

12 January 2026

To whom it may concern,

This note aims to clarify why the ADHERE Trial was prospectively registered on the Open Science Framework (OSF), despite already being listed on ClinicalTrials.gov (NCT07205991).

Our project was first submitted on 25 September 2025 and published on 2 October 2025, with a single comment requesting an update to the anticipated start date. Our planned start (29 September 2025) became outdated during the review process. However, on 1 October 2025—one day before publication—the United States government entered a shutdown, which made it impossible to correct this minor issue, as ClinicalTrials.gov went offline.

Image 1 - Screenshot of the ADHERE record showing that we are unable to release the trial for evaluation



To ensure transparency and avoid further delays, we have created a secondary pre-registration on OSF (<https://osf.io/57kjc>), and recruitment started on 30 October 2025.

Sincerely,



Filipe Luis Souza,
on behalf of the author team

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STATISTICAL ANALYSIS PLAN

Version 0.10 – Date: 25 September 2025

Assisting Digital HEalth REtention (ADHERE Trial): protocol for a study within a trial (SWAT)

Authors: Filipe Luis Souza, Isha Mishra, Rodrigo Rossi Nogueira Rizzo, James McAuley

SUMMARY

1. ADMINISTRATIVE INFORMATION	4
2. ABSTRACT.....	5
3. BACKGROUND	6
4. OBJECTIVE	7
5. HYPOTHESES	7
6. METHODS	8
6.1 Trial design.....	8
6.2 Participants	8
6.3 Settings.....	8
6.4 Recruitment.....	8
6.5 Interventions	9
6.6 Outcomes	10
6.7 Moderation analysis	10
6.8 Sample Size	11
6.9 Randomisation and Allocation procedure.....	11
6.10 Implementation	12
6.12 Patient withdrawal	12
6.13 Blinding.....	12
6.14 Statistical Analysis.....	12
7. ETHICS	14
7.1 Informed consent	14
7.2 Confidentiality	14
7.3 Autonomy	14
7.4 Beneficence.....	14
7.5 Non-maleficence.....	14
7.6 Justice	15
7.7 Data Consistency.....	15
7.8 Quality Control and Assurance	15
7.9 Trial Sponsorship and Financing.....	15
7.10 Indemnity	15
8. APPENDIX	17

8.1. CRediT (Contribution Roles Taxonomy)	17
8.2. Sample Size Calculation Code (R Version 4.5.1).....	18
9. REFERENCES.....	20

1. ADMINISTRATIVE INFORMATION

Trial registration: This trial will be prospectively registered on ClinicalTrials.gov.

Version: 0.10 (September 25, 2025)

Funding: 2021 Primary Health Care Digital Innovations - Medical Research Future Funding (MRFF) project grant (ID# 2023373 - 2023).

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Supervision: R.R.N.R. and J.M.

Visualisation: F.L.S., R.R.N.R. and J.M.

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ADHERE SWAT Protocol

Version 0.10 – Date: 25 September 2025

2. ABSTRACT

Background: Digital health interventions are increasingly recognised as promising tools to expand access to care and reduce healthcare costs, particularly for individuals with chronic conditions. While randomised controlled trials (RCTs) remain the gold standard for evaluating such interventions, few studies have investigated adherence to digital psychosocial treatments for chronic pain—despite adherence being a key determinant of both clinical and economic outcomes. A key challenge in digital health trials is low adherence, especially in behavioural interventions, where participant engagement is central to treatment effectiveness. Dropout rates tend to be higher in interventions delivered digitally among individuals with chronic conditions. This compromises statistical power and threatens the internal validity of RCTs, with dropout rates ranging from 19% to 45%. Strategies such as phone calls may improve adherence; however, the evidence remains limited. To address these gaps, we embedded a Study Within a Trial (SWAT) into a host RCT to evaluate whether proactive phone calls or text messages can improve adherence to a digital psychosocial intervention for chronic pain. **Methods:** This SWAT will be embedded into an ongoing host RCT evaluating an 8-week app-based clinical hypnosis intervention for adults with chronic low back pain. Participants allocated to the intervention arm of the host trial will be randomly assigned (1:1:1 ratio via REDCap) to receive either standard app notifications alone (control), notification plus up to two text messages or notifications plus up to two telephone calls from the study investigators. Each contact via phone or text will be spaced at least one week apart. The primary outcome is the mean number of completed sessions during the 8-week intervention period. Secondary outcomes include the proportion of completers, responder rates, and dropout rates in the host trial. Outcome assessors and statisticians will remain blinded to SWAT allocation. **Results:** Analyses will compare the mean number of completed sessions between groups, with 95% confidence intervals and standard deviation. Secondary outcomes will be analysed descriptively and inferentially. **Conclusion:** Findings from this SWAT will provide empirical evidence to inform the design of future RCTs delivered digitally for various chronic conditions, particularly regarding the use of telephone support to improve adherence. Although no cost-effectiveness analysis will be conducted, the results can help researchers weigh the operational costs of implementing phone-based support against the expected benefits in adherence when planning future trials.

Keywords: SWAT; Study Within A Trial; Adherence methods; Embedded Randomised Controlled Trial

3. BACKGROUND

Digital health interventions are increasingly recognised as promising tools for improving access to care and reducing healthcare costs, particularly for patients with chronic conditions (Steinhubl et al., 2013). To evaluate the effectiveness of such interventions, randomised controlled trials (RCTs) are considered the gold standard (Hariton & Locascio, 2018). However, for people living with chronic pain, there is a lack of high-quality RCTs assessing the effects of digital psychosocial interventions, either on pain reduction or healthcare cost mitigation (Rosser et al., 2023). Despite known challenges, digital tools continue to show promise in advancing healthcare across multiple domains.

A persistent issue in RCTs investigating digital health interventions is low adherence. This problem is exacerbated in non-pharmacological or behavioural interventions, where individual behaviour change is a critical mechanism for treatment effect. These trials tend to show higher dropout rates (Middleton et al., 2013; Vancampfort et al., 2024), which increase further when interventions are delivered digitally (Hasnan et al., 2022; Forbes et al., 2023; Giebel et al., 2023), and particularly among patients with chronic conditions (Macea et al., 2010; Moshe et al., 2022; Kidman et al., 2024). Still, the scalability and convenience of digital delivery have encouraged growing interest from both patients and researchers.

The internal validity of RCTs is frequently questioned when attrition exceeds 15%, as emphasised by critical appraisal tools (Maher et al., 2003; Cashin & McAuley, 2020). High dropout rates can compromise statistical power, introduce bias, and lead to the inefficient use of research resources. Notably, dropout rates in digital trials range from 19% to 45% (Enock et al., 2014; Ivanova et al., 2016; Pham et al., 2016), underscoring the need for strategies to boost adherence.

Multiple factors contribute to low adherence in digital trials, including limited motivation, low digital literacy, psychological distress, perceived low benefit, and lack of human support (van Gaalen et al., 2022; Moshe et al., 2022). To counteract these, interventions like text messaging and phone calls have been tested. Meta-analyses suggest that text messaging improves adherence to antiretroviral therapy (Finitis et al., 2014) and cardiovascular medication regimens (Park et al., 2014). Similarly, phone calls have been shown to support patients with mental health conditions (Aku et al., 2024), enhance medication adherence among cancer patients (Akerley, 2021), and increase engagement with digital treatments (Gardner et al., 2022).

Nevertheless, high-quality evidence on the comparative effectiveness of these strategies in digital psychosocial trials remains limited, particularly in chronic pain populations. To address this limitation, this paper will embed a Study Within a Trial (SWAT; Treweek et al., 2018) in a larger RCT, aiming to test whether proactive phone calls, compared to no additional support, can enhance adherence to a digital intervention for chronic pain.

This SWAT evaluates the hypothesis that phone calls will lead to higher treatment adherence compared to app notifications alone. These findings may inform future digital health trial designs and guide the development of strategies to optimise participant engagement in behavioural research.

4. OBJECTIVE

Research question

Do phone calls or text messages increase adherence compared to app notifications in patients receiving a digital health intervention for chronic back pain?

5. HYPOTHESES

- a) We hypothesise that the phone calls, compared to standard app notifications alone, will result in greater adherence in the mobile app at the 8-week time point after randomisation.
- b) We hypothesise that the text messages, compared to standard app notifications alone, will result in greater adherence in the mobile app at the 8-week time point after randomisation.
- c) We hypothesise that the phone calls, compared to text message notifications alone, will result in greater adherence to the mobile app at the 8-week time point after randomisation.

6. METHODS

The study will be reported in accordance with the Guideline for Reporting the Results of Randomised Studies Within a Trial (SWATs; Arundel et al., 2024) and the Consolidated Standards of Reporting Trials (CONSORT 2025; Hopewell et al., 2025).

6.1 Trial design

This protocol will be prospectively registered as a randomised controlled trial (RCT) within a trial (SWAT) (Treweek et al., 2018), characterised as a type of clinical research in which participants are randomised into a group after having been previously randomised into an intervention group in a host trial (NOTUS trial). The study will randomly allocate participants from the intervention group of the NOTUS Trial into one of three parallel arms in a 1:1:1 ratio.

6.2 Participants

Participants in this SWAT will be individuals who meet the eligibility criteria of the host trial and were allocated to the mobile app intervention. Eligible participants are adults (≥ 18 years old) residing in Australia who consult a general practitioner for chronic low back pain (LBP). LBP is defined as pain persisting for at least 12 weeks in the region between the 12th rib and the buttock crease. Participants must report a mean pain intensity of $\geq 3/10$ on the Numeric Rating Scale (NRS) in the past week and at least a moderate level of pain interference with normal activities based on question 8 on the SF-36 physical functioning component. Additional inclusion criteria include the ability to understand English (both written and audio materials), access to a mobile device with at least 300MB available for app download, and a stable internet connection.

6.3 Settings

Participants from the host trial intervention group will receive pain education and clinical hypnosis via a mobile app for managing chronic LBP. Only outpatients will be recruited for the study. The trial will be coordinated from Neuroscience Research Australia (NeuRA; Sydney, AU). The data of interest (i.e., sessions completed) for this SWAT will be monitored in real time by our research team via the app platform (Mindset Health - app infrastructure provider; Victoria, AU).

6.4 Recruitment

Participants with chronic LBP will be recruited from general practices using the BetterConsult pre-consultation tool in Australia. This digital platform collects patients' demographic and clinical details and summarises this information for GPs during consultations. The tool includes a question assessing the patient's interest in receiving an SMS after the consultation, containing information about a clinical trial that evaluates the effectiveness of digital health interventions. Individuals who express interest in participating will receive, via SMS, details of the study and the Participant Information Statement Form (PISF). After 24 hours, participants will be invited to complete an eligibility screening. Eligible participants who complete the required questionnaires will provide electronic

consent, complete baseline assessments, and then be contacted by an investigator for randomisation and allocation. The investigator will guide participants on how to access and initiate the digital intervention.

Participants who are randomised to the NOTUS mobile app will be randomly allocated to one of the SWAT study groups (phone calls, SMS or app notifications) (Figure 1):

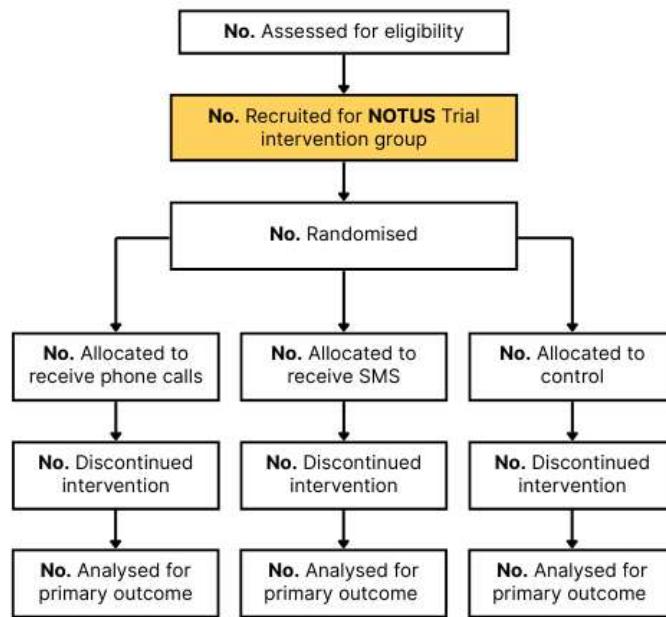


Figure 1 – ADHERE Trial flowchart based on CONSORT2025.

6.5 Interventions

- Control group:** Participants will receive the standard app notifications. Reminders are automatically sent at 8pm each day. A user can change the time of their reminder or turn off reminders in the app. The purpose of the app notifications is to increase motivation to complete the app sessions. An example app notification is: *Your path to pain management is just a session away. Have you listened today?*
- Phone calls:** Participants will receive standard app notifications, and if they do not engage with the intervention for more than three consecutive days, they will be contacted for adherence with up to two phone calls or voice messages, one week apart. The purpose of these calls will be to increase motivation and assess whether participants are experiencing any difficulties using the app or completing the sessions. We expect the calls to last no longer than five minutes. The phone call will include the following communication: *Hi [Name], it's [Researcher] from Neuroscience Research Australia calling about the NOTUS back pain trial. I saw that you've done a few sessions on the NOTUS app - great job! We haven't seen you in the Relio app lately, so I wanted to check in and see if everything is working okay or if you need any help with anything. We look forward to seeing you back on the app as you continue retraining your pain system.*
- Text messages:** Participants will receive the standard app notifications, and if they do not engage with the intervention for more than three consecutive days, they will be contacted for adherence with up to two SMS reminders, one week apart. The purpose

of these SMS will be to increase motivation and assess whether participants are experiencing any difficulties using the app or completing the sessions. The text messages will include the following: *Hey [Name], this is [Researcher] from Neuroscience Research Australia. I saw that you've done a few sessions on the NOTUS app - great job! We haven't seen you in the Relio app lately, so I wanted to check in and see if everything is working okay or if you need any help with anything. We look forward to seeing you back on the app as you continue retraining your pain system.*

6.6 Outcomes

Primary outcome measure

Number of sessions completed: Mean difference of the number of sessions completed over 8 weeks between groups.

This outcome pertains to the number of sessions (new or repeated) that participants completed over the 8-week treatment period. Although participants receive a treatment consisting of 42 different audio scripts, they are informed immediately after randomisation to the mobile app that they may skip sessions or repeat those they find most effective or enjoyable.

Secondary outcome measures

Adherence rate (completer vs. non-completer): Participants will be classified as “completers” if they have attended at least 24 sessions (new or repeated) during the 8-week treatment period of the host trial. This threshold represents an average of three clinical sessions per week over 8 weeks.

Missing follow-up rate: Participants will be classified as “follow-up completer” when they completed all primary, secondary and intermediate measures or as “follow-up missing” when they did not complete all primary, secondary and intermediate measures at the 8-week follow-up.

Withdrawal rate: Participants will be classified as “withdrawal” if they formally withdrew consent, or as “non-withdrawal” if they remained enrolled in the trial at the 8-week follow-up.

Cost-effectiveness: The mean difference in costs and adherence between groups will be used to calculate the incremental cost-effectiveness ratio (ICER), representing the average additional cost (expressed in Australian dollars - AUD) required to achieve one additional completed session. This outcome reflects the economic efficiency of each engagement strategy (SMS or phone call) compared to others.

6.7 Moderation analysis

To explore whether the effect of group allocation on adherence differs across participant characteristics, we will conduct moderation analyses using linear regression models.

The primary outcome will be the number of sessions completed over 8 weeks. The main predictor will be group allocation (e.g., SWAT intervention vs control), and candidate moderators will include age, gender, pain intensity, disability, occupational status, digital literacy, depression, and anxiety (Fuhr et al., 2018; Gutierrez & Sakulbumrungsil, 2021).

Each model will include:

- Main effects of the group and the moderator
- A group \times moderator interaction term

6.8 Sample Size

The objective of the host trial is to recruit a total of 720 patients, providing 90% power, $\alpha = 0.025$ (adjusted for co-primary outcomes), to detect a standardised mean difference (SMD) of 0.3 between the (fixed) groups at the primary endpoint at 8 weeks post-randomisation. Randomised studies within trials commonly do not include a formal statistical power calculation (Liu et al., 2018; Bensaoud et al., 2020; Woodford et al., 2020; Coleman et al., 2021), as their sample size is determined by the number of participants randomised in the host trial. This SWAT will be incorporated into the intervention arm of the NOTUS trial, which is currently ongoing. Eligible participants will be continuously recruited as they are randomised to the mobile app arm. Not all 360 participants originally projected for this intervention will be available for inclusion in this SWAT. Participants will be randomised in a 1:1:1 ratio to receive either phone calls, SMS or app notifications only (control group).

Based on consensus after discussing unpublished pilot data, an average difference of 4 completed sessions between groups was estimated ($SD = 8$). Although this difference was not defined according to a formally established minimal clinically important difference (MCID), due to the absence of a known MCID in the literature, the calculated difference and variability were based on expertise (Schmidt et al., 2018), providing a solution for the lack of prior data in the literature on mobile app interventions for chronic back pain. Thus, a between-group difference of four sessions would represent approximately one fewer week of app use. Using a significance level of 0.05 and a statistical power of 80%, it is estimated that at least 258 participants (86 per arm) would be required to detect this effect (Cohen's $d = 0.5$ or 4 sessions between groups; calculation also available in Appendix, see 8.2 section).

Given that the projected number of participants to be recruited for the intervention arm of the host trial exceeds this value ($N = 258$), the SWAT is adequately powered to detect the hypothesised difference. This effect size ($d = 0.5$) is typically classified as moderate, suggesting that the study is sufficiently powered to detect modest differences in session completion rates between groups. The analysis was performed using R (version 4.5.1; see Appendix 8.2 details).

6.9 Randomisation and Allocation

Participants of the host trial will be randomised automatically using block randomisation (4 to 6 per block) using REDCap. The SWAT randomisation will use "Realtime-randomisation" integrated with REDCap. The investigator or research assistant will click the "randomise" button on REDCap. REDCap will use the hidden Excel spreadsheet to allocate participants to the group code with the pre-built randomisation spreadsheet. At this stage, the investigator or research assistant will know the group participant was randomised. For the adherence of the

intervention, an investigator will access the REDCap randomisation page and contact participants via telephone or SMS.

6.10 Procedure

In the host trial, participants will be recruited via an automated referral process through HealthShare (Sydney, NSW). This external partner organisation sends patients an SMS with the trial advertisement after their GP consultation. Participants will access the Participant Information Statement Form (PISF), complete the screening and consent forms and baseline questionnaires before randomisation. Participants can be randomised into one of two groups (factsheet or mobile app) via the REDCap. Participants allocated to the mobile app intervention will be automatically randomised to one of the three interventions of the SWAT trial via REDCap in a 1:1:1 ratio.

6.12 Patient withdrawal

Participants have the right to withdraw from the host trial at any time. Participants wishing to withdraw will be sent an online withdrawal form in REDCap. If participants in the host trial refuse to complete the withdrawal form, research assistants will withdraw participants as soon as the intention to withdraw is expressed. The SWAT will not be affected by the number of patients who drop out, since this data (number of dropouts) is one of the study outcomes.

6.13 Blinding

General practitioners and statisticians will be blind to group allocation. Blinding will be maintained for the entire duration of the trial until all data have been collected, and data analysis and interpretation have been completed. The personnel involved in the daily operations of the trial (e.g., research assistants and investigators who will provide possible technical support to participants and trial managers) will be unblinded to group allocation and will not be involved in the analyses.

6.14 Statistical Analysis

- **Primary outcome:** The effectiveness data will be analysed by a statistician blinded to group allocation, comparing the mean number of sessions completed by the participants in each group over 8 weeks, using R software (version 4.5.1). The analysis will follow the intention-to-treat (ITT) principle, including all randomised participants for analysis. As this outcome is a count variable and based on pilot data, overdispersion is expected to be present in the research.

A negative binomial regression model will be used to compare the mean number of sessions completed between the three study arms (Hilbe, 2011). The model will include group assignment as a categorical predictor. If relevant baseline covariates (e.g., age, baseline motivation) are meaningfully unbalanced across groups, we will conduct adjusted analyses including these covariates. Model fit and assumptions will

be evaluated, and estimated incidence rate ratios (IRRs) with 95% confidence intervals and standard deviation (SD) will be reported.

- **Secondary outcome:** Binary categorical variables will be analysed using binary logistic regression models. These include adherence rate, follow-up completion rate, and dropout rate at the 8-week follow-up period. Each model will include the intervention group (telephone calls, SMS, or control) as the primary predictor. Odds ratios (ORs) and corresponding 95% confidence intervals will be reported to quantify the likelihood of each outcome occurring in the intervention arms compared to the control group.

The economic evaluation will be conducted from the trialist or provider perspective, expressed in AUD. To estimate costs, published guidelines will be followed (Russell et al., 2021). Costs will include all resources required to deliver the each of the interventions. The costs for the control group will be considered zero, and the costs regarding the phone calls and SMS will include expenses related to equipment (e.g. mobile phones), computer platforms (e.g. NOTION, San Francisco), staff (e.g. research assistant), incentives (e.g. gift cards), and supplies for each group per participant.

As performed by previous SWATs (Bracken et al., 2019), the difference in mean costs per participant between the groups (incremental costs or ΔC) will be calculated (i.e., control – phone calls; control – SMS; phone calls – SMS). The difference in the mean adherence (ΔE) between the two groups for each comparison will also be calculated. Incremental cost-effectiveness ratios (ICERs) will be determined as $ICER = \Delta C / \Delta E$, which indicates the additional AUD per extra session completed. If $\Delta E \leq 0$, the intervention will be interpreted as providing no improvement ($\Delta E = 0$) or being less effective ($\Delta E < 0$) than the comparator. If $\Delta E < 0$, the intervention will be interpreted as performing worse. If there is a difference greater than one, trialists or providers will be encouraged to calculate the Net Benefit (NB) considering their willingness-to-pay values (λ) per extra session ($NB = \lambda * \Delta E - \Delta C$). A positive NB indicates that the intervention is cost-effective at the chosen λ . NB will be calculated for each bootstrap replication to generate cost-effectiveness acceptability curves (CEACs) showing the probability that each intervention is cost-effective across the range of λ values.

- **Moderation analysis:** Moderation analyses will be conducted to explore whether the effect of group allocation on the number of sessions completed varies according to participant characteristics. These analyses will use negative binomial regression models including main effects and a group \times moderator interaction term. As the study is not powered to detect moderation effects, these analyses will be interpreted with caution and considered exploratory. The characteristics to be examined will include age, gender, pain severity, baseline level of disability and occupational status.

7. ETHICS

The proposed study will adhere to the ethical principles for conducting research on humans: informed consent, confidentiality, autonomy, beneficence, non-maleficence, and justice (Bošnjak, 2001) and will be conducted in accordance with Good Clinical Practice (GCP) guidelines (NHMRC, 2018). Recruitment will not commence until ethical approval has been granted for the project.

7.1 Informed consent

Participants will be given a participant information sheet outlining the details of the study and asked to provide informed consent by signing the informed consent form.

7.2 Confidentiality

All participants will be provided with a unique identification number. All data will be coded with this number so that any data collected will only be identifiable by the code. All analyses will be done using de-identified data. Results will be disseminated using group data to ensure confidentiality is preserved. The participants' privacy will be protected according to NeuRA's privacy policy available on <https://neura.edu.au/resources/common/COM03-Privacy-Policy-v2.2.pdf>.

7.3 Autonomy

Participants will take part in the study willingly without being unduly persuaded. Should the participants wish to withdraw from the study, they will be allowed to do so without any punitive consequences. Participants wishing to withdraw will be sent an online withdrawal form in REDCap. Should participants decline to complete the withdrawal form, research assistants will withdraw participants once the intention to withdraw is expressed.

7.4 Beneficence

High-quality systematic reviews of randomised controlled trials have shown that patients benefit from interventions aimed at improving their treatment adherence, as this behaviour increases their chances of reducing the primary treatment target symptoms (Kim et al., 2025; MacLean et al., 2025)

7.5 Non-maleficence

The treatments in the host trial involve self-management approaches and have a very low risk. The responsible investigators will ensure that the study is completed in accordance with the guidelines in:

- Australian Clinical Trials Handbook guidance on conducting clinical trials in Australia using 'unapproved' therapeutic goods (Version 2.2 October 2018).
- The National Statement on Ethical Conduct in Human Research 2007 (updated 2018).

- International Council for Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP).

NOTUS/ADHERE SWAT researchers accept responsibility for the accuracy of the information provided in this application and ensure that the qualifications and/or experience of all members of the NOTUS/ADHERE SWAT research team involved with the project are appropriate to their role. NOTUS/ADHERE SWAT researchers will maintain valid ICH-GCP certification for the duration of the trial.

7.6 Justice

Participants will be treated in an unbiased, fair, and just manner, despite their race, gender, ethnicity, or socio-economic status. In this study, there will be an equitable distribution of clinical resources to all participants at no cost.

7.7 Data Consistency

Participant data will be self-entered and recorded online directly to REDCap. REDCap is a data capture software that ensures the curation of data via the use of standardised data collection. REDCap's electronic capture and pre-defined fields ensure data consistency.

7.8 Quality Control and Assurance

Any amendments will be submitted to the Health Research Ethics Committee (HREC) and the ADHERE SWAT Steering Committee for review prior to implementation as per HREC guidelines.

7.9 Trial Sponsorship and Financing

The trial Sponsor is Neuroscience Research Australia. The host trial is funded by the 2021 Primary Health Care Digital Innovations Medical Research Future Funding (MRFF) project grant (ID# 2023373 - 2023). The costs being covered include:

- Research staff salaries
- Adaptation of the intervention into the digital infrastructure
- Delivery of the mobile app intervention
- Recruitment and costs (e.g., advertising)
- Data collection platform

7.10 Indemnity

We are taking reasonable precautions against harm by having the research team monitor adverse events for the duration of the study. All serious adverse events will be reviewed by the steering committee within 48 hours.

The sponsor, Neuroscience Research Australia, is covered by UniMutual Clinical trials Protection insurance to the value of \$30M. Neuroscience Research Australia adheres to the principles outlined in the Medicines Australia Guidelines for Compensation for Injury Resulting from Participation a Company-Sponsored Clinical Trial (<https://www.medicinesaustralia.com.au>).

8. APPENDIX

8.1. CRediT (Contribution Roles Taxonomy)

- Conceptualization: Ideas; formulation or evolution of overarching research goals and aims;
- Data Curation: Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse;
- Formal Analysis: Application of statistical, mathematical, computational, or other formal techniques to analyse or synthesize study data;
- Funding Acquisition: Acquisition of the financial support for the project leading to this publication;
- Investigation: Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection;
- Methodology: Development or design of methodology; creation of models;
- Project Administration: Management and coordination responsibility for the research activity planning and execution;
- Supervision: Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team;
- Visualization: Preparation, creation and/or presentation of the published work, specifically visualization/data presentation;
- Writing – Original Draft Preparation: Creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation); and
- Writing – Review & Editing: Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre- or post-publication stages.

8.2. Sample Size Calculation Code (R Version 4.5.1)

```
## ===== Pairwise planning with Bonferroni (3-arm RCT) =====

## Goal: detect a mean difference of 4 (SD = 8) between any two arms

## Power = 80%, FWER alpha = 0.05 (two-sided), k = 3

# install.packages("pwr") # uncomment if needed
library(pwr)

## Inputs

delta      <- 4      # minimal detectable difference
sd         <- 8      # standard deviation
power_goal <- 0.80
alpha_fwer <- 0.05
k          <- 3
attrition <- 0

## Bonferroni per-test alpha (3 pairwise comparisons)
m_pairs     <- k * (k - 1) / 2
alpha_per_test <- alpha_fwer / m_pairs

## Effect size for two-sample t-test
d <- delta / sd # Cohen's d

## Required sample size per arm (analyzable), using noncentral t
res <- pwr.t.test(d = d,
                   sig.level = alpha_per_test,
                   power = power_goal,
                   type = "two.sample",
                   alternative = "two.sided")
```

```

n_per_arm_analyzable <- ceiling(res$n)

## Optional: adjust for attrition

n_per_arm_recruit <- ceiling(n_per_arm_analyzable / (1 - attrition))

total_recruit <- n_per_arm_recruit * k

## Report

cat("Pairwise Bonferroni planning (k=3)\n",
    "Delta:", delta, "| SD:", sd, "| d:", round(d, 3), "\n",
    "FWER alpha:", alpha_fwer, "| per-test alpha:", signif(alpha_per_test, 4), "\n",
    "Power:", power_goal, "\n\n",
    "Per arm (analyzable):", n_per_arm_analyzable, "\n",
    "Per arm to recruit (attrition =", attrition, "):", n_per_arm_recruit, "\n",
    "Total to recruit:", total_recruit, "\n")

```

9. REFERENCES

Ahmed, S., Airlie, J., Clegg, A., Copsey, B., Cundill, B., Forster, A., Heaven, A., Johansson, J. F., Kime, N., Moreau, L., Ozer, S., Parker, C., Richards, S. H., Thompson, E., & Farrin, A. J. (2022). A new opportunity for enhancing trial efficiency: Can we investigate intervention implementation processes within trials using SWAT (study within a trial) methodology? *Research Methods in Medicine & Health Sciences*, 3(3), 66–73.
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