continue the trial and will therefore **NOT** be withdrawn.

During scheduling/completion of semi-structured telephone interview:

* Researchers will speak with participants via phone call a maximum of 3 times to schedule in the telephone interview. If the participant is not responding after 3 weeks, a final email will be sent to the participant before being considered lost to follow up.
* If participant is uncontactable during the time of the scheduled interview, researchers will contact participant through 1 email and 1 SMS before being considered lost to follow-up.

## **Consent**

Online Consent

Interested participants can access the study through the study landing page (Appendices P & Q). Parents will be provided with the parent PISCF (Appendices R & T) at the start of the data collection instrument on Qualtrics and will be required to read through it and select if they agree and consent to participate. Following parent consent, parents will be asked to pass their device to their child. The child will then be provided with the child PISCF (Appendices S & U) and will be required to read through it and select if they consent to participate. Both parent and child need to consent to be able to participate in this study. Participants are informed in the PISCF that participation in the research study is entirely voluntary and if they do not wish to take part, they do not have to.

Following parent and child consent, parents will complete the screening and demographic questions (Appendix E) and online questionnaires (Appendices F-I).

Screening

Interested participants will answer the screening questions (Appendix E). If they do not meet the eligibility criteria, they will automatically be directed to a thank you page stating they are not eligible to participate. This page will also include details to contact the research team if they have any questions, as well as resources for additional support (e.g., Kids Helpline, Lifeline, Crisis support information).

Ongoing Consent

As stated in Section 10.3, parents will be emailed a reminder to complete the study questionnaires. The email will also include instructions for parents (and children) to withdraw their consent from the study. Participants can withdraw from the study at any time.

Interview Consent

Confirmation of consent will occur prior to the semi-structured interview at the start of the telephone call (Appendix K). Consent to be recorded will also occur at the state of the telephone call.

Therapist Support Consent

Consent to be video and audio recorded will occur at the start of each therapist support session (Appendices B & D).

Withdrawal of Consent

Parents and children will be able to withdraw their consent from the study at any point by completing the withdrawal of consent form (Appendices R-U). This form will be hosted on Qualtrics. The link to this form will be included in all emails to participants. Participants are informed in the PISCF that their decision to not participate or withdraw their consent will not affect their relationship with UNSW Sydney or the Black Dog Institute.

## **Reimbursement**

Study 1: Pilot case series of the Courage Quest intervention

All participants will receive exposure-focused therapy – an evidence-based strategy to reduce anxiety. However, we cannot guarantee that children will show a reduction in anxiety following their participation in this study. Nonetheless, parents and children will receive resources and clinician guidance to support their child’s anxiety. Parents will also receive a feedback report with information about their child’s mental health after the KSADS-COMP (Appendix M). In terms of reimbursement, children and their parents who have completed the intervention, both assessments, and the qualitative interview will receive an online $100 gift card to spend at a store of their choosing at the completion of the study.

Study 2: RCT to evaluate the Courage Quest intervention

All participants will receive evidence-based strategies to support their child’s anxiety. However, we cannot guarantee that children will show improvements in their mental health following their participation in this study. Nonetheless, parents and children will receive resources to support their child’s anxiety. Parents will also receive a feedback report with information about their child’s mental health after the KSADS-COMP (Appendix M). Participants who will receive $30 for completing the first assessment, $50 for the second, and $70 for completing both the 10-week program (either the Courage Quest intervention or the Raising Healthy Minds intervention (control condition)) and the third assessment, totalling to $150 for the entire study. These will be paid via online gift cards within 30 days of the participant completing their assessments.

#  **Treatment of Subjects**

Please refer to section 8 “Methodology” for more information on the treatment of subjects and group differences.

## **Investigational Medical Product and Trial Intervention**

Please refer to section 8 “Methodology” subsection “8.2 Description of the Interventions” for more information on the Investigational Medical Product and Trial Intervention.

## **Storage, dispensing and product accountability.**

* Courage Quest intervention (intervention condition): The website hosting the Courage Quest intervention will be developed by Palo IT and maintained by IT and Development teams at BDI. All accountability and management of the Courage Quest intervention will be managed by the research team. Data from the app will be stored using the Amazon Relational Database Service (RDS) and Amazon DynamoDB. This information is stored in Amazon’s secured Amazon Web Services (AWS) servers in Australia. Amazon is the world’s leading cloud IT infrastructure provider providing high-performing, robust and secure infrastructure maintaining several compliance certifications, including ISO 27001, SOC1, SOC2, SOC3, PCI DSS, IRAP, ISO 9001, CSA, ICO 27017 and ISO 27018.
* Raising Healthy Minds intervention (control condition):Data collected from the Raising Healthy Minds intervention is stored in the Raising Healthy Minds database (AWS Sydney data centre), which the app developers are dedicated to keeping personal information safe. The data storage software used is password protected and encrypted, and the data will be stored using a secure network where it can only be viewed by Raising Healthy Minds team members. The app has firewalls to protect against intruders, and redundancies throughout the network and testing for and protecting against network vulnerabilities. Only Dr Gina-Maree Sartore, Senior Researcher at Parenting Research Centre and data manager for the Raising Healthy Minds intervention, will have access to our participants’ identifiable data entered into the Raising Healthy Minds intervention. This is solely for the purpose of ensuring that Dr Sartore can distinguish our participants’ data from other users of the Raising Healthy Minds intervention. Dr Sartore will provide usage data from our participants in an email as a password protected and encrypted ZIP file. Following receipt of this data, the research team will store this data as per the “Data Storage” point below. The Raising Children Network (the creators/owners of the Raising Healthy Minds intervention) list that information may be used for the purposes of “conducting approved research” (link: https://raisingchildren.net.au/legal/privacy).
* Data Collection: Questionnaire data will be stored online via Qualtrics
* Data Storage: Participant data collected through Qualtrics, Zoom, the Courage Quest intervention, and the Raising Healthy Minds intervention will be encrypted and stored within UNSW. This research will be stored electronically on a UNSW password protected OneDrive only accessible to the approved research investigators. Only the research team listed on this application will have access to the data and will login using multi-factor authentication. Participant data will be deidentified by the PI, with the identifiable data and unique code stored in a password protected xls file saved on UNSW Shared Drive. Investigators and research personnel listed on this application will have access to this data. This data also includes data from participants who provide opt-in consent for their name and contact details to be retained in a register so they can be contacted about future research projects (see consent forms in Appendices R and T). The data custodian for this data will be Prof Jennie Hudson. All data will be stored on UNSW secure servers for 15 years after study completion, or until the participants reach 25 years of age (as per the retention period for clinical trials involving children). Following publication, all de-identified individual participant data (IPD) will be shared through a secure global databank of child anxiety intervention data (HREC no. HC220857). This global databank will be accessible to researchers wishing to access the global databank for conducting individual patient meta data analyses with aims of improving child anxiety treatment. Access to the global databank will be through the secure cloud infrastructure ERICA, which has a UNSW instance, and access will be subject to approval by the data custodian of the databank.
* The Trial Management groupwill meet weekly to fortnightly to trouble shoot any issues or concerns that arise relating to the trial. This group includes the researchers listed on this application. Notes and documents arising from this meeting will be stored securely on UNSW One Drive. Only the research team listed on this application will have access to the data.
* Ethical considerations for confidentiality: If any data indicates that participants pose an imminent danger to themselves or others, those participants’ details will be shared with a clinician (Dr Francis, Dr Sicouri, Dr Aji, Dr Chen, or Prof Hudson). Clinicians are mandated to break confidentiality if the child poses an imminent danger to themselves or others. The limits of confidentiality are stated in the parent consent forms and will be explained to parents during the therapist support sessions and qualitative interviews.

## **Randomisation and Allocation**

Please refer to section 8 “Methodology” subsection “8.4 Procedure” sub-subsection “Outcome Assessments and Intervention” for more information on the randomisation and allocation of participants.

# **Safety and Monitoring**

## **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.

1. Known Adverse Effects
* There is a likely risk that children (and their parents) using the Courage Quest intervention in Studies 1 and 2 will experience anxiety and distress when undergoing the graded exposure, as this involves having children face their fears. This risk will however be minimised through the adoption of a graded exposure technique whereby children will face less intimidating fears first, before gradually building up to more strongly feared situations over time. The experience of anxiety and some distress is anticipated and inherently critical to the success of exposure-focused interventions as this allows patients to create new memories and reduce their levels of distress associated with the feared situation (i.e., the situation was not as bad as they had anticipated, or their levels of anxiety reduced with exposure).
1. Known Harms, Risks or Discomforts
* In addition to the KSADS-COMP measuring anxiety levels, the questionnaire will also be used to screen for other primary diagnoses such as ADHD, oppositional defiant disorder, conduct disorder, or depression. Therefore, there is a risk that participants may self-report symptom levels that indicate a diagnosis that the participant is unaware of. While the parent will not view the results of the KSADS-COMP, the researchers will notify parents that their answers to the questionnaire indicate their child may have some difficulties in those areas. Note that we will clarify that this does not comprise a formal diagnosis, but an indication that their child may require additional support. For participants whose children have depression, ADHD, oppositional defiant disorder, or conduct disorder as secondary diagnoses (and are therefore still included in the study), we will communicate to them that we will provide recommendations for additional support at the end of the trial. This is to ensure that additional therapy effects do not interact with the effects from the study. Please see Appendix M for a template of the latter we will send to parents in these cases.
* There is a small risk that parents and/or children may feel a mild level of distress when completing the study questionnaires.
* For parents who self-report suicidal ideation in the child during the screening questions, there is a risk that they will experience distress when they are informed that are ineligible to participate (see Appendix E).To mitigate any harm, resources and support services will be listed on screen for participants indicating suicidal ideation. Additionally, a clinician (Dr Francis, Dr Sicouri, Dr Aji, Dr Chen, or Prof Hudson) will complete a risk assessment follow-up with parents who report suicidal ideation in their child. This follow-up will occur via telephone within 72 hours of the self-report.

To minimise the risk of these discomforts/harms, the researchers will adopt the following processes:

* Communication with participants via email will include a reminder that participants can stop or withdraw from the study at any time. In all emails, we will include reminders for participants to contact the research team if they have any concerns over their child’s mental health while using either the Courage Quest or the Raising Healthy Minds interventions. We will also list the contact details for crisis support, with a note for parents/children to contact these services if they need. Hudson, Francis, Aji, Chen, and Sicouri are trained mental health professionals and can respond accordingly to triggers.
* The PISCF (Appendices R-U) will include information on crisis management services, for families in need of crisis support. These services include NSW Health Mental Health Line (1800 011 511), Beyond Blue (1300 22 4636), Lifeline (13 11 14), the Kids Helpline (1800 55 1800).
* The Courage Quest intervention will contain detailed information to parents on how to facilitate the graded exposure. This will include what to expect (to prepare parents for their child being distressed), and how to best support them through this distress (including resources for additional support). The therapist/research team can be contacted throughout the research study, and there will also be 3 x therapist support sessions to problem solve concerns (Appendices B & D).

## **Adverse Events**

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to the investigational medical device.

AEs 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 24 hours. All adverse event reports must be recorded in the [UNSW Safety Monitoring Register Template](https://research.unsw.edu.au/document/UNSW%20Safety%20Monitoring%20Register%20Template.xlsx).

We will report any of the following adverse events following the HREC reporting procedure:

* For children using the Courage Quest intervention, we will monitor their feelings rating before and after completing their graded exposure practice. If there is a 4-point increase in worry rating before and after the graded exposure practice on 2 consecutive practices, then this will automatically trigger an alert to the research team. The research team will follow up with the parent to provide support around delivering the graded exposure and helping the parent and child to try out the modified graded exposure activity. If there is a trigger warning on a second occasion, the process above will be followed again. If the participant chooses to withdraw their child from the study, the research team will provide them with information for support. Details of the risk assessment follow-up will be recorded in a register (see Appendix V). In Study 2, any additional support provided will be recorded to note any differences between the control and intervention groups.
* For children using the Courage Quest intervention, we will monitor their free-text responses when adding their worries, goals, activities, and feelings after their graded exposure activities. We will screen for words that indicate a child may be at risk, e.g., "depressed", "depression", "kill", "suicide", "suicidal", "cut", and "harm". If any of these words are entered, this will automatically trigger an alert to the research team. The research team will examine the free-text responses entered, and if necessary a clinician (Dr Francis, Dr Sicouri, Dr Aji, Dr Chen, or Prof Hudson) will complete a risk assessment follow-up via telephone within 72 hours of the free-text being entered. Details of the risk assessment follow-up will be recorded in a register (see Appendix V).
* For children in both intervention and control conditions, 3 therapist support sessions will be conducted with their parents. In the second support session, a brief risk safety check will be conducted by the therapist (see Appendices B and D). If any information is disclosed during these sessions that indicates a child may be at risk, this will be followed by a risk assessment conducted by the therapist. Details of the risk assessment follow-up will be recorded in a register (see Appendix V).
* Withdrawal due to severe distress (parent or child) and the need for crisis management support. A clinician (Dr Francis, Dr Sicouri, Dr Aji, Dr Chen, or Prof Hudson) will complete a risk assessment follow-up with parents who wish to withdraw due to severe distress and the need for crisis management support. Details of the risk assessment follow-up will be recorded in a register (see Appendix V). This follow-up will occur via telephone within 1 week of the self-report.
* Any protocol deviations or violations will also be reported to the HREC. Safety event reports, including adverse and serious adverse events will be reported by Francis, Lim, Songco, or Hudson. Significant safety issues and urgent safety measures will be reported to the UNSW Sponsors Delegate (humanethics@unsw.edu.au) immediately but no later than seven days. The Trial Management Group (comprised of all investigators) will meet regularly to discuss any potential safety issues or concerns relating to adverse events. Research Assistant McDermott, and Project Manager Allsop will immediately notify Francis, Lim, Songco, and Hudson if there are any indications of protocol deviations, violations, safety issues or adverse events that may arise. Single case reports of Adverse Events and Serious Adverse Events will not be reported to the UNSW Sponsors delegate, though all case reports will be recorded in the Safety Monitoring Register, assessed as per trial safety standards, and be reported to the UNSW Sponsor’s Delegate at the conclusion of the study.
* The research team’s process to assess whether the event was related to the clinical trial, its procedures, or the interventions, is as follows: Any investigator who receives information sufficient for an adverse event or safety issue regarding a participant is required to report this to Francis, Lim, Songco, and Hudson, where this will be recorded in the Safety Monitoring Register.

The benefits of this research outweigh these potential risks of discomfort/harm given the strong evidence-base for cognitive behavioural therapy interventions to reduce anxiety for children.

## **Adverse Device Effect**

An adverse device effect (ADE) is related to the use of an investigational medical device. Including adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

ADE 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.

ADE must be reported to the Coordinating Principal Investigator immediately, within 24 hours. All adverse event reports must be recorded in the [UNSW Safety Monitoring Register Template](https://research.unsw.edu.au/document/UNSW%20Safety%20Monitoring%20Register%20Template.xlsx).

## **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 investigational medical product, the trial intervention, or procedures:

* 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. SAE reports are reported to the Coordinating Principal Investigator within 48 hours of the event occurring. SAR reports must be recorded in the [UNSW Safety Monitoring Register Template](https://research.unsw.edu.au/document/UNSW%20Safety%20Monitoring%20Register%20Template.xlsx).

## **Serious Adverse Device Effects**

A Serious Adverse Device Effect (SADE) is an SAE that is related to the investigational medical product, the trial intervention, or procedures. 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.

#### **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 investigational medical product or intervention safety information are classified as a SAR report. SAR reports are reported to the Coordinating Principal Investigator within as soon as possible but no later than 7 days for multicentre clinical trials. Serious Adverse Reaction reports must be recorded in the [UNSW Safety Monitoring Register Template](https://research.unsw.edu.au/document/UNSW%20Safety%20Monitoring%20Register%20Template.xlsx).

#### **Suspected Unexpected Serious Adverse Reaction (SUSAR)**

A serious adverse reaction by its nature, incidence, severity, or outcome is unanticipated and not identified in the investigational medical product, the trial intervention, or procedures for use safety information are classified as a SUSAR.

Fatal or life-threatening Australian SUSAR reports are reported to the Therapeutic Goods Administration, the Coordinating Principal Investigator, and the sponsor’s delegate 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 Therapeutic Goods Administration, the Coordinating Principal Investigator, and the sponsor’s delegate 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](https://research.unsw.edu.au/document/UNSW%20Safety%20Monitoring%20Register%20Template.xlsx).

## **Significant Safety Issue (SSI**)

A safety issue that could adversely affect participants’ safety or materially impact the continued ethical acceptability or conduct of the trial. The Therapeutic Goods Administration, 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](https://research.unsw.edu.au/document/UNSW%20Safety%20Monitoring%20Register%20Template.xlsx).

## **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 Therapeutic Goods Administration, 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](https://research.unsw.edu.au/document/UNSW%20Safety%20Monitoring%20Register%20Template.xlsx).

## **Safety** **Assessment Flow Chart Investigational Medical Device Trials**



## **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.

## **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.

##

#### **Emerging Safety Issues**

The Trial Management Group, Trial Safety Committee or the Data Safety Monitoring Board 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, Trial Safety Committee or the Data Safety Monitoring Board must seek the advice of the human research ethics committee and sponsor’s delegate.

#### **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, Trial Safety Committee or the Data Safety Monitoring Board (e.g., meeting minutes) confirming that regular reviews of safety 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.

# **Non-compliance, Protocol Deviation and Serious Breaches of Good Clinical Practice**

## **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 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.

## **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 has the potential to) result in participant harms.

## **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.

## **Reporting of a Serious Breach**

* A serious breach occurring at a participating site must be reported by the site Principal Investigator 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.

## **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.

# **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, to establish whether the proposed CAPA is appropriate and establish whether there is or will be an ongoing impact on the 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](https://www.gs.unsw.edu.au/policy/documents/researchmisconductproc.pdf) to establish whether a breach of the [UNSW Research Code of Conduct](https://www.gs.unsw.edu.au/policy/documents/researchcode.pdf) 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](https://www.nhmrc.gov.au/about-us/publications/australian-code-responsible-conduct-research-2018) has occurred.

# **Statistics**

Please refer to section 8 “Methodology” subsection “8.5 Data Analysis Plan” for more information on the statistical analyses used in analysing data.

# **Data Handling, Ownership and Access**

All research data collected during this trial is governed and handled following the Research Data Governance and Materials Handling [policy](https://www.gs.unsw.edu.au/policy/documents/researchdatagovernancepolicy.pdf). 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.

# **Authorship**

Requirements for authorship include a significant contribution to the study in terms of design, development, and analyses.

# **Recording 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.

Participants will be assigned a participant ID, and data will be reported using Qualtrics. In this trial we are collecting self-report data, reported entirely online on Qualtrics, the KSADS-COMP platform, and through the Courage Quest app.

Data from the app will be stored using the Amazon Relational Database Service (RDS) and Amazon DynamoDB. This information is stored in Amazon’s secured Amazon Web Services (AWS) servers in Australia. Amazon is the world’s leading cloud IT infrastructure provider providing high-performing, robust and secure infrastructure maintaining several compliance certifications, including ISO 27001, SOC1, SOC2, SOC3, PCI DSS, IRAP, ISO 9001, CSA, ICO 27017 and ISO 27018.

Data collected from the Raising Healthy Minds intervention is stored in the Raising Healthy Minds database (AWS Sydney data centre), which the app developers are dedicated to keeping personal information sage. The data storage software used is password protected and encrypted, and the data will be stored using a secure network where it can only be viewed by Raising Healthy Minds team members. The app has firewalls to protect against intruders, and redundancies throughout the network and testing for and protecting against network vulnerabilities. Only Dr Gina-Maree Sartore, Senior Researcher at Parenting Research Centre and data manager for the Raising Healthy Minds intervention, will have access to our participants’ identifiable data entered into the Raising Healthy Minds intervention. This is solely for the purpose of ensuring that Dr Sartore can distinguish our participants’ data from other users of the Raising Healthy Minds intervention. Dr Sartore will provide data from our participants in an email as a password protected and encrypted ZIP file. Following receipt of this data, the research team will store this data as per the “Data Storage” point below. The Raising Children Network (the creators/owners of the Raising Healthy Minds intervention) list that information may be used for the purposes of “conducting approved research” (link: https://raisingchildren.net.au/legal/privacy).

Once all data is collected through the platforms, data will be downloaded and personally identifiable information will be removed from the dataset by the research team. The de-identified data will be stored on the UNSW OneDrive with access restricted to research staff via password protection. OneDrive is appropriate for research data classified from Public to Highly Sensitive. Any change or correction to data 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.

All data will be stored on UNSW secure servers for 15 years after study completion, or until the participants reach 25 years of age (as per the retention period for clinical trials involving children)

In the UNSW OneDrive, the data is encrypted in the cloud; a secure link is required to access and share the data. Only members of the UNSW and Black Dog Institute research team listed on this protocol will have access to the data.

18.1 Confidentiality

Information collected in the trial must be handled following the requirements of the Privacy and Personal Information Protection Act 1998 (NSW). Trial subjects have right of access to personal information held about them by the UNSW and can request correction and amendment of it. The UNSW requirements to ensure that personal information is protected is available in the [UNSW Privacy Management Plan](https://www.legal.unsw.edu.au/compliance/privacyhome.html).

18.2 Direct Access to Source Data and Documents

Site principal investigator(s) and institution(s) will permit trial-related monitoring, audits, HREC review, and regulatory inspection(s), providing direct access to source data/documents. The sponsor will not have access to source data however, site(s) and institutions will allow the sponsors monitor or auditor access to source documentation for auditing purposes.

# **Trial Management Group, Data Safety Monitoring Board, Independent Safety Committee**

The Trial Management group will meet weekly to fortnightly to trouble shoot any issues or concerns that arise relating to the trial. Notes and documents arising from these meetings will be stored securely on UNSW OneDrive.

The Data Safety Monitoring Board will meet halfway through the trials to review the data, with additional meetings as required. Outcomes from analyses and any meeting minutes will be stored securely on UNSW OneDrive.

**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.

# **Good Clinical Practice Requirements**

Coordinating Principal Investigators, Principal Investigators and all site personnel or trial-related staff have current Good Clinical Practice Training. Evidence of training confirmation is 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)](https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf)

# **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)](https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf)   are retained by all trial investigators.

## **Qualifications and Curriculum Vitae**

Copies of CVs for all principal investigators will be stored as an essential document. The [TransCelerate CV template](https://research.unsw.edu.au/document/TransCelerate%20CV%20template.pdf) can be used as a template.

# **Clinical Trial Delegation and Responsibilities Log**

| **Protocol / Study Number:** | HC230097 | **Sponsor Name:** | UNSW |
| --- | --- | --- | --- |
| **Principal Investigator Name:** | Prof Jennie Hudson | **Site Number:** | N/A |
| **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)** |
| Prof Jennie Hudson |  | JH | 20/02/2023 |  |
|  |  |  |  |  |

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)** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Dr Deanna Francis |  | DF | Trial management | 1, 2, 3, 14, 18, 21 | 20/02/2023 |  | JH 20/02/2023 |
| Mrs Abigail Allsop | A picture containing whip, earphone  Description automatically generated | AA | General Project Assistance | 1, 2, 3, 21 | 20/02/2023 |  | JH 20/02/2023 |
| Dr Chloe Lim |  | CL | Trial management and General Project Assistance | 1, 2, 3, 14, 18, 21 | 20/02/2023 |  | JH 20/02/2023 |
| Ms Emma McDermott | A picture containing text  Description automatically generated | EM | General Project Assistance | 1, 2, 3, 21 | 20/02/2023 |  | JH 20/02/2023 |
| Dr Gemma Sicouri |  | GS | General Project Assistance | 1, 2, 3 | 20/02/2023 |  | JH 20/02/2023 |
| Dr Annabel Songco |  | AS | General Project Assistance | 1, 2, 3 | 20/02/2023 |  | JH 20/02/2023 |
| Dr Melissa Aji |  | MA | General Project Assistance | 7, 8 | 12/04/2023 |  | JH 12/04/2023 |
| Mr Debopriyo Bal |  | DB | Data management | 21 | 12/04/2023 |  | JH 12/04/2023 |
| Mr Cesar Anonuevo |  | CA | IT infrastructure management | 22 | 13/04/2023 |  | JH 13/04/2023 |
| Dr Wendy Chen |  | WC | General Project Assistance | 7, 8 | 01/05/2023 |  | JH 01/05/2023 |
| Ms Paige Todd |  | PT | General Project Assistance | 1, 2, 3, 21 | 23/08/2023 |  | JH 23/08/2023 |

|  |
| --- |
| **Comments:**  |
|  |

|  |
| --- |
| **Electronic Signature Declaration for Principal Investigator and Site Staff**1. 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.
2. 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:**  20/02/2023 |

**Task Key:**

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

\*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.

# **Safety Monitoring Register Template**

* [UNSW Safety Monitoring Register Template](https://research.unsw.edu.au/document/UNSW%20Safety%20Monitoring%20Register%20Template.xlsx)
* [UNSW Adverse Event or Incident Event Case Report Form Example](https://research.unsw.edu.au/document/Adverse%20Event%20Incident%20Report%20Form%20September%202019%20.docx)

# **Corrective and Preventive Action Form**

|  |  |  |  |
| --- | --- | --- | --- |
| Raised by:  | Assigned to:  | Date:  | Remarks:  |
| Description:  |
| Proposed immediate action (correction):  |
| Completed by:  | Date:  | Remarks:  |
| Root cause analysis required: Yes [ ]  No [ ]   |
| Underlying / root cause:  |
| Determined by:  | Date:  | Remarks:  |
| Proposed action for long term solution (corrective/preventive action):  |
| Completed by:  | Date:  | Remarks:  |
| Comments on effectiveness of action taken:       |
| Closed out by:  | Date:  | Remarks:  |