# RELEASE: REdressing Long-tErm Antidepressant uSE in adults: A 3-arm cluster RCT effectiveness-implementation hybrid type-1 in general practice

*"Please RELEASE me, let me go. RELEASE me, and let me love again ..."*
Engelbert Humperdinck - *RELEASE Me* (1966)

## Study Protocol

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# Background

***Our vision*** is to improve Australian health outcomes by decreasing unnecessary and potentially harmful long-term antidepressant prescribing in general practice.

**The problem:** Australia is the second highest user of antidepressants per capita (around 1 in 7 adults)[1] among 30 OECD countries excluding the US.[2] In the 2016-17 year, there were over 27 million prescriptions for antidepressants (ATC N06) at a cost to the government of AU$250 million and patient contribution of $280 million (totalling about $530 million for the year).[3] Increasing use is driven mostly by increasing long-term use (>12 months).[4-6] General practitioners (GPs) prescribe most antidepressants (86.3%).[1] Clinical guidelines recommend psychological therapies for mild depression and anxiety, and 6-12 months antidepressants for a single episode of moderate to severe depression.[7-9] Yet in Australia the average duration of antidepressants is now about four years.[4] Adverse drug effects from long-term antidepressant use include weight gain; diabetes; increased risk of falls and fractures;[10] sexual dysfunction which may be persistent including failure to orgasm in both sexes;[11,12] and emotional numbing (“reduced sympathy and empathy”[13] and “caring less about others”[14]*)*. The relational and societal effects are unchartered. The 2020 Productivity Commission Mental Health Inquiry report recommended to “*address adverse outcomes from prescribing practices of mental health medication*” as a “*priority reform*” (p.3).[15] The report stated:

> “*while antipsychotic prescribing in aged care facilities is one element of this … arguably a greater concern, given its frequency, is antidepressant prescribing*” (p.713).[15]

Data suggest that 30-50% of long-term antidepressant users have no indication for continued use and could try stopping (1.5-2 million Australians).[16] But stopping antidepressants can be challenging because of a physiological withdrawal syndrome. Withdrawal symptoms are readily misconstrued, by both patients and doctors, as relapse, perpetuating ongoing prescribing and long-term use.[17,18]

> *“I was hoping to wean this year, but it seems that it will not work. I never want to take these drugs again ... I need something that gives me hope that I can get rid of the drug.”*[19]

**The solution:** Evidence supports hyperbolically slow tapering of drug dose to minimise withdrawal, and this is now recommended in clinical guidelines.[8,9,20] However, implementation in Australia is negligible. We will address this evidence-practice gap with an effectiveness-implementation 3-arm cluster RCT in general practice to assess two multi-strategy interventions (RELEASE and RELEASE+) that target both patients and GPs to support safe cessation of long-term antidepressants (>12 months) where there is no clinical indication for continued use.

RELEASE is highly responsive to the priorities of government, including the Productivity Commission report, generating a validated antidepressant discontinuation model with proven implementation strategies to support translating evidence into practice.

**Increasing long-term antidepressant prescribing against clinical guideline recommendations:** One in 8 GP encounters are mental health related, most are managed with medication (61.6%).[1] The most commonly prescribed antidepressants are Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) (>85%).[5] In the year to June 2020, for the first time an antidepressant was in the top ten PBS/RPBS drugs by defined daily dose/1000 population/day (no. 9 sertraline 25.67 DDD/1000 pop/day).[21] Sertraline increased to no. 8 in 2021 (27.42 DDD/1000 pop/day).[22] Prescribing rates are *higher for older people* and for people in *regional and lower socio-economic regions*.[23] Half of users are long-term users.[6] Withdrawal symptoms, which can last for weeks or months with severity and duration likely proportional to duration of use, make stopping antidepressants challenging for many people.[24] Withdrawal symptoms are frequently misconstrued as relapse prompting fear and perpetuating ongoing antidepressant use. Recent research has been roundly criticised for failing to adequately distinguish between withdrawal and relapse, and thus whether continuing antidepressants prevented relapse or merely prevented withdrawal.[25,26]

The Productivity Commission Mental Health Inquiry report recommended that GP "*mental health training and professional development*" be improved to increase *"adherence to evidence-based clinical practices (including the clinical appropriateness of GP's [sic] prescribing practices for mental health medication, management of medication side effects and de-prescribing)"* (p.34).[15] The Commission recommended "*more research focused in these areas, and uptake of its resulting lessons among treating clinicians"* (p.38).[15] Online discussion forums confirm the need for support.[27,28]

**Addressing the evidence-practice gap:** To curb unnecessary and prolonged antidepressant prescribing, we need to raise awareness of withdrawal symptoms and support GPs to initiate antidepressants less often and review and stop them more often. *Hyperbolically slow tapering* of antidepressant drug dose is critical to safe and successful stopping of antidepressants,[29] confirmed by widespread patient-led experience,[30] and observational evidence.[31]

**Implementation challenge:** Despite clinical guidelines now recommending hyperbolically slow tapering of dose to mitigate withdrawal symptoms, implementation in Australia is minimal.[7-9] The ANZ College of Psychiatrists' guidelines lament that: *"reducing the antidepressant in such a way is impractical as current preparations of antidepressant do not allow for the dose to be reduced by such small decrements".*[9] In Australia, drug-specific tapering protocols and requisite antidepressant drug mini-doses are not readily available.[32] The RELEASE proposal addresses these implementation challenges.

## Principles of the RELEASE Interventions

We have completed preliminary research with both GPs and people-with-lived-experience to develop the two multi-strategy interventions.

The RELEASE interventions are user-informed multi-modal interventions based in general practice that target both GPs and patients and have the following guiding principles:

(i) All prescribing decisions are made as usual by the GP and patient together.
(ii) Empowering patients.
(iii) Acceptable and translatable in routine general practice.
(iv) Resources developed to raise awareness, prompt medication review, support decision-making, and guide safe cessation of long-term antidepressants where indicated.

Professor Wallis's safer prescribing (SPACE) work interviewing GPs about barriers and facilitators to deprescribing in general practice,[33] then developing and testing in a multisite cluster trial an intervention designed to prompt medication review and support safer prescribing in general practice,[34,35] has informed development of the RELEASE interventions. A 2021 Cochrane review co-authored by investigators Horowitz and Donald reported an urgent need for trials that focus on approaches to discontinuation of long-term antidepressants in the primary care setting and that test slower tapering schemes.[36] Work by A/Professor Donald identified GPs' reluctance to risk destabilising a stable situation, 'set-and-forget' prescribing, lack of confidence in skills in this area, and lack of time.[37] Investigators Wallis, Donald and Moncrieff co-authored a paper in the Australian Journal of General Practice to raise awareness of the issue in the GP community.[32]

## Objectives and Hypotheses

Primary objectives and hypotheses

1.a To assess the effectiveness of RELEASE compared to usual care in supporting safe cessation of long-term antidepressants. Hypothesis: The RELEASE multi-strategy intervention will significantly increase the proportion of people stopping long-term antidepressants compared to usual care.

1.b To assess the effectiveness of RELEASE+ compared to usual care in supporting safe cessation of long-term antidepressants. Hypothesis: The RELEASE+ multi-strategy intervention will significantly increase the proportion of people stopping long-term antidepressants compared to usual care.

Secondary objectives

2. Assess the cost-effectiveness of RELEASE, RELEASE+ and usual care.

3. Evaluate implementation of the two multi-strategy interventions (e.g. barriers and enablers and implementation outcomes).

# Research Plan

## Study design

This study was begun as a 2-arm cluster RCT (effectiveness-implementation hybrid type 1) testing RELEASE versus usual care in 24 general practices. After receiving additional funding to test the RELEASE+ intervention, for reasons of efficiency the study transitioned to a 3-arm cluster RCT (effectiveness-implementation hybrid type 1) testing RELEASE and RELEASE+ (more intensive intervention) versus usual care in 28 general practices. . The unit of randomisation is the general practice, while the unit of analysis is the individual patient. In a type 1 hybrid design, the primary objective is to determine effectiveness of the intervention and the secondary objective is to assess determinants of implementation success, acceptability, feasibility and cost-effectiveness.[38] This design is highly suited to evaluate service delivery interventions and increase speed of translation. The study catchment is south-east Queensland.

Figure 1 shows the flow of practices, GPs and patients through the study.

## Sample size

Based on a 2020 trial, we assume 12% of participants in the control group and 30% of participants in each of the intervention groups will achieve the primary outcome (stopped antidepressants by 12 months).[39]

Because the study involves two comparisons, usual care vs RELEASE and usual care vs RELEASE+, we will allocate more participants to the usual care arm as this increases the overall efficiency of the trial (that is, for fixed type I and type II errors we require fewer total participants). The ratio chosen for allocation is 1.5:1:1. Using a two-sided alpha significance level of 0.035 (chosen to facilitate comparison of the two intervention arms against a single control arm) and 90% power then, without accounting for clustering, we would require 142 participants in the usual care arm and 95 in each of the intervention arms (332 total).

As this is a cluster RCT, we need to account for the non-independence of observations from individual participants recruited from the same practice. We assume there will be a mean of 20 participants recruited from each practice who will provide data on the primary outcome, and that the within-practice intra-cluster correlation=0.03, giving a design effect of 1.57. Consequently, we require 522 participants to provide data. To achieve this number, and to account for the possible drop-out of practices once enrolled, we will recruit 28 practices. Assuming 20% attrition, we require 653 participants to enrol and provide baseline data, this requires 28 practices recruiting an average of 23.3 patients.

Conservatively estimating each practice to have on average 4500 adult patients, of whom 1 in 10 are on antidepressants (SSRIs, SNRIs, and other antidepressants) (450 patients per practice), half of them long-term (>12 months) (225 patients per practice), of whom an estimated 90% could be eligible to participate in the RELEASE study (203 potentially eligible patients per practice). To achieve recruitment of 653 participants requires 28 practices - each enrolling 11.5% of the 203 invited potentially eligible patients (5,684 invited in total)

## General practice recruitment, eligibility, and consent

Twenty-eight GP practices will be recruited through The University of Queensland's Practice-based Research Network (UQGP Research) using email (Appendix B) (a domain specific email will be established: release.study@uq.edu.au), telephone calls and outreach visits. A Practice Liaison Officer based with the research team will lead recruitment of practices and their GPs.

**GP practice inclusion criteria**

- Practice uses *Best Practice* or *Medical Director* software (compatible with recruitment software - TorchRecruit®).
- Practice located in south-east Queensland

A Letter of Agreement (LoA) between participating practices and The University of Queensland outlines expectations, including allowing a UQ researcher to be located in the practice to support practices to recruit patients (Appendix C). Each practice will be asked to nominate a Practice Champion and GP Clinical Lead to support RELEASE.

We will seek to recruit all or the majority of GPs in each practice to participate. A brief descriptive practice survey will include the practice address and postcode, an estimate of the number of practice patients, RACGP accredited (yes / no), the total number (and FTE) of GPs in the practice and who agree to participate. The Practice Liaison Officer will facilitate completion of this brief survey.

## Patient recruitment, eligibility, consent and baseline data

Patients will be recruited via their GP-Practice using TorchRecruit®. TorchRecruit® was developed by the University of Melbourne, Department of General Practice to support recruitment of trial patients through general practice. TorchRecruit® ensures that patient privacy and confidentiality is protected as all identifiable patient data remains within the practice and no patient personal health information is removed from the practice. The researcher supports the practice to download and install the TorchRecruit® tool.

**Patient inclusion criteria**

- 18 years or older AND
- Currently on antidepressant medication AND
- On any combination of antidepressant medication with a total duration of longer than 12 months including:

  **SSRIs**:
  Sertraline (Zoloft, Eleva, Sertra, Setrona)
  Escitalopram (Lexapro, Loxalate, Cilopam, Esipram, Esitalo, Lexam)
  Fluoxetine (Prozac, Fluotex, Lovan, Prozet, Zactin)
  Paroxetine (Aropax, Extine, Paroxo, Paxtine, Roxet, Roxtine)
  Fluvoxamine (Luvox, Faverin, Movox)
  Citalopram (Celapram, cipramil, Citalo, Talam)

  **SNRIs**:
  Venlafaxine (Efexor, Elaxine, Enlafax)
  Desvenlafaxine (Pristiq, Desfax, Desven)
  Duloxetine (Cymbalta, Andepra, Deotine, Duloxecor, Dytrex, Tixol)

  **Other antidepressants**:
  Mirtazapine (Avanza, Axit, Mirtanza, Mirtazon)
  Vortioxetine (Trintellix and Brintellix)
  Mianserin (Lumin)
  Moclobemide (Amira, Clobemix, Aurorix)
  Reboxetine (Edronax)

Agomelatine (Valdoxan, Domion)

**Patient exclusion criteria**

- GP considers the patient not suitable for medication review (for example, recent personal crisis)
- Bipolar disorder
- History of psychotic or obsessive-compulsive disorder
- Currently under care of a psychiatrist
- Current substance use disorder
- Non-psychiatric indication for antidepressant (for example, neuropathic pain)
- Dementia or unable to give informed consent
- Aged care residents

Based on the above trial inclusion and exclusion criteria, TorchRecruit® will use technology to automatically generate a list of potentially eligible patients for each GP. GPs review their list of patients and de-select ineligible patients (recording reason for exclusion).

**Patient Recruitment**

Step 1: The practice invites, with support from a UQ-researcher, patients remaining on the list via letter/email/SMS (depending on practice preference) (Appendix D, E, F) to participate in the study, advising patients that there will be a follow-up phone call to discuss the study. Included in this invitation is study information for patients (PIS for patients) (Appendix G) accessible via a QR Code (letter), or pdf attachment (email), or a link where possible (SMS). Some practices prefer not to send an SMS containing a link and some practices' software only allows SMS of 160 characters. Also included in the invitation is the option for patients to opt out of receiving the phone call and any further communication about the study by contacting the practice.

Step 2: The practice phones patients on the list who have not opted out, supported by a researcher (script, Appendix U), informing patients about the study, and asking again if they would like to participate.

Step 3: Patients who express an interest in participating at the phone call will then be sent an email (Appendix V) and 'closed' link via REDCap, (Research Electronic Data Capture, Vanderbilt, USA). REDCap is a secure web application for building and managing online surveys and databases. Patients then provide e-consent to participate (Appendix H) and complete the baseline e-survey. Patients will be sent an automated email reminder from REDCap to complete the baseline e-survey at day 3, day 6 and day 9.

Consent to participate includes consent for researchers to access patients' GP health records and permission to be invited to participate in future relevant follow-up research. Participants will be assigned a Study ID at the point of survey invitation.

REDCap will be set to close to patient enrolment and baseline data collection before the time of practice randomisation, after which time no further patients from that practice can enrol. Time to the REDCap cut-off will be set to 14 days after each patient participant is sent the baseline e-survey invitation. After this date, all Study IDs that did not complete consent will be removed from REDCap.

## Randomisation

Randomisation is clustered at the practice level to avoid contamination between intervention and usual care arms. Practice randomisation will occur after baseline data collection to avoid bias in GP de-selection (see Figure 1). Randomisation will occur in a 1.5:1:1 usual care:RELEASE:RELEASE+ ratio via a central web-based randomisation service (Griffith University). Practices will be stratified by size (>5 / ≤5 FTE GPs). Randomisation will occur in blocks of size 7 or 14, with block size

randomly assigned in a 1:1 ratio. Due to the previously outlined additional funding received after the start of the trial and subsequent transition from a 2-arm to a 3-arm cluster RCT, the first two practices recruited were randomised and allocated into one of two arms (usual care or RELEASE) and thereafter practices were randomised and allocated into one of three arms (usual care or RELEASE or RELEASE+).

Researchers contact practices and GPs for both intervention and usual care groups to inform them which group they have been assigned to (Appendices I, J, K, L). Notification for patient participants in the intervention group is via email and post with a study package that includes invitation to medication review and printable resources (see below under RELEASE-for-patients), and for the usual care group notification is via REDCap (Appendix M).

## RELEASE Intervention arms

The two interventions are informed by the 3As for patient-centred care (Ask, Advise, Assist). The 3As is an evidence-based behaviour change model with demonstrated feasibility in the general practice setting.[40,41] The 3As in our context includes - **asking** patients how long they have been on antidepressants, and whether they know that guidelines recommend only 6 to 12 months for most people; **advising** the patient about withdrawal, distinguishing withdrawal from relapse and hyperbolic tapering of antidepressants; and **assisting** the patient using the RELEASE decision aid, tapering protocols, and follow-up support.

A Practice Liaison Officer will work with PI Wallis to deliver RELEASE and RELEASE+ for GPs.

### Intervention arm 1: RELEASE-for-GPs

RELEASE for GPs includes:

1. Interactive e-Learning module for GPs: a 30-minute interactive e-Learning module including PI Wallis and vignettes with experts in the field CIs Moncrieff and Horowitz.
2. One-on-one outreach training: The Practice-Liaison Officer will visit each GP to provide training in the RELEASE conversation, prescribing for hyperbolic tapering of antidepressants and where to access printable resources including drug-specific tapering protocols; provide printed copies of printable resources including copies of drug-specific tapering protocols; provide the GP with a list of their enrolled patients; and provide adverse events proforma.
3. Tailoring of practice management software: to include bespoke prescriptions for antidepressants with requisite quantities of drug mini-doses available via compounding chemist; and printable RELEASE drug-specific tapering protocols.
4. Local community pharmacists near intervention practices will be provided with a letter outlining the study and informing pharmacists that patients may inquire about compounding of min-doses of antidepressants (Appendix W).
5. Monthly engagement emails for GPs: to discuss ways to support GP confidence in supporting safe cessation of long-term antidepressants.

### Intervention arm 1: RELEASE-for-patients

RELEASE empowers and prompts patient participants to seek medication review with their GP. Collaborating investigator Horowitz's extensive work with people-with-lived-experience, clinical psychiatric practice that focusses exclusively on psychiatric drug discontinuation including antidepressants, and personal lived experience identify the three most important factors for stopping as: (i) *tapering guidance*, (ii) availability of *drug mini-doses*, and (iii) close monitoring and *reassurance* to address fear of relapse.[18] Horowitz's Lancet Psychiatry publication highlights that antidepressant target receptors provide the pharmacological rationale for *hyperbolically slow tapering* to mitigate withdrawal symptoms.[29]

Research identified barriers to antidepressant discontinuation for patients to include an expectation that the doctor would suggest discontinuation if it were warranted, in addition to withdrawal symptoms and fear of relapse.[17,42]

We conducted a Think Aloud study with 15 lived-experience participants (i.e. long-term users of antidepressants) to optimise RELEASE resources for patient participants (publication in preparation). A series of one-to-one, semi-structured interviews were conducted face-to-face or via videoconferencing (as necessitated by the COVID-19 pandemic). Interviews were based on think-aloud methods, whereby participants read written resources and said their thoughts out loud. This study identified modifications to optimise the RELEASE resources, to make them as acceptable, engaging, persuasive, and motivating as possible for patients taking long-term antidepressants.

Consistent with these research findings, RELEASE for patients includes:

1. ***RELEASE Study Package (email / post)*** including:
   i. ***Letter*** informing patients of allocation to the intervention group and ***inviting patients to schedule a medication review*** with their GP (Appendices N.i and N.ii). REDCap will be programmed to send email prompts (every 4 weeks for 6 months) to remind intervention patient participants to schedule a medication review (Appendix R).
   ii. A ***medicines information brochure*** (Appendix O) to raise awareness of antidepressant adverse effects and physiological withdrawal effects, and to address the common misconception that depression is a long-term condition caused by a chemical (serotonin) deficiency in the brain that requires long-term medication.
   iii. A ***decision aid*** (Appendix P)[43] to help patients to weigh up the pros and cons of stopping antidepressants and to help them decide whether to stop taking antidepressants.
   iv. A ***drug-specific tapering protocol*** (Appendix Q), demonstrating how people can wean slowly off antidepressants over 9-18 months, including advice on flexibility of tapering speed and availability of drug mini-doses via compounding chemists. Tapering protocols advise patients that if withdrawal symptoms occur and are unbearable to return to previous drug dose for symptom relief and, when ready to try again, use a more gradual taper with smaller dose reductions and/or longer steps.
   v. A ***family and friends brochure*** (Appendix O.i) to help patients communicate with family and friends by raising awareness of antidepressant adverse effects and physiological withdrawal effects, to address the common misconception that depression is a long-term condition caused by a chemical (serotonin) deficiency in the brain that requires long-term medication, and to provide ways in which to support someone stopping antidepressants as a friend or family member.
2. ***Medication review and RELEASE conversation:*** Participants will schedule and attend the medication review with their GP. The review includes the RELEASE conversation and shared decision-making. If the decision is to discontinue, the GP will provide a drug-specific tapering protocol and prescriptions for antidepressant drug mini-doses required for tapering. Drug mini-doses are available via compounding pharmacy, including online compounding chemist. Cost is 50c-$1 per capsule depending on quantity. *All prescribing decisions are made as usual by the GP and patient together*. Usual fee applies for GP appointments to ensure scalability.
3. ***Follow-up with GP:*** Follow-up with GP as determined by the GP and patient together.

RELEASE patient participants will have the contact details for a RELEASE researcher who can direct them to supports.

**Intervention arm 2: RELEASE+ for GPs**

RELEASE+ for GPs includes all the RELEASE strategies outlined above plus:

1. **Practice outreach audit and feedback**: practice antidepressant prescribing data; Continuing Professional Development (CPD) eligible activity for GPs.

**Intervention arm 2: RELEASE+ for patients**

RELEASE+ for patients includes all the RELEASE strategies outlined above plus:

1. **CareMonitor App** (shared care and remote monitoring platform): patients can access RELEASE resources, links to information and e-mental health supports, and receive prompts and messages from the App.

### Usual Care

Usual care practices may provide medication review as usual. This is permitted as in both arms of the trial *all prescribing decisions are made by GP and patient together as usual*. Patients in usual care arm will be asked to complete a questionnaire at 6- and 12- months follow-up.

### Follow-up data collection

Participant e-survey data at 6- and 12-months will be collected via REDCap. Practices will send an SMS to participants three days before the e-survey due date to foreshadow an email coming from REDCap inviting participants to complete the 6- and 12-month e-surveys (Appendix V.i). REDCap will be programmed to email all participants on the survey due date to invite survey completion. For participants who do not respond to this email invitation, REDCap will send a reminder email on days 7, 14, and 21 following the due date; and an SMS reminder on day 4 and if no response again on day 9 (Appendix V.i). For participants who have not responded, the researcher will phone to invite participation at two weeks after the due date. REDCap will be programmed to only send email and SMS reminders to participants who have not yet completed their survey.

### Remuneration and retention

Practices will receive $1000 to reimburse for personnel time (including facilitating outreach visits and patient recruitment). The Practice Champion in both groups will receive a $200 e-voucher for supporting the RELEASE research project. For some practices a GP Clinical Lead will be designated and receive a $100 e-voucher for supporting the RELEASE research project. GPs in all three groups will receive a $100 e-voucher for reviewing patient list and deselecting ineligible patients. GPs in the two intervention arms will receive an additional $100 e-voucher for completing the 30-minute e-Learning module and $100 e-voucher for participating in the one-on-one outreach training.

Patient participants in all three groups will receive a $40 e-voucher at each of the three data collection points (baseline, 6- and 12-month follow-up) ($120 e-vouchers in total).

## Participant flow

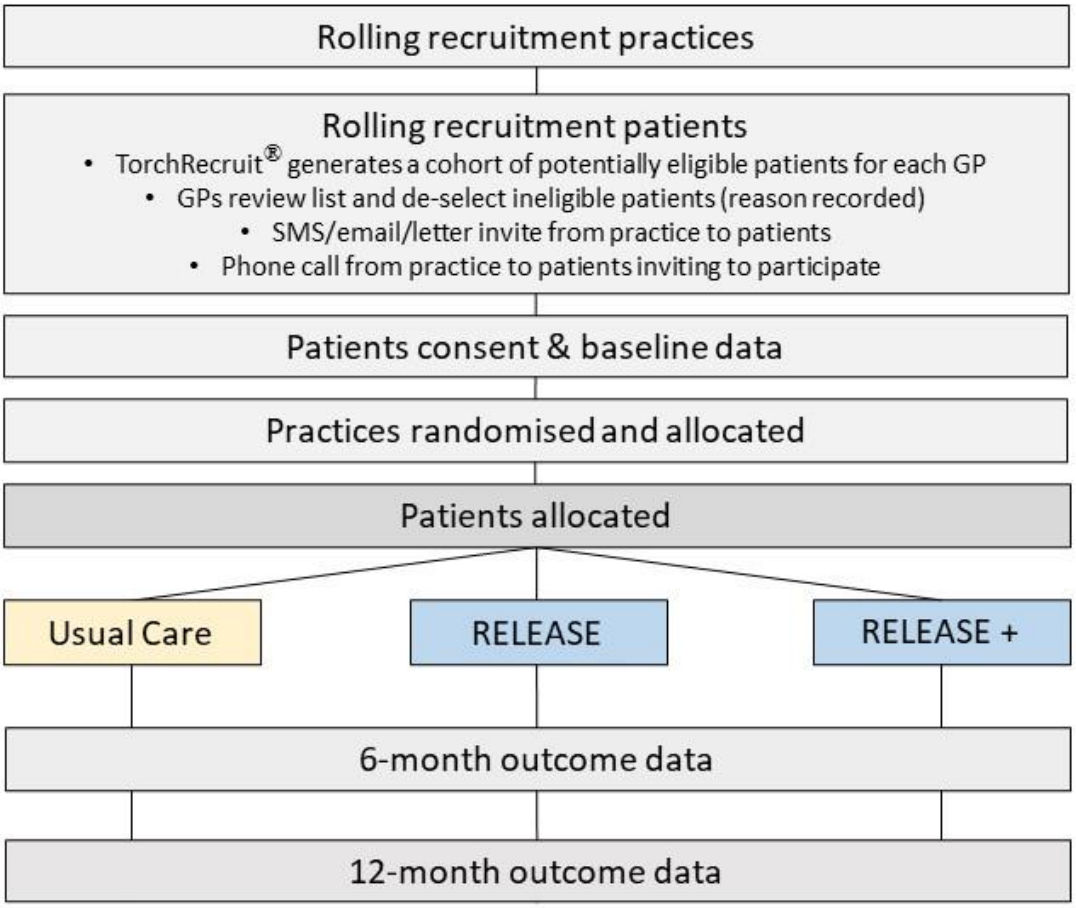


**Figure 1: Participant flow**

## Effectiveness outcome measures

**Primary outcome**

1. *Antidepressant discontinuation at 12-months* post patient allocation, self-reported by patients. Discontinuation is defined as 0mg antidepressant maintained for at least 2 weeks.

**Secondary outcomes**

1. *Proportion achieving 75% reduction at 12-months.* A 75% reduction is likely more achievable for people who have been on antidepressants for many years and has health benefits.[30]
2. *Health-related quality of life:* 12-item short-form health survey (SF-12).[44]
3. *Antidepressant side effects*: 12-item Antidepressant Side Effect Checklist (ASEC-12).[45]
4. *Wellbeing*: The Warwick Edinburgh Mental Well-being Scale (WEMWBS-14)
5. *Withdrawal symptoms:* 15-item Distinctive Antidepressant Withdrawal Scale
6. *Emotional numbing:* Emotional Reactivity Numbing Scale: General subscale (ERNS-8).[46]
7. *Beliefs about antidepressants:* Beliefs about Medications Questionnaire-Specific.[47]
8. *Depressive symptoms:* Patient Health Questionnaire (PHQ9).
9. *Anxiety symptoms:* Generalized Anxiety Disorder measure (GAD7).
10. *Aggregated practice level antidepressant prescribing data at baseline and 12-months follow-up*.

**Other measures**

1. *Demographics*: Age, Gender, Relationship status, Educational level, Employment status, Living arrangements, ATSI, Ethnicity, Household income, Address and Postcode

2. *Antidepressant prescriptions including dose*: self-reported, and via GP health record
3. *Health and lifestyle:* BMI (weight and height); falls in the past 6 months; co-morbidities (e.g., diabetes); current smoking; alcohol use
4. *Health service utilisation:* self-report and via GP health record including GP visits, outpatient department visits, Emergency department presentations, hospitalisations, specialist appointments.

**Costing measures**

The primary outcome will be the incremental net monetary benefit, defined as the incremental benefit, measured in quality adjusted life years (QALYs) multiplied by the threshold value of a QALY minus the incremental cost from a health sector perspective. Secondary analysis will also be undertaken from a broader societal perspective. The cost of the intervention will be estimated based on resource use and implementation data collected during the trial (including educator and doctor time, costs for RELEASE and RELEASE+ resources and website, practice nurse time for search, GP time to review list, and cost of compounding capsules). A cost questionnaire will be administered to participants to collect data on health and social service resource use, out of pocket spending, and time off work. A review of GP records will be conducted to extract additional health service usage, including medication, GP consultations, outpatient appointments, and emergency department attendances.

**Safety measures**

Only patients assessed by the GP as eligible for medication review will be invited to participate. Further, participants can only taper and stop antidepressants under the care and support of the GP who provides the prescriptions needed for tapering. Our emphasis on patient-centred care means RELEASE and RELEASE+ include flexible tapering protocols tailored to each patient, and the safety valve whereby patients are advised that if withdrawal symptoms become too distressing, return to previous dose for symptom relief and, when ready, try again with a more gradual taper.

REDCap will be programmed to score the GAD-7 and the PHQ-9. If a patient participant scores 15 or greater on the GAD-7[48] and/or 15 or greater on the PHQ-9[49] and/or above 1 (i.e. 2 or 3) on the ninth question of the PHQ-9 survey (about suicide/self-harm), REDCap is programmed to send an email to the patient participant recommending that they seek support and advice from their GP (Appendix T).

GPs will record any adverse events including hospitalisations, deaths and suicide attempts on a proforma and carefully monitored by the Data Monitoring and Safety Committee (see Oversight and Monitoring section below). The Data Monitoring and Safety Committee will develop this proforma at the inaugural meeting in October 2022.

## Statistical analysis

The unit of analysis is the individual patient. Summary statistics will be described using either mean (standard deviation) or median ($25^{th}$-$75^{th}$ percentile) for continuous variables, according to distribution, or as frequency (percentage) for categorical variables. The primary outcome will be assessed using mixed-effects logistic regression, with effect estimates presented as odds ratio and 95% confidence interval (95% CI). Treatment group (RELEASE/RELEASE+/Usual care) will be included as the main fixed effect and GP practice will be included as a random effect to account for probable non-independence of results from participants who attend the same GP practice. The primary outcomes of interest are the between-group comparisons of RELEASE vs usual care and RELEASE+ vs usual care. A sensitivity analysis will be conducted to assess any effect of the first two practices randomised prior to the transition to a 3-arm trial.

Secondary outcomes will also be analysed using mixed-effects models, using linear regression for interval outcomes, logistic regression for binary outcomes, and Poisson regression for count outcomes. All models will include GP practice as a random effect. Longitudinal associations will be investigated using analyses that account for the multiple observations per participant, with the

particular analysis determined by data structure, for example, three-level hierarchical mixed-effects models with 'patient' nested within 'GP' nested within 'GP practice' where appropriate. Outcomes will be analysed on an intention-to-treat basis. With regard to missing data, sensitivity analyses will be conducted using imputation models. Patients who drop out before assessment will be classified as 'not able to stop'. Data will be stored de-identified.

### Cost-effectiveness analysis

Differences between groups in total cost for the within trial analysis will be assessed using a general linear model (gamma family, log link). QALYs will be estimated for the within trial analysis based on responses to the SF-12 Short Form QoL instrument and Australian utility algorithm using an area under the curve approach. Differences between groups will be tested using a student t-test where the assumption of normal distribution holds and generalised linear models in the case of non-normally distributed data. Multi-level regression analysis to correct for correlation of error at each cluster will be used to characterise uncertainty around the estimated incremental net monetary benefit for the within trial analysis. A Markov model will also be used to estimate the costs and QALYs over a patient's lifetime under a range of extrapolation scenarios. The determination of whether RELEASE or RELEASE+ represents value for money will be determined based on ranking of their incremental net monetary benefit values. A cost-effectiveness acceptability curve (CEAC) will assess the probability that RELEASE and RELEASE+ is the most cost-effective option over a range of threshold values.

### Evaluation of implementation strategies and implementation outcomes

We will use a multi-method approach to evaluate ***determinants*** and ***implementation outcomes*** including *acceptability* of RELEASE and RELEASE+ to patients and GPs (e.g., content and complexity); *appropriateness* - whether GPs consider RELEASE or RELEASE+ a 'good fit' for practice workflows and could be translated into routine care; *adoption* - number of practices and GPs approached to take part, interested in taking part, and taking part, number of patients de-selected by GPs and why, % of eligible patients that enrol; *fidelity:* % GPs engage with the one-on-one outreach training and interactive e-Learning module, % patients attend medication review and follow-up visits with GP.

*Quantitative data:* implementation and participation tracking data (*fidelity and adoption outcomes*), and GP log recording reasons for patient de-selection (*adoption outcomes*). Quantitative data will be analysed using descriptive statistics.

*Qualitative data:* a separate ethics application will be submitted to conduct in-depth interviews with a purposive sample of 15-20 GPs (both intervention and usual care) and 15-20 patients (both intervention and usual care). Recruitment for these interviews will commence at about 6-months post the first practice randomisation. Interviews will take place face-to-face or via telephone or zoom guided by an interview schedule. Interviews will be audio-recorded with permission and transcribed verbatim. Audio transcripts will be de-identified and potentially identifiable information will be removed. Interviews will be analysed using a combination of inductive and deductive coding, beginning with an emphasis on barriers and facilitators and expanding to measure implementation outcomes including acceptability and appropriateness. Our ***theory informed*** deductive analysis will be guided by the five domains of the Consolidated Framework for Implementation Research to identify determinants crucial in understanding what happens (and why) and optimising our likelihood of effecting change through identification and resolution of actionable ***barriers*** and enhancement of identified ***enablers***. Reporting will follow the Consolidated Criteria for Reporting Qualitative Research.

## Oversight and Monitoring

## Investigator Committee

An **Investigator Committee** chaired by PI Wallis includes all investigators, and representatives from the researcher team. The role of the committee is to:

(i) Ensure academic rigour
- Affective academic oversight of the quality of the research
- Provide competent advice to the RELEASE Project Team, including advice on methodology and research outcomes
- Assess RELEASE progress, including monitoring of potential risks

(ii) Advise and provide comment on new research, including international research, relevant to RELEASE

Responsibilities of Investigator Team include to:

(i) Understand RELEASE goals, objectives, and desired outcomes.
(ii) Take an interest in the project's outcomes and overall success.
(iii) Prepare for, attend and participate in scheduled meetings wherever possible to maintain continuity and consistency
(iv) Support open discussion and debate and encourage fellow Committee members to voice their insights.

The Committee Meets as needed but no less than 3 times per year. Meetings will be held face-to face, or via videoconference (Zoom).

## Steering Committee

A **Steering Committee** chaired by PI Wallis includes relevant members of the investigative and research team as well as representatives from RACGP, ACCRM, RANZCP, PHNs, rural and urban general practice, mental health policy, pharmacy and lived experience representation. The role of the Steering Committee is to:

(i) Use influence and authority to assist RELEASE in achieving its outcomes
(ii) Championing of RELEASE
(iii) Inform strategic directions and the achievement of strategic goals relevant to stakeholder groups and wider health policy
(iv) Provide guidance on appropriate dissemination channels and develop a long-term governance framework that supports scalability of RELEASE

Responsibilities of Steering Committee members include to:

(i) Understand RELEASE goals, objectives, and desired outcomes.
(ii) Understand and represent the interests of project stakeholders.
(iii) Take an interest in the project's outcomes and overall success.
(iv) Prepare for, attend and participate in scheduled meetings wherever possible to maintain continuity and consistency
(v) Support open discussion and debate, and encourage fellow Steering Committee members to voice their insights.

The committee will meet 2 times in years 2 and 3. Meetings will be held face-to face, or via videoconference (Zoom).

### Data Monitoring and Safety Committee

A **Data Monitoring and Safety Committee** will be chaired by PI Walls and will include PI Donald, CI Horowitz, Practice Liaison Officer and other appropriate research staff to manage and assess relevant research risks (Appendix S). The role of the Committee includes:

(i) Incident reporting
- Develop incident (including hospitalisations, deaths and suicide attempts) reporting proforma and processes for GPs.
- Monitor and report any serious adverse events to UQ HREC

(ii) Data confidentiality
- Establish data confidentiality statement and best practices to ensure appropriate access, distribution and use of confidential data.
- Verify staff signing of data confidentiality agreement as necessary.

The committee meets as needed but at least once per year. Meetings will be held via videoconference (Zoom).

## Data management

### REDCap Database

REDCap is a secure web application for building and managing online surveys and databases. The University of Queensland has been a REDCap consortium member since June 2012, having a full REDCap server available to staff in October 2013. UQ's REDCap server provides a web interface using the industry standard SSL (SHA256 RSA 2048 bit keys) to ensure data privacy. The entire REDCap database is backed up daily to a secure file server in the same facility with access restricted to the IT administration staff. Access to the REDCap service is via the UQ network using SSL (secure sockets layer) through the University's firewalls. Alterations to the data are logged by REDCap, these logs are made available to the appropriately privileged project staff. Login usernames are allocated by the REDCap administrative staff using email addresses supplied by the individual study staff. Passwords are managed by the REDCap system and the user.

No individuals will be identified in any findings reported.

### Data storage

All quantitative datafiles will be stored on the secure RDM with access restricted to the relevant research team members. UQRDM complies with the Australian Code for the Responsible Conduct of Research which assigns researchers and their institutions a shared responsibility to manage research data and primary materials well, by addressing aspects of ownership, storage and retention, and accessibility.

## Results, Outcomes and Future Plans

### Data retention

After completion of the data collection phase, data related to individuals will be de-identified and coded in a potentially re-identifiable format and stored on the secure, password protected UQRDM. Storing the data in a re-identifiable format is necessary to enable linking with MBS, PBS and Queensland Health hospital and outpatient service utilisation data (through a Public Health Act application) if funding for this is secured and ethics approval obtained.

At this stage, electronic information generated from this research will be held indefinitely. This will allow for access to the data at a later date should this be required. This will enable the full potential and value of the data produced to be realised via data sharing processes. To ensure data sharing is undertaken appropriately and to safeguard our participants, data sharing protocols will be used.

Paper based records produced from this research will be destroyed 15 years after the last publication related to this is produced; this is in line with the NHMRC Code for the Responsible Conduct of Research guideline. Paper based records will be scanned and then destroyed by shredding to ensure their security.

### Dissemination plans

We will work with the Steering Committee in year 3 to determine the most appropriate dissemination channels, which will include:

- Summaries for Practices
- Publication in peer-reviewed journals
- Publicise through general practice-based research networks
- Summary results on RELEASE and UQGP research network websites

## Outcomes and significance

This project will enable implementation of the RELEASE antidepressant discontinuation model in Australian general practice. RELEASE significance is substantial, redressing antidepressant prescribing in general practice, the Productivity Commission's "priority reform", to "*address adverse outcomes*" (p.3).[15] Key project outcomes include:

1. **An effective antidepressant discontinuation model:** that includes practical resources where currently there are none, to address an area of unmet need.
2. **Proven implementation strategy:** the RELEASE model is generalisable, using existing practice staff to enable widespread transformation in general practice.
3. **Improved Australian health outcomes:** decreasing long-term antidepressant use and associated harms and costs to improve patient quality of life.
4. **Education/training resource:** our evidence-based approach will provide sustainable access to educational opportunities and online resources for GPs, including for rural and remote Australia.
5. **Maximise cost-effectiveness and sustainability of implementation:** outcomes will provide evidence of cost-effective ways to implement the RELEASE model and achieve benefits sustainably.

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