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Extended Research Article

Internet and telephone intervention to support patients discontinuing long-term antidepressants in primary care: the REDUCE research programme including RCT

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This article

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Abstract

Background: There is significant concern about increasing long-term antidepressant use in Western countries, much of which is not evidence-based. Median duration of treatment is more than 2 years in the United Kingdom, and more than 10% of adults are taking antidepressants, risking potentially significant adverse effects, particularly for older patients.

Objectives: To develop internet- and telephone-based support for practitioners and patients, through a process of co-design, and to determine its effectiveness and cost-effectiveness in helping people discontinue antidepressants without increasing depression, in a randomised controlled trial.

Design: Two systematic reviews (one qualitative); qualitative interviews with patients; qualitative interviews and focus groups with healthcare practitioners; co-production of online interventions with patients and practitioners; feasibility randomised controlled trial; definitive non-inferiority cluster randomised controlled trial with health economic evaluation; and quantitative and qualitative process evaluations. A booklet and video version of the patient intervention was also developed in Urdu.

Setting: Primary care (131 general practices in England and Wales).

Participants: Adults on antidepressant treatment for more than 1 year for a first episode of depression, or more than 2 years for recurrent depression, who were no longer depressed or judged to be at significant risk of relapse.

Interventions: Tailored internet support (*ADvisor* for patients, and *ADvisorHP* for health professionals), plus three telephone support calls from psychological well-being practitioners.

Primary outcome: Depressive symptoms on the Patient Health Questionnaire-9 items questionnaire at 6 months.

Secondary outcomes: Depressive symptoms over 12 months, antidepressant discontinuation, anxiety, quality of life, withdrawal symptoms, adverse events, mental well-being, patient enablement, patient satisfaction, health service use and costs over 12 months.

Sample size: The original sample size calculation gave a target of 402 patients for 90% power with one-sided significance of 2.5% to determine non-inferiority of the intervention, within 2 points on the Patient Health Questionnaire-9 items. This was reduced to 360 on finding a significant correlation between baseline and follow-up values for the Patient Health Questionnaire-9 items part-way through the trial.

Randomisation: Remote cluster randomisation of practices by computerised sequence generation, with minimisation by practice size, urban/rural location and deprivation index.

Blinding: Participants and researchers could not be blinded given the pragmatic open design, but self-complete measures avoided observer rating bias, and analyses were conducted blind.

Analyses: Linear mixed modelling was used to determine differences in outcomes, adjusting for previous depression, baseline outcome values, baseline anxiety, sociodemographic characteristics, and practice as a random effect. Primary analysis was performed by intention to treat, with per-protocol and complier-average sensitivity analyses. Multiple imputation was used to account for missing values.

Qualitative interviews: Semistructured topic guides were used for interviews and focus groups, informed by normalisation process theory, which were audio-recorded, transcribed verbatim and analysed using reflexive thematic analysis.

Results: Systematic reviews, qualitative interviews and focus groups indicated that barriers to discontinuing treatment include a fear of relapse of depression and withdrawal symptoms. If practitioners do not broach possible discontinuation, patients will usually continue treatment without questioning it. Patients wanted information on antidepressant mechanisms and effects, withdrawal symptoms and coping strategies. Practitioners wanted guidance on initiating discontinuation, antidepressant tapering regimens, and distinguishing withdrawal from relapse.

The definitive trial randomised 330 patients (5% of those approached; 178 in intervention practices and 152 in controls), of whom 275 (83%) were followed up at 6 months, and 240 (73%) at 12 months. Mean Patient Health Questionnaire-9 items scores were slightly higher among controls at 6 months [5.0 vs. 4.0; adjusted difference 1.07 (95% confidence interval 0.09 to 2.06; $p = 0.033$)]. Antidepressant discontinuation rates at 6 months were slightly higher in the intervention arm, but not significantly (45.5% vs. 41.9% in the control arm). Antidepressant withdrawal symptoms and mental well-being were significantly better in the intervention arm. There were no significant differences in anxiety, quality of life, adverse events, patient enablement, or satisfaction with care.

The adjusted mean cost of services used was lower in the intervention arm by −£69 (95% confidence interval −£77 to £207). The incremental cost-effectiveness ratio was a mean saving of −£2839 per quality-adjusted life-year gained (95% confidence interval −£30,024 to £22,227). The probability of the intervention being cost-effective compared to review alone, at the National Institute for Health and Care Excellence thresholds of societal willingness to pay of £20,000 and £30,000 per quality-adjusted life-year, was > 89% for both.

Qualitative interviews suggested advice to taper slowly, and information on the difference between relapse and withdrawal symptoms, contributed significantly to the success of the interventions.

Participants were well and willing to attempt antidepressant discontinuation, and general practitioners excluded people considered at high risk of relapse of depression. This may explain why more than 40% of participants in each arm discontinued. The results may not generalise to an unselected sample of people on long-term antidepressants, including people at greater risk of relapse.

Conclusions: Comparatively high rates of discontinuation of long-term antidepressants are achievable through enabling patients, who are ready to consider stopping them, to get tapering advice and support from their general practitioners. Tailored internet and psychologist telephone support may help protect patients coming off long-term antidepressants against depressive and withdrawal symptoms, and conserve mental well-being. The interventions appear highly cost-effective at thresholds for societal willingness to pay used by the National Institute for Health and Care Excellence.

Trial registration: Workstream 4 (feasibility trial) is registered as International Standardised Randomised Controlled Trial Number ISRCTN15036829 and Workstream 5 (definitive trial of effectiveness and cost-effectiveness) is registered as ISRCTN12417565.

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Contents

List of tables

List of figures

List of supplementary material

Report Supplementary Material 1	Guide for Psychological Well-being Practitioner telephone support calls
Report Supplementary Material 2	Workstream 4 acceptance checklist for clinical effectiveness pilot trials (ACCEPT)

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/BTBL3945).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

AMED	Allied and Complementary Medicine Database
ASEC	Antidepressant Side Effects Checklist
BCW	behaviour change wheel
CACE	complier-average causal effect analysis
CBT	cognitive–behavioural therapy
CEAC	cost-effectiveness acceptability curve
CEP	Council for Evidence-based Psychiatry
CEQ	Collective Efficacy Questionnaire
CONSORT	Consolidated Standards of Reporting Trials
CSFQ-C	Changes in Sexual Functioning Questionnaire
CSRI	Client Service Receipt Inventory
DESS	Discontinuation Emergent Signs and Symptoms Scale
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
GAD-7	Generalised Anxiety Disorder-7
GP	general practitioner
HCP	healthcare practitioner
ICER	incremental cost-effectiveness ratio
IMD	Index of Multiple Deprivation
ITT	intention to treat
MBCT	mindfulness-based cognitive therapy
MHN	mental health nurse
MISS	Medical Informant Satisfaction Scale
NICE	National Institute for Health and Care Excellence
NP	nurse practitioner
NPT	normalisation process theory
PBA	person-based approach
PEI	Patient Enablement Instrument
PHE	Public Health England
PHQ-9	Patient Health Questionnaire-9 items
PPA	per-protocol analysis
PPI	patient and public involvement
PSS	Personal Social Service
PSSRU	Personal Social Services Research Unit
PWP	psychological well-being practitioner
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
REC	Research Ethics Committee
SAP	statistical analysis plan
SF-12	Short Form questionnaire-12 items
SSRI	selective serotonin reuptake inhibitor
WEMWBS	Warwick-Edinburgh Mental Wellbeing Scale
WS	workstream

Plain language summary

The REDUCE programme developed and tested internet and telephone support for people trying to stop long-term antidepressants when they no longer needed them for depression.

Our searches for previous research, together with patient and practitioner interviews, showed that stopping antidepressants can be difficult, due to fear of depression returning, and withdrawal symptoms.

Working with patients, general practitioners and other practitioners, we developed two websites to provide information and advice on stopping antidepressants, called *ADvisor* for patients and *ADvisorHP* for health professionals. We also developed guidance for psychological well-being practitioners to give support to people coming off antidepressants, through three telephone calls.

We tested this approach in a trial. One hundred and seventy-eight people registered with 66 randomly selected practices were offered general practitioner treatment reviews plus internet and telephone support, and their success with stopping antidepressants was compared with success among 152 people from 65 practices offering general practitioner reviews alone.

We found that people given the telephone and internet support in addition to the general practitioner treatment review had slightly better depression scores than those without the additional support (4.0 vs. 5.0), but the difference in antidepressant discontinuation rates was not significant (46% vs. 42%). People who received the support also had fewer withdrawal symptoms, and better mental well-being. This seemed to be because the support included advice to taper treatment slowly, and gave reassuring information on the difference between symptoms of depression and withdrawal symptoms, and what to do about them if they developed.

The general practitioner's support was found to be important to patients. Both groups in the trial had little change in their quality of life, and harmful events were few and usually not serious. So, attempting to taper off long-term antidepressants is a safe thing to do as long as the general practitioner is monitoring a person's progress and can adjust treatment as necessary.

Scientific summary

Background

There is significant concern about increasing long-term antidepressant use in Western countries, much of which is not evidence-based. The median duration of treatment is more than 2 years in the UK, and more than 10% of adults are taking antidepressants, risking potentially significant adverse effects, particularly for older patients. Patients may continue treatment due to fear of relapse of depression, or to experiencing withdrawal symptoms which can make discontinuation difficult. If practitioners do not broach attempting discontinuation, then patients will assume they must continue to take repeat prescriptions.

Many patients want the option of being reviewed and attempting discontinuation with appropriate support, but general practitioners (GPs) often lack experience in reducing antidepressants flexibly, and their advice to withdraw treatment may not be successful. Trials of simply prompting GPs to review patients eligible for antidepressant discontinuation have found only 6–8% of patients succeed.

Patients anxious about discontinuing treatment may have to be persuaded of the potential benefits, then actively engaged in the process and supported through withdrawal. We considered that providing self-management internet and telephone support for patients and practitioners might facilitate antidepressant withdrawal at scale, without adding to the workload of primary care or psychological therapies.

Aim and objectives

Aim

To identify feasible, safe, effective and cost-effective ways of helping patients taking long-term antidepressants to withdraw from treatment where it is appropriate for them to do so.

Objectives

1. To conduct a systematic review of quantitative and qualitative literature, to identify interventions that have been used to help patients withdraw from antidepressant treatment.
2. To identify factors that promote or inhibit the implementation of treatment withdrawal, through interviews with patients taking them long term, and focus groups with GPs, nurse practitioners (NPs) and primary care mental health workers who treat patients.
3. To develop an internet-supported cognitive–behavioural therapy-based intervention for primary care practitioners and patients to support patient withdrawal from antidepressant treatment, through a process of co-design and co-production with practitioners and patients, taking their views into account throughout its development and implementation, in an iterative process.
4. To determine the effectiveness of the intervention in helping patients stop treatment through a randomised controlled trial (RCT), and to estimate its cost-effectiveness from a health service perspective.
5. To build a translational framework describing the intervention and addressing how it should be delivered, including overcoming practitioner and patient-related barriers, to facilitate implementation of treatment cessation.

Methods

We conducted six workstreams.

In workstream 1 (WS1), two systematic reviews were completed: one of quantitative studies of interventions to facilitate antidepressant discontinuation, and one of qualitative studies of barriers and facilitators to antidepressant discontinuation identified by patients and health professionals.

In workstream 2 (WS2), qualitative interviews were carried out with people taking long-term antidepressants, and focus groups and interviews were carried out with GPs, NPs and mental health practitioners.

In workstream 3 (WS3), we developed internet-based interventions for patients ('*ADvisor*') and primary care practitioners ('*ADvisorHP*') to support antidepressant discontinuation, through co-design and co-production with patients and practitioners, taking their views into account in an iterative process. Prototype interventions were tested using 'think-aloud' interviews where participants described their opinions while using the prototypes. We also developed guidance for psychological well-being practitioners (PWPs) to provide support to people coming off antidepressants through three telephone calls, one of 30 minutes and two follow-up calls of 15 minutes.

Workstream 4 (WS4) was a feasibility RCT to assess procedures for a definitive RCT to follow, including practice and patient recruitment (from both medical record searches and opportunistically in consultations); follow-up rates; the acceptability and feasibility of our internet and PWP telephone interventions; the acceptability and feasibility of the trial procedures and outcome measures; and participants' views of involvement in the trial, through qualitative interviews with patients and practitioners.

Workstream 5 (WS5) was a definitive non-inferiority cluster RCT with health economic evaluation; and quantitative and qualitative process evaluations. Randomisation was by remote computerised sequence generation, with minimisation by practice size, urban/rural location and deprivation index. Participants and researchers could not be blinded given the pragmatic open design, but self-complete measures avoided observer rating bias, and analyses were conducted blind.

The participants were adults on antidepressant treatment for more than 1 year for a first episode of depression, or for more than 2 years for a recurrent episode, who were no longer depressed or judged to be at significant risk of relapse.

The primary outcome was depressive symptoms on the Patient Health Questionnaire-9 items (PHQ-9) questionnaire at 6 months. Secondary outcomes were depressive symptoms over 12 months; antidepressant discontinuation at 6 and 12 months; withdrawal symptoms at 3 and 6 months; and anxiety, quality of life, adverse events, mental well-being, patient enablement, patient satisfaction, health service use and costs over 12 months.

The original sample size calculation gave a target of 402 patients for 90% power with one-sided significance of 2.5% to determine non-inferiority of the intervention, within 2 points on the PHQ-9. This was reduced to 360 on finding a significant correlation between baseline and follow-up values for the PHQ-9 part-way through the trial.

Linear mixed modelling was used to determine differences in outcomes, adjusting for previous depression, baseline outcome values, baseline anxiety, sociodemographic characteristics and practice as a random effect. Primary analysis was by intention to treat, with per-protocol and complier-average sensitivity analyses. Multiple imputation was used to account for missing values.

A quantitative process evaluation looked at participants' use of the online interventions (automatically recorded), and the fidelity of the PWP calls against the guidance provided. A qualitative process evaluation involved interviewing practitioners and patients. Semistructured topic guides were used for interviews which were audio-recorded, transcribed verbatim and analysed using reflexive thematic analysis. Normalisation process theory was used as a framework to identify issues related to implementing the interventions in practice beyond the trial.

An additional workstream was requested by the Programme Grants Board, aimed at developing a prototype intervention for a major ethnic minority group. We worked with Urdu-speaking people of South Asian origin in the north-west of England to develop a culturally acceptable version of the *ADvisor* patient intervention using the methods of co-production used in WS3.

Results

Our systematic reviews, qualitative interviews and focus groups indicated that barriers to discontinuing treatment include a fear of relapse of depression and withdrawal symptoms. If practitioners do not raise possible discontinuation,

patients will usually continue treatment without questioning it. Patients wanted information on the underlying mechanisms, effects and side effects of antidepressants, withdrawal symptoms and coping strategies. Practitioners wanted guidance on initiating discontinuation, antidepressant-tapering regimens, and distinguishing withdrawal from relapse.

Practices and patients

In the feasibility trial, we successfully recruited 14 practices, 7 randomised to each arm. In the definitive trial, we recruited 131 practices, 66 randomised to the intervention arm, and 65 to the control. We recruited a total of 330 patients (178 in intervention practices and 152 in controls), of whom 275 (83%) were followed up at 6 months, and 240 (73%) at 12 months. The 330 included 52 recruited for the feasibility trial, which was approved as an internal pilot as the protocol was not changed significantly.

Clinical outcomes

The intervention proved non-inferior to the control for the development of depression. In fact, mean PHQ-9 depression symptom scores were slightly higher among controls at 6 months {5.0 vs. 4.0; adjusted difference 1.07 [95% confidence interval (CI) 0.09 to 2.06; $p = 0.033$]}. Antidepressant discontinuation rates at 6 months were slightly higher in the intervention arm, but not significantly (45.5% vs. 41.9% in the control arm).

Over 6 months antidepressant withdrawal symptoms on the Discontinuation Emergent Signs and Symptoms Scale were fewer in the intervention arm, although the difference, while statistically significant, was small [adjusted mean difference −1.56 points (95% CI −2.85 to −0.26); $p = 0.018$]. Similarly, over 12 months, mental well-being scores on the Warwick-Edinburgh Mental Wellbeing Scale were slightly better in the intervention arm [mean difference 2.17 points (95% CI 0.21 to 4.14); $p = 0.030$]. There were no significant differences in anxiety, quality of life, patient enablement, or patient satisfaction. Adverse events occurred for 15% of patients in each arm, which were mostly not serious. One serious adverse reaction to discontinuation occurred in each arm.

Health economic outcomes

The adjusted mean cost of services used was lower in the intervention arm by −£69 (95% CI −£77 to £207). The incremental cost-effectiveness ratio was a mean saving of −£2839 per quality-adjusted life-year gained (95% CI −£30,024 to £22,227). The probability of the intervention being cost-effective compared to usual care at the National Institute for Health and Care Excellence thresholds of societal willingness to pay, of £20,000 and £30,000, was > 89% for both.

Qualitative interviews

Qualitative interviews suggested successful antidepressant discontinuation was more likely if the invitation for a review came at a time when the person was feeling well and stable, and ready to try to discontinue. Advice to taper slowly, and information on the difference between relapse and withdrawal symptoms, seemed to contribute significantly to the success of the interventions.

Urdu version of ADvisor

Interviews and focus groups with Urdu-speaking patients, practitioners and community leaders informed the development of a prototype Urdu version of the *ADvisor* intervention for patients, but as a booklet and online videos, as participants did not consider an interactive online intervention would be acceptable. The prototype was optimised through think-aloud interviews and is available for future testing and implementation.

Limitations

In our WS1 qualitative evidence synthesis, coding to generate themes was performed by one researcher and discussed with two others, due to time constraints. Similarly, in the systematic review, one researcher performed study selection, data extraction and risk of bias assessment, checked by another reviewer. Ideally, coding, study selection, data extraction and bias assessment would be done independently by two reviewers.

The use of focus groups to elicit barriers and facilitators to discontinuation from health professionals in WS1 facilitated discussion and candid responses from participants. However, discussions can become polarised or influenced by dominant members in a group, and some participants' views may be less well represented.

The GPs we enrolled were interested in mental health research and may be more knowledgeable than practitioners generally, which may explain why some felt that some of the information in *ADvisorHP* was not new. Other GPs may have learnt more from the intervention, particularly trainees and GPs new to UK practice. The development work included only two NPs, which made it difficult to identify differences between GP and NP perspectives.

In the main WS5 trial, we recruited 330 patients, falling short of the (revised) target sample size of 360. We had sufficient power to address the primary outcome, as 6-month follow-up (83%) was greater than the 80% predicted. However, only 73% were followed up at 12 months which reduced the power of the sample to exclude differences in depression and discontinuation of antidepressants developing beyond 6 months. In the missing cases multiple imputation analysis, while the non-inferiority conclusion remained, the intervention no longer appeared superior to the control.

Vetting by GPs of patient lists generated by the medical records searches would have introduced selection bias, towards including people who were well and considered ready to try tapering by the GP, and excluding people who were considered to be at greater risk of relapse. This may explain why we found a high rate of discontinuation compared to the 6–8% found in previous trials of GP reviews. In the previous trials, patients identified from medical records searches were approached directly by the researchers and many were found to be unwilling to try discontinuing their antidepressants.

Finally, we had no information on the numbers of patients in each arm who did not taper their antidepressant, or embarked on tapering, but subsequently resumed the original dose. The qualitative interviews indicated some patients went quickly back on to their original dose of antidepressants when new symptoms developed, and were not supported by their GPs to try and get through them by going back up in dose temporarily, but we do not know how many did this.

Conclusions

Rates of discontinuation of long-term antidepressants of more than 40% are achievable through enabling patients who are ready to consider reducing them to get active support from primary care practitioners.

Online and telephone support appears to help protect patients against depressive and withdrawal symptoms, and conserve mental well-being, although the benefits are modest. Advice to taper slowly and information on differences between relapse and withdrawal symptoms appear to be major factors contributing to successful discontinuation.

Adverse events from attempting discontinuation are likely to be few, and usually not serious, so this is a relatively safe thing to do in primary care, where relapse of depression is likely to occur in a minority of patients, and treatment can be quickly restarted if patients are monitored. Patients may be greatly reassured by being able to ask questions through telephone support calls.

Implications for practice and future research

In the definitive RCT, only 8% of patients approached were willing to take part and only 5% could be consented and enrolled in the trial. However, uptake in routine clinical practice is likely to be higher now the interventions have been shown to be effective.

Our qualitative process evaluation suggested that implementation methods need to include:

1. Creating opportunities for discussing antidepressant discontinuation (more active reviews of people on long-term treatment and fewer routinely repeated prescriptions).
2. Flagging the electronic records of patients who qualify for considering discontinuation.
3. Delegation of medication reviews and tapering support to other professionals besides GPs.
4. Making patients more aware of how withdrawal symptoms differ from relapse, and how to cope with them.
5. Adopting tapering regimens over months rather than weeks, to reduce the occurrence and severity of withdrawal symptoms, with flexibility to go back up in dose if necessary.
6. Proactive follow-up during tapering where possible, including brief telephone calls or text messages.
7. Embedding links to alternative treatment resources in the electronic patient record.

Future research should:

1. Try to engage a greater proportion of people taking antidepressants, including younger people, unemployed people, people from deprived areas and of ethnic minority groups.
2. Follow people more closely through their attempts to taper antidepressants, record the development of depressive and withdrawal symptoms, distinguish where possible between withdrawal and relapse, and determine relationships between symptoms and progress in tapering.
3. Assess barriers and facilitators to wider implementation of support to practitioners and patients in clinical practice for antidepressant discontinuation.
4. Assess the potential for involvement in deprescribing of other healthcare professionals (HCPs) besides GPs and NPs, in particular pharmacists, and mental health professionals.
5. Compare new interventions against best practice, that is active review of medication by HCPs, rather than usual care, which currently often means no active review for many people taking long-term antidepressants.

Permissions

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Synopsis

Context for the REDUCE programme

A review article on the background to the programme was published in Kendrick.[1]

There is significant concern about increasing long-term antidepressant use, which doubled in Western countries from 2003 to 2013.[2] By 2014, the Health Survey for England found that 11% of adults were taking antidepressants, including 17% of women in economically deprived areas.[3] This cost more than £280M annually.[4] In 2018, Public Health England (PHE) reported that 7.3 million adults in England (16.6%) were taking antidepressants,[5] and by 2022 the figure was 8.3 million.[6]

While antidepressants are used for insomnia and pain, the large majority are prescribed for depression,[3,7] and the main reason for increased prescribing is that patients are being treated for longer.[8–10] Median length of treatment is more than 2 years in the UK,[11,12] and 5 years in the USA.[13,14]

Long-term antidepressants are appropriate for some patients to minimise the risk of relapse.[15,16] However, most people diagnosed with depression in primary care do not need long-term treatment: 35–60% experience a stable recovery after a first episode, and only 0–17% have a chronic course.[17] National Institute for Health and Care Excellence (NICE) guidance does not recommend long-term antidepressants for first episodes,[18] and surveys of long-term antidepressant users indicate 30–50% have no evidence-based indications to continue treatment.[19–24]

The most commonly prescribed antidepressants, selective serotonin reuptake inhibitors (SSRIs), can cause side effects including weight gain, sleep disturbance, sexual dysfunction and gastrointestinal bleeding.[25] Antidepressant use in older patients is associated with increased risks of stroke/transient ischaemic attack, falls, fractures, epilepsy/seizures, hyponatraemia and death.[26]

However, stopping antidepressants risks withdrawal symptoms including anxiety, mood swings, lethargy, sleep disturbance, dizziness and sensory symptoms including distressing 'brain zaps'.[27] A systematic review of 14 studies suggested 56% of people discontinuing antidepressants experienced withdrawal effects, 46% reporting them as 'severe'.[28] The mood symptoms may appear to be a recurrence of the original problem requiring treatment,[27] and restarting medication before withdrawal symptoms can resolve spontaneously quickly relieving the symptoms, reinforcing this perception.

Unfortunately, medication reviews of patients taking antidepressants by general practitioners (GPs) decline in frequency with longer use,[29,30] reducing opportunities to review the appropriateness of continuing treatment. Patients on repeat prescriptions, reviewed infrequently, may assume they are expected to continue treatment without checking back with the doctor.[31]

The rationale for taking SSRIs presented by GPs in the past was a deficiency of serotonin in the brain, which has not been demonstrated, but patients may have concluded, erroneously, that treatment had to be for life.[24] Qualitative research shows many patients believe they need indefinite treatment, fearing that discontinuation would threaten their stability,[32] and many GPs report they feel they need to keep prescribing them, despite significant reservations.[33]

Importance and relevance of the REDUCE programme

Our pre-programme patient and public involvement (PPI) consultation, and discussions with Depression Alliance and the Council for Evidence-based Psychiatry (CEP), revealed that many patients were not happy with taking antidepressants long term and wanted the option of being reviewed and attempting withdrawal with appropriate support.

However, GPs often lack experience in reducing antidepressants flexibly, and their advice to withdraw treatment may not be successful. Simply prompting GPs to review patients eligible for withdrawal was tested in a RCT in the Netherlands and found to be ineffective, with only 6% discontinuing in the intervention group, and 8% in the control.[23,24] Similarly, an uncontrolled trial of pharmacist-prompted GP review of long-term users in Scotland resulted in only 7% stopping treatment.[12] Therefore, it appears that without a specific intervention addressing patient and practitioner behaviours, many patients will continue antidepressants unnecessarily.

Tapering off treatment in primary care when appropriate is likely to be possible for many people, without greatly increasing the risk of relapse. A placebo-controlled trial in New Zealand of withdrawal of fluoxetine after 12 months or more of treatment found that 23.3% of patients in the discontinuation arm had a recurrence of depression over 18 months, compared to 10.5% in the continuation arm, an absolute difference of 12.8%.[34] The UK ANTLER placebo-controlled trial of discontinuation of SSRIs and mirtazapine, among patients with recurrent depression, found 56% relapsed after discontinuation, but 39% relapsed in the continuation group.[16] However 47% of patients in the discontinuation arm remained off antidepressants at 12 months follow-up, and there was no difference in quality of life (QoL) between intervention and control arms.[16] So, it appears many primary care patients can discontinue antidepressants without relapsing, at least over 12–18 months.

Cognitive–behavioural therapy (CBT) and mindfulness-based cognitive therapy (MBCT) have been shown to help patients stop antidepressants while preventing relapse in depression and anxiety disorders,[35–39] but these therapies are intensive, and access to them may not be timely. As the numbers of people taking antidepressants unnecessarily run into millions nationally, any intervention has to be readily scalable to make it widely available, and designed to avoid significant additional demands on hard-pressed primary care and NHS Talking Therapies services.

Patients anxious about stopping treatment may have to be persuaded of the potential benefits, then actively engaged in the process and supported through withdrawal. We had experience in Southampton of providing self-management support through the internet and over the telephone for a number of long-term conditions, and considered that online and telephone interventions for patients and practitioners could provide around-the-clock access to support for withdrawal at scale.

Original aims and objectives

Aim

To identify feasible, safe, effective and cost-effective ways of helping patients taking long-term antidepressants to withdraw from treatment where it is appropriate for them to do so.

Objectives

1. To conduct a systematic review of quantitative and qualitative literature, to identify interventions that have been used to help patients withdraw from antidepressant treatment.
2. To identify factors that promote or inhibit the implementation of treatment withdrawal, through interviews with patients taking them long term, and focus groups with GPs, nurse practitioners (NPs) and primary care mental health workers who treat patients.
3. To develop an internet-supported CBT-based intervention for primary care practitioners and patients to support patient withdrawal from antidepressant treatment, through a process of co-design and co-production with practitioners and patients, taking their views into account throughout its development and implementation, in an iterative process.
4. To determine the effectiveness of the intervention in helping patients stop treatment through a randomised controlled trial (RCT), and to estimate its cost-effectiveness from a health service perspective.
5. To build a translational framework describing the intervention and addressing how it should be delivered, including overcoming practitioner and patient-related barriers, to facilitate implementation of treatment cessation.

Summary of any alterations to the programme's original aims/design

There were no significant alterations to the programme's original aims or design.

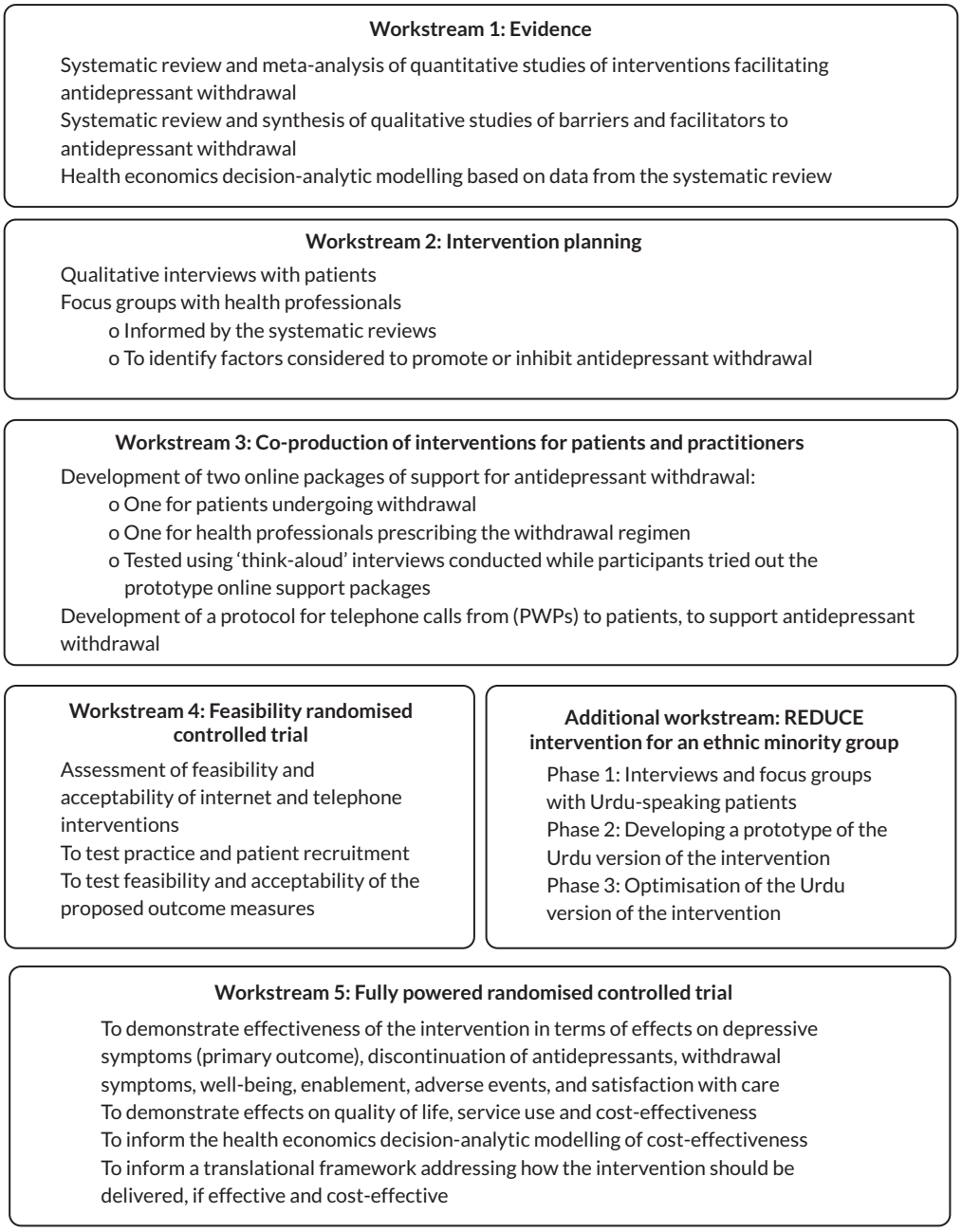

FIGURE 1 Overview of REDUCE workstreams.

The original grant application included an intention to explore whether buddying or peer support may be of benefit. However, early discussions with our patients and public representatives revealed a reluctance to take this on among people who had successfully come off long-term antidepressants, because decisions about whether to stop antidepressants are not clear-cut, unlike decisions to stop using nicotine, alcohol, or illicit drugs, and such decisions were considered to require professional rather than lay advice from a buddy, however experienced.

The original grant application also referred to inclusion of a survey of inappropriate antidepressant treatment among three practices during workstream 2 (WS2). However, this proved a much bigger and more time-consuming task than originally thought, because the experience within practices of identifying patients for whom it was reasonable to attempt tapering off treatment showed this could not be done without a prescriber examining each individual patient's medical record to make decisions about treatment appropriateness. It was, therefore, not pursued, due to a lack of practice staff time to do this for all patients on long-term antidepressants.

The original application also referred to undertaking a retrospective audit of usual practice in control patients over the previous 3 years to determine whether participation in the study changed this.

The original application also included the aim of using the brief Patient Health Questionnaire-9 items (PHQ-2) questionnaire clinically by a primary care mental health worker as a rapid weekly measure of mood, to determine whether the patient needed to return early to their GP. In the event we decided, after discussion with our patient colleagues on the team, that this was too burdensome for patients, and we replaced it with PHQ-9 questionnaire assessments by the psychological practitioners during their support call.

We were unable to carry out planned health economics decision-analytic Markov modelling during WS2, as the systematic review in WS1 did not identify any health economics literature to inform values for the model.

We revised the target sample size for WS5, the definitive RCT of effectiveness and cost-effectiveness of the REDUCE interventions to support antidepressant discontinuation. This was in light of finding a significant correlation between baseline and follow-up values of the primary outcome measure, which reduced the variance in the measure and therefore the number of patients needed to give us 90% power.

We also needed to request two no-cost extensions to the grant to enable completion of the programme, mainly due to delays incurred during the COVID-19 pandemic and the need for primary care to concentrate on COVID-19-related clinical care and COVID-19-related research for several months during 2020.

Programme achievements

The programme successfully achieved its intended objectives to develop and evaluate online interventions to support antidepressant withdrawal for both patients and practitioners, together with telephone support to patients from psychological well-being practitioners (PWPs). The package of support proved feasible, effective in reducing depressive and withdrawal symptoms, and cost-effective at the threshold for implementation in the NHS set by NICE.

In addition, we have produced 9 significant peer-reviewed publications so far (plus another 5 planned), 1 PhD, and 33 peer-reviewed international, national and local conference presentations.

Workstreams

Figure 1 shows the programme workstreams.

Workstream 1: Systematic reviews of interventions facilitating antidepressant cessation, and perceived barriers and facilitators to discontinuation – October 2016–September 2017

Two systematic reviews were completed in WS1: one of quantitative studies of interventions to facilitate antidepressant discontinuation, and one of qualitative studies of barriers and facilitators to antidepressant discontinuation identified by patients and health professionals.

Workstream 1.1: Quantitative systematic review

This work was published in Maund *et al.*[40]

Aim

The aim of the quantitative systematic review was to identify what interventions were effective in helping adult patients successfully withdraw from antidepressant treatment.

Methods

The databases searched were MEDLINE (Ovid), EMBASE (Ovid), PsycInfo (EBSCO*host*), Allied and Complementary Medicine Database (AMED) (EBSCO*host*), the Health Management Information Consortium, OpenGrey and the WHO International Clinical Trials Registry Platform. The searches and selection of papers were carried out by Emma Maund, and Tony Kendrick and Rachel Dewar-Haggart reviewed 10% each as a check. Data extraction was carried out by Emma Maund and checked by Tony Kendrick. The study was registered on PROSPERO (no. CRD42017072702). The search strategy and terms used are available at: www.annfammed.org/content/suppl/2019/01/22/17.1.52.DC1

Results

Overall 4694 potential papers were identified, of which 35 were included, on 15 studies. A flow chart of study selection was included in the published work.

Interventions included: prompted review of patient records by treating physicians; tapering of doses versus abrupt discontinuation; pharmacological strategies (e.g. switching antidepressant to fluoxetine to facilitate slower dose reduction); and psychological therapies including CBT and MBCT. The two primary outcomes were discontinuation of antidepressants and discontinuation symptoms. Secondary outcomes were relapse/recurrence of depression; QoL; social and occupational function, well-being, sexual function and quality of relationships. A narrative review was produced but with meta-analyses for two pairs of studies: one pair on substituting CBT for antidepressants, and one on substituting MBCT.

One trial evaluated a letter to the GP recommending discontinuation. At 12 months, there was no difference in cessation rate (6%) compared to usual care (8%), but a statistically significant greater risk of relapse (36% vs. 14%). Two studies compared CBT + tapering of antidepressants versus clinical management + tapering. There was no difference in the rate of cessation at 20 weeks (95% vs. 91%). However, at 2 years and at 6 years, there was a statistically significant lower risk of relapse in the CBT + tapering group [risk ratios (RRs) 0.34 (0.18, 0.67) and 0.55 (0.37, 0.82), respectively]. Two studies compared MBCT + tapering compared to maintenance antidepressants and reported high cessation rates of 75% at 6 months in one study and 70% at 24 months in the other. Meta-analysis showed that compared to maintenance antidepressants there was no statistically significant difference in relapse at ≥ 6 months [RR 0.90 (0.75 to 1.07)], or in physical, psychological or social QoL (on the World Health Organization Quality of Life-BREF) at ≥ 12 months.

Conclusions and implications for the REDUCE programme

We concluded CBT or MBCT could help patients discontinue antidepressants without increasing the risk of relapse/recurrence but were resource intensive. More scalable interventions incorporating psychological support were needed.

Hence the need for psychological self-help techniques based on CBT and MBCT to be incorporated into the online support for patients we aimed to develop.

Workstream 1.2: Qualitative systematic review and synthesis

This work was published in Maund *et al.*[41]

The author's accepted manuscript is freely available at: https://eprints.soton.ac.uk/425405/; accessed 27 November 2024.

Aim

The aim of the qualitative review and synthesis was to identify, from patient and HCP perspectives, factors that promote or inhibit discontinuation of antidepressant use in adults.

Methods

The databases searched were MEDLINE (Ovid), PubMed, EMBASE (Ovid), PsycInfo (EBSCO*host*), Cumulative Index to Nursing and Allied Health Literature (EBSCO*host*), AMED (EBSCO*host*), the Health Management Information Consortium, OpenGrey and the Networked Digital Library of Theses and Dissertations. Of 3456 potential papers identified, 21 were selected for inclusion by Emma Maund. A flow chart of study selection was included in the study publication. Tony Kendrick and Rachel Dewar-Haggart again reviewed 10% of those identified. Data extraction from the 22 included papers on 22 studies was carried out by Emma Maund and checked by Adam WA Geraghty. The study was registered on PROSPERO (no. CRD42016053941).

Results

A thematic synthesis was performed for patient perspectives only, due to insufficient data from health professional perspectives. Thematic synthesis yielded nine themes: (1) psychological and physical capabilities; (2) perception of antidepressants; (3) fears of relapse and of withdrawal; (4) intrinsic motivators and goals; (5) the doctor as a navigator to maintenance or discontinuation; (6) perceived cause of depression; (7) aspects of information that support decision-making; (8) significant others – a help or a hindrance; and (9) support of other health professionals.

Conclusions and implications for the REDUCE programme

We concluded that barriers and facilitators to discontinuing antidepressant use were numerous and complex. The subthemes of barriers and facilitators associated with each theme are listed in *Appendix 1*, *Table 2*. The most significant facilitator identified, in terms of shaping the consequent intervention, was the doctor's recommendation to discontinue treatment, with active support and guidance. The most significant barrier to be addressed in the intervention was fear of precipitating a relapse of depression, among patients but also among practitioners. Conversations about discontinuation were likely to happen only if GPs broached the issue. This analysis informed the development of prototype internet interventions for both patients and health professionals.

Workstream 2: Qualitative interviews and focus groups with patients and practitioners – October 2016–September 2017

Workstream 2.1: Qualitative interviews with patients

Aim

To identify, characterise and explain patient factors that shape decision-making around antidepressant discontinuation.

Methods

Letters of invitation to be interviewed were sent, between January and May 2017, from seven general practices around Southampton to 254 patients who met the inclusion criteria, which were:

- Patients on antidepressant treatment for more than 1 year for a first episode of depression, or for more than 2 years for a recurrent episode, who were:

- no longer depressed or judged to be at significant risk of relapse
- over 18 years of age
- sufficiently fluent in English to participate.

A total of 19 patients participated in an individual qualitative interview with Samantha Williams, either face to face (18) or over the telephone (1). Normalisation process theory (NPT) informed the development of the semistructured interview topic guides, addressing barriers and facilitators to reducing and stopping antidepressants when appropriate. Interviews were audio-recorded, transcribed verbatim and analysed using inductive thematic analysis, with constant comparison.

There were 12 women and 7 men, ranging in age from 35 to 72 years; 15 were married or widowed and 4 divorced or single, and they had been on antidepressants for between 2 and 20 years. Interviews ranged from 26 to 83 minutes. A further 25 patients expressed an interest but either subsequently declined to take part (8), were ineligible on screening (15), uncontactable (1), or were excluded because data saturation had been reached (1).

Results

Five themes were developed from the patient interviews:

1. the importance of patient–practitioner interactions
2. personal factors that impact on antidepressant discontinuation
3. the impact of patient beliefs and perceptions on intentions towards long-term treatment
4. the influence of significant others (friends, family etc.)
5. what patients wanted to see in the REDUCE intervention.

Patients expected the GP to raise the issue of discontinuation when appropriate, and were less likely to do this themselves, assuming they had to continue their antidepressant in the absence of a request from the doctor to discuss possible discontinuation.

Participating patients reported that personal factors, including age, physical health, alcohol use, sleep patterns and current working conditions, all impacted on their perceived ability to cope without antidepressants. Their personal beliefs and perceptions of medication and withdrawal influenced their decisions about whether or not to try to discontinue long-term treatment. For example, patients who reported that antidepressants were ‘unnatural’ and would have preferred not to take daily medication were more likely to say that they wanted to stop. This contrasted with patients who believed they had a ‘chemical imbalance’ and therefore reported a need to stay on antidepressants long term to keep them well. Other examples of barriers included antidepressants being a ‘crutch to deal with life’, a belief they were ‘not doing any harm’ and fear of both relapse and withdrawal symptoms.

Family and friends could either be a stimulus to cessation or a hindrance. Elements patients wanted to see in the intervention included explanation of how antidepressants work, support for anxiety/fear of discontinuing, coping strategies, and information on withdrawal symptoms, all presented in an accessible and pleasing format.

Conclusions and implications for the REDUCE programme

Patients’ individual perceptions of personal, medication and healthcare factors impact on their decision to withdraw from antidepressants, and these need identifying when discussing their options for continuing or trying to discontinue long-term treatment. The doctor needs to broach the subject or, alternatively, patients need to be empowered to broach the subject.

The patient perspectives were crucial to the process of development of the patient intervention and were incorporated into the publication [5] on the patient intervention from WS3, reported below.

Workstream 2.2: Focus groups and interviews with healthcare practitioners

Aim
To identify, characterise and explain clinician factors that shape decision-making around patients' antidepressant discontinuation.

Methods
Four focus groups and three interviews with 38 health professionals were conducted by Samantha Williams and Wendy O'Brien, and analysed by Samantha Williams using inductive thematic analysis with constant comparison. Participants were 21 GPs, 4 GP assistants, 7 nurses and 6 community mental health team workers/psychotherapists, recruited by letter of invitation from 7 primary care clinical commissioning group areas and 2 community mental health trusts in southern England between January and May 2017. HCPs who expressed an interest were invited to take part in one of four focus groups between March and May 2017. Individual interviews were offered to HCPs from groups under-represented in the sample. Focus groups ranged in duration from 43 to 59 minutes. Emerging findings were discussed in the monthly study management team meetings. Focus groups and interviews continued until data indicated saturation.

Results
Four themes were developed from the health professional focus groups and interviews:

1. the importance of patient–practitioner interactions
2. health professional roles in antidepressant discontinuation
3. factors that impact antidepressant discontinuation
4. what practitioners wanted to see in the REDUCE intervention.

Participants highlighted several barriers and enablers to discussing discontinuation with patients (see *Appendix 2*, *Figure 2*). Responsibility for broaching the subject of discontinuation was again a key factor identified. Practitioners held a range of views around this, with some suggesting it was their responsibility, and others that it rested with the patients. HCPs were concerned about destabilising the status quo, discussed how continuity and knowing the patient facilitated discontinuation discussions, and how confidence in their professional skills and knowledge affected whether they raised discontinuation in consultations with their patients.

Where consultations included discussion of antidepressant withdrawal, HCPs reported that they would provide support and advice, assess risk and manage patient expectations, but the outcome of the consultation could be affected by their own perceptions of the patient, the antidepressant medication, their own beliefs and perceived patient response to treatment. This in turn could affect whether attempting discontinuation of the medication was accepted by the patient. The interactions between barriers and facilitators are illustrated in *Appendix 2*, *Figure 2*.

Further analysis of the health professional interview data using NPT[42] highlighted factors related to promoting engagement with an intervention to support patients discontinuing their antidepressant medication treatment under the four core constructs of NPT:

1. *Coherence:* The results suggested that providing consistent messages about antidepressants, advice to patients, additional support and increased awareness of antidepressant use and withdrawal could have a positive impact on a patient's discontinuation experience.
2. *Cognitive participation:* Agreement that the practitioner is responsible for raising the issue of discontinuation when appropriate, and that this is the right thing for the patient to do, appeared to be crucial. Other factors such as shared decision-making, making time, and involving other HCPs (where appropriate), plus specific actions and/or information in an online intervention, were thought likely to impact considerably on its success.
3. *Collective action:* To enable patient and health professional interaction, practices needed to consider how to optimise use of an intervention, including specific roles for HCPs; better integration of services and continuity of care; standardised procedures/guidelines/advice; easy access for patients; developing in-house protocols to prevent patients getting 'lost in the system'; organisational support; and flagging of potential patients in the electronic medical record.

4. *Reflexive monitoring:* Participants indicated that clear evidence that an intervention was beneficial to patients would encourage its use. A cost-effective intervention that worked well within an organisation could have a positive impact on patient and health professional engagement with discontinuation of antidepressants.

Conclusions and implications for the REDUCE intervention development

The findings indicated a need to consider support for HCPs in the management of antidepressant discontinuation, in particular around their awareness of when and how to initiate discussions about discontinuation with their patients, and their fears of patient relapse. Patient–practitioner interactions, and in particular the questions likely to be raised within a consultation, were also important factors to consider. The practitioner interviews therefore highlighted important topics and information to include in the REDUCE interventions for both patients and practitioners, and how to encourage their use over time.

We carried out two analyses of these data. The initial analysis described above focused on barriers and facilitators to antidepressant discontinuation to identify elements needed in the developing intervention. This was, therefore, included in this report. The subsequent analysis more broadly explored practitioners' perspectives on discontinuation with less focus on intervention development, to address a gap in the literature we had identified in our WS1 qualitative meta-synthesis.

The broader subsequent analysis identified five themes, and was published in Bowers *et al*.[43]

Workstream 3: Co-production of internet-supported patient and practitioner interventions to support antidepressant discontinuation – October 2017–September 2018

Aim

Workstream 3 addressed the third objective of the programme: to develop an internet-supported CBT-based intervention for primary care practitioners and patients to support patient withdrawal from antidepressant treatment, through a process of co-design and co-production with practitioners and patients, taking their views into account throughout its development and implementation, in an iterative process.

The work with patients was published in Bowers *et al*.[44] and the work with practitioners was published in Bowers *et al*.[45]

Intervention development group

Intervention planning and development were led by three health psychologists expert in intervention development: Adam WA Geraghty, Hannah Bowers and Marta Glowacka, and guided by our multidisciplinary study management team, including three PPI contributors, six academic GPs, three psychiatrists, two medical sociologists and an academic pharmacist. The study group helped interpret the findings of the development study and gave feedback on the intervention plans.

Methods

The *person-based approach (PBA)* is a mixed-methods approach developed by Lucy Yardley at the University of Southampton, used to guide the development of behavioural interventions, integrating commonly applied theory and evidence-based methods.[46] It systematically integrates in-depth open-ended qualitative interviews, meta-syntheses and '*think-aloud*' intervention optimisation interviews, with relevant theory and quantitative evidence.

Development of guiding principles

The WS1 systematic quantitative and qualitative reviews of the literature, together with the WS2 qualitative interviews and focus groups with patients and practitioners, identified important barriers and facilitators to antidepressant discontinuation. Based on these findings, guiding principles were developed: broad design objectives that guide the application and implementation of the core intervention strategies, aiming to increase participants' engagement.

Behavioural analysis

Behavioural and implementation theories were drawn on, with triangulation between qualitative and quantitative evidence, and our team's expert views, to identify important components of the intervention. The behaviour change wheel (BCW) and COM-B model of behaviour (capability, opportunity, motivation-behaviour)[47] and our qualitative research informed a *'behavioural diagnosis'*.[48] In behavioural diagnosis, factors likely to affect the target behaviours are considered in terms of capability, opportunity and motivation.

Once we had proposed initial intervention components and content, these were mapped theoretically using the BCW, social cognitive theory,[49] the necessity-concerns framework[50] and NPT.[42] As well as providing a mapped full description of the proposed intervention, this process ensured we did not miss areas of theory that may have improved the interventions.

Logic models

The behavioural analyses in turn informed the development of a '*logic model*' for each of the two interventions (see *Appendix 3*, *Figures 3* and *4*) which were the bases for intervention content selection, writing and development. Logic models represent proposed or hypothesised theories of change outlining problems, issues and barriers, mechanisms of ingredients, and how they may affect target outcomes.[51]

Two prototype interventions (one for patients and one for practitioners) were designed by the start of Year 3 of the programme. The content of each intervention was transferred into online pages using *LifeGuide* software developed at Southampton (www.lifeguideonline.org), and further amendments to the content and presentation of each were made by the development team in discussion with the wider study team, before moving on to their optimisation through further interviews with patients and practitioners.

Think-aloud interviews

The prototype interventions were shown to potential users (15 patients and 19 health professionals) recruited through participating general practices in the South of England, using think-aloud interviews, where interviewees engage with the online intervention by sitting next to the researcher and saying their thoughts about it aloud in real time. After each round of three to five interviews, the data were analysed using the PBA, and the intervention amended according to participant feedback.

There were three rounds of iterations of the patient intervention during the think-aloud interviews. Six themes developed from them, namely: flexible use; familiarity with content; reassurance; utility of information; teaching of useful skills; and feeling supported. Changes to the intervention arising from them included making the tone less formal, revising the introduction navigation and making the wording gentler. The '*My notes*' section was reorganised to be clearer, and buttons to exit the intervention at the end of each module were removed to try to keep patients on-site for longer. In round 3, changes included further revision of the tone, presenting some information in a more aesthetically pleasing way, and removing some links within the intervention to other modules, as these were confusing for patients.[44]

Five themes developed from the practitioner interviews: how the intervention would be used in practice; pitching it at the right level; its evidence base; the need for brevity and quick access; and its usefulness.[44] Practitioners highlighted needing information in easily accessible formats because of time constraints in practice. Some felt that some information was already well known to them but understood why this was included for less experienced practitioners. Practitioners differed in their ideas about how they would use the intervention in practice, with some preferring to read it in its entirety and others wanting to dip in and out as needed. The development work also highlighted a need for clarity about who was responsible for broaching the subject of discontinuation, and guidance on antidepressant tapering schedules. Changes were made to the wording and structure of the intervention in response to the feedback.

Further iterations of the interventions were made at different stages during WS3 and recruitment for interviews ceased when feedback no longer resulted in further changes to the interventions. As a result of these interviews, two interventions were developed that were informed by the needs and preferences of their users. Following the

completion of interviews, the interventions went through rigorous testing to ensure all the digital elements could be accessed from a range of devices including computers, pads and telephones, and still worked as intended. The interventions were then ready for use in the feasibility trial, WS4. The content of the two online interventions is summarised in *Appendix 3*, *Tables 3* and *4*, together with the relevant literature. Screenshots of the opening pages of each intervention are shown in *Appendix 3*, *Figures 5* and *6*.

Example antidepressant tapering schedule from the general practitioner online intervention ADvisorHP

The tapering schedules in *ADvisorHP* were devised by our pharmacist team member, Chris Johnson. Specific tapering schedules were given for all antidepressants except monoamine oxidase inhibitors, as these are usually managed by psychiatrists rather than GPs. The following example is for sertraline, the most commonly prescribed antidepressant in the UK (June 2023).

Schedule A

Suggested starting schedule for a person who has been on it for < 2 years, has no past history of distressing withdrawal, no particular fear of undergoing withdrawal over 6 weeks, and does not wish to prolong tapering, is as follows:

Reduce every 2 weeks: 200 mg – 150 mg – 100 mg – 50 mg – Stop.

However, reducing it every 4 weeks (12 weeks in all) may be more practical for working patients in terms of arranging prescriptions and follow-up appointments in general practice.

Schedule B

For *those who have been on sertraline for more than 2 years, or are particularly anxious about withdrawal*, reducing every 4 weeks initially may be preferred, with follow-ups between each reduction (by telephone or face to face if preferred).

Schedule C

For *patients who have a history of difficult or distressing withdrawal*, an even slower, hyperbolic, withdrawal schedule might be offered, as follows:

Reduce every 4 weeks: 200 mg – 150 mg – 100 mg – 50 mg – 25 mg – 15 mg – 10 mg – 7.5 mg – 5 mg – 2.5 mg – 1.25 mg – Stop.

Ideally, this should be done using a liquid sertraline preparation arranged with the pharmacist. If a liquid preparation is not available, then switching to fluoxetine liquid and tapering that preparation hyperbolically is an option. Fluoxetine 20 mg is equivalent to sertraline 50 mg (and citalopram 20 mg, escitalopram 10 mg, fluvoxamine 50 mg, or paroxetine 20 mg).

A hyperbolic reduction schedule for fluoxetine liquid (4 mg/ml) is given in *Table 1*.

Citalopram 40 mg/ml and escitalopram 20 mg/ml liquid are not recommended due to the difficulty involved in accurately measuring small doses. However, where necessary, similar principles could be applied.

Psychologist telephone support calls

In addition to the online interventions, a schedule for patient telephone support calls from PWPs was developed. The first call was scheduled within 2 weeks of the patient's appointment with their GP to discuss tapering their antidepressants, and designed to last for 30 minutes. Two follow-up calls of 15 minutes each were scheduled, the timing being at the discretion of the patients and PWPs, depending on the progress in tapering.

The calls aimed to support the patient and encourage use of the *ADvisor* online intervention. Checks on symptoms of depression were built in, using the PHQ-9,[52] with which the PWPs were familiar. The PWPs advised patients to contact their GPs if they revealed significant withdrawal symptoms, possible relapse of depression, or thoughts of self-harm.

TABLE 1 Hyperbolic reduction schedule for fluoxetine liquid

Step	mg/day	ml/day
1	20	5
2	12	3
3	8	2
4	4.8	1.2
5	3.2	0.8
6	1.6	0.4
7	0.8	0.2
8	0.4	0.1
9	0	0
10	Then stop	Then stop

The PWP schedules were developed iteratively with the practitioners, to ensure their acceptability and feasibility. The guidance developed is reproduced as *Report Supplementary Material 1*.

Workstream 4: Feasibility randomised controlled trial, to assess acceptability, recruitment, retention and outcome measures – October 2018–November 2019

Aim

Workstream 4 was a pilot feasibility RCT, which aimed to assess the acceptability of the online and telephone interventions, recruitment of practitioners and patients, and acceptability of the planned outcome measures, for a definitive RCT to follow. Success in demonstrating feasibility and acceptability was a prerequisite for receiving funding for the second half of the 6-year REDUCE programme, and proceeding to carry out the definitive trial.

Methods

We aimed to recruit 40 patients, from 14 general practices (7 randomly allocated to the intervention arm and 7 to the control in a cluster randomised design) over 6 months, and follow them up for 6 months. Hannah Bowers led on practice and patient recruitment.

The inclusion and exclusion criteria, design, and recruitment methods were all as described below for WS5, the definitive trial.

We assessed practice and patient recruitment (from both medical record searches and opportunistically in consultations); loss of patients to follow-up; the acceptability and feasibility of our internet and PWP telephone interventions; the acceptability and feasibility of the trial procedures and outcome measures; and participants' views of involvement in the trial through qualitative interviews with patients and practitioners.

Results

Practice recruitment

Twenty-four GP practices expressed an interest in taking part in the study. Three were excluded because they had previously taken part in WS3 and had seen the *ADvisorHP* online intervention which would result in contamination if they were randomised to the control arm. Four later withdrew their expressions of interest; one did not respond to e-mails to arrange a site initiation visit (SIV); one was not within the Wessex region where we had approvals and was

therefore excluded; and one was excluded due to its remote location, making patient visits difficult and costly. We therefore met our target recruitment of 14 practices, and 7 were randomised to each arm by the Southampton Clinical Trials Unit.

Patient recruitment and follow-up

The recruitment methods worked well: both records searches and mail-outs, and opportunistic recruitment. A total of 791 invitation letters were sent from the practices, and 211 responses were received (26.6%) of which 100 were positive about taking part in the trial (12.6%). Of these 100 patients, 80 were screened, and 52 consented to participate, exceeding our target of 40. At the 3-month follow-up point, 42 patients (81%) provided outcome data, and at 6 months we achieved collection of outcome measures for 47 (90%). The Consolidated Standards of Reporting Trials (CONSORT) diagram is shown in *Appendix 4*, *Figure 7*.

Qualitative interviews

We completed 10 qualitative interviews with HCPs (we wanted to interview 15–20 practitioners but only 10 consented in the event). We had 22 expressions of interest in being interviewed from patients but 4 changed their minds, so interviews were conducted with 18 (within our target of 15–20): 13 women and 5 men, aged 37–72 years, 11 from intervention and 7 from control practices, who had been taking antidepressants for between 2 and 20 years.

We conducted rapid analyses on the verbatim transcriptions in order to understand how the trial and interventions should be improved before moving to WS5. Health professional interviews were coded using NPT as a framework, by Claire Reidy (see *Appendix 4*, *Table 5*).

Healthcare practitioner interviews showed overall:

- A positive response to the study: practitioners were keen to take part due to the importance of the topic and the good patient response to invitations.
- Recruitment methods worked well: both records searches and mail-outs, and opportunistic.
- Facilitators to recruitment included funding from the Clinical Research Network, receptionist training, patients arriving at the first GP appointment 'well prepped by the study team', a manageable number of patients (target three per practice), good contact from the study team, and more than one GP per practice working on the study.
- Barriers to recruitment included: GP's lack of time and appointment waiting times, difficulty maintaining continuity with patients, difficulties with record database searches, a negative experience with the first recruit impacting on future recruitment, and an inability in a number of practices to get more than one GP involved.
- Some GPs wanted more data about the safety of supporting people to come off medication and commented that the referral process for involving the PWPs created extra work.
- In common with the qualitative work in WS2 and WS3 was the importance of the trial not adding to, and the intervention reducing, (a) professional and patient risks in participation, and (b) the cognitive and administrative burdens for HCPs participating in the intervention.

All patient transcripts were coded and organised by Samantha Williams into descriptive themes including the patients' experience of being on antidepressants; factors that impacted on their decision to withdraw from treatment; their experiences of reducing antidepressants; and their experiences of participating in the study, including subthemes of: Positive aspects of the study, Negative aspects of the study, Questionnaires, Telephone support calls and the Intervention. See *Appendix 4*, *Table 6* for a full list of the themes and subthemes identified.

Patient interviews showed overall:

- Experience of taking part in the study was mostly positive: it improved motivation and confidence to stop, provided an opportunity to 'think about' medication; improved self-awareness; and patients coming off medication reported experiencing a fuller range of emotions, for example:
  - *'Wasn't expecting how easy it was to reduce'.*
  - *'Got me off some pills in a safe and guided way'.*

- *'Amazed what it's done for my life [. . .] it has turned my life around'.*
- *Would have liked extra support for 'the ones who are left'* (a control arm participant, disappointed to be in the control arm).

- Shopping vouchers were welcomed.
- The extra support was invaluable.
- They were pleased to help themselves and others.
- The study was clear/easy/straightforward, with friendly researchers.

In relation to the PWP telephone support calls, a number of problems were identified, however. Patients were sometimes unclear about the purpose of the calls and role of the PWP. The PHQ-9 checks could feel like tick-box exercises or just data collection rather than support. Some calls were delayed or not delivered at all – in one case a patient had already finished tapering before the first call. Relapse prevention plans were often not covered in any detail and some calls were perceived as too short. Some patients had little choice about the timing of calls due to PWPs' limited availability.

These findings were used to inform changes to the trial procedures for WS5. All intervention arm interviews (both patient and practitioner) were additionally coded using the PBA's Table of Changes to identify positive and negative views about the interventions and cultivate potential changes (see *Appendix 4*, *Table 7* for a summary of changes made).

Conclusions and implications for the REDUCE programme

The WS4 results therefore met the criteria we were set for proceeding to WS5, the main REDUCE RCT, namely:

- recruitment of sufficient practices (14 against the target of 14)
- recruitment of sufficient patients (52 against the target of 40)
- participation rate of patients (12.6% against the target of 9%)
- evidence from patients and practitioners of the acceptability of the procedures and outcome measures
- evidence from patients and practitioners of the engaging aspects of the interventions, although with a need to improve the PWP calls
- acceptable follow-up of patients (90% against the target of 80%).

Specific individual comments made in the qualitative interviews were discussed within the study management team, and a number of changes were agreed to the procedures and interventions (see *Appendix 4*, *Table 7*). The changes were largely to the standard operating procedures for the practice SIVs, induction of practitioners, consenting of patients, and patient assessments at baseline and follow-up. We needed to emphasise the potential help on offer through the on-line interventions, at all of these contacts with practitioner and patient participants.

We decided to change service provider for the PWP calls as the WS2 PWPs were sometimes too busy to be available, and we recognised a need to make the PWP guidance clearer, emphasising the supportive nature of the calls and the opportunity to reassure and encourage patients during their antidepressant tapering.

However, none of the refinements to our procedures required a substantial amendment to the protocol, according to the ACCEPT checklist for clinical effectiveness pilot trials[53] (see *Report Supplementary Material 2*). We were therefore permitted by our Programme Steering Committee and the Programme Grants Board to consider the feasibility trial as an internal pilot, and to include the 52 patients recruited as part of the total sample size required for the definitive trial in WS5.

Workstream 5: Randomised controlled trial of internet and telephone support for antidepressant discontinuation – October 2019–March 2023

Objectives

Workstream 5 addressed the fourth objective of the programme, which was to determine the effectiveness of the intervention in helping patients reduce treatment (while avoiding worsening depression) through a RCT, and to estimate its cost-effectiveness.

The protocol for the definitive effectiveness and cost-effectiveness trial in WS5 was published by Kendrick *et al.*[54] and the main results of the WS5 trial were published by Kendrick *et al.*[55]

Methods

The published protocol gives details of the patient inclusion and exclusion criteria, consent procedure, description of interventions, primary and secondary outcome measures, original sample size calculation, recruitment procedures, participant timeline, data management, statistical methods and trial oversight.[54] The methods of the trial are described further in *Appendix 5*.

The primary outcome was depressive symptoms at 6 months, and the trial was powered to determine non-inferiority of the intervention in terms of depression, within 2 points on the PHQ-9.

Secondary outcomes measured at relevant outcome-specific time points were depression over 12 months, antidepressant discontinuation at 6 and 12 months, anxiety over 12 months, QoL over 12 months, withdrawal symptoms at 3 and 6 months, mental well-being at 6 and 12 months, patient enablement at 6 and 12 months, patient satisfaction at 12 months, and service use, adverse events and costs over 12 months. We also determined past history of depression, and sociodemographics at baseline, side effects of antidepressants at 6 and 12 months, patients' beliefs about antidepressant discontinuation at 3 and 12 months, and the strength of support from friends and family at 3 months, to assess their importance in predicting the outcomes.

The original sample size calculation indicated that we needed to recruit 402 patients, but we agreed a reduction to a target of 360 patients with the Programme Steering Committee, on finding a significant correlation between baseline and 6-month follow-up scores on the primary outcome, the PHQ-9, part-way through the trial (see *Appendix 5* for more details).

In a quantitative process evaluation, we assessed relationships between patients' use of the *ADvisor* intervention (automatically recorded by the Southampton *LifeGuide* software) and their outcomes, and analysed the fidelity of the provision of telephone support provided by the PWPs compared to the guidance given them, through recording a sample of their calls.

In a qualitative process study, we aimed to interview 15–20 purposively sampled patients and 15–20 practitioners in each arm from all those consenting to be interviewed, after patients had completed their 6-month follow-ups. We interpreted themes arising from the practitioner interviews in light of NPT[42] with the intention of constructing a taxonomy of factors likely to affect the uptake and implementation of the intervention, and patient outcomes.

Results

The CONSORT diagram for WS5 is shown in *Appendix 5*, *Figure 8*. A total of 6725 invitation letters were sent from 131 practices and 1495 responses were received (22%), of which 548 (8%) were positive about taking part. Of the 548, 330 patients were recruited, of whom 325 were eligible at baseline assessment, and consented to take part (5% of those contacted), including 178 in intervention arm practices, and 147 in control practices. A total of 275 patients (83%) were followed up at 6 months, and 240 (73%) at 12 months.

As expected, the practices randomised were well balanced at baseline (see *Appendix 5*, *Table 8*), as were key patient characteristics (see *Appendix 5*, *Table 9*). We controlled for baseline past history and demographic factors in the analyses, which were carried out on an intention-to-treat (ITT) basis.

Primary outcome

The mean PHQ-9 score was slightly higher among control patients than intervention arm patients at 6 months {5.0 vs. 4.0; adjusted mean difference 1.07 points [95% confidence interval (CI) 0.09 to 2.06; p = 0.033; *Appendix 5*, *Table 10*]}. The intervention arm was therefore non-inferior to the control, and in fact, the difference was in the direction of superiority, although the mean difference of 1 point on the PHQ-9 is not considered to be a clinically significant difference.

An exploratory post hoc analysis of rates of patient 'relapse', to scores of 10+ and 12+ on the PHQ-9, found somewhat higher rates in the control arm (17.1% vs. 11.0%, and 10.1% vs. 6.9%, respectively), but these differences were not statistically significant (see *Appendix 5*, *Table 10*).

In a missing cases multiple imputation analysis, the effect was slightly attenuated and while the non-inferiority conclusion remained, the intervention no longer appeared superior. Per-protocol analysis (PPA) and complier-average causal effect (CACE) analysis both gave the same inferences as the ITT approach (see *Appendix 5*, *Table 10*).

Main secondary outcome: antidepressant discontinuation

Antidepressant discontinuation rates at 6 months were slightly higher in the intervention arm, but not significantly different (45.5% vs. 41.9% in the control arm). At 12 months, the rates were 43.8% and 38.0%, respectively (again not significantly different; *Appendix 5*, *Table 11*). Adding in those patients who managed to reduce the dose of their antidepressant gave combined discontinuation/dose reduction rates at 6 months of 74.5% in the intervention arm and 67.4% in the control arm (again not significantly different).

Predictors of antidepressant discontinuation

An analysis of possible predictors of discontinuation was carried out, including all patients across the intervention and control arms, including baseline depressive or anxiety symptoms; number of previous episodes of depression; gender; age; marital status; dependents; ethnic group; urban/rural location; withdrawal symptoms; beliefs about depression; and collective efficacy.

Only a higher score for perceived necessity for antidepressants on the beliefs about depression questionnaire was associated with lower odds of discontinuation, with an odds ratio of 0.72 (95% CI 0.62 to 0.84) (see *Appendix 5*, *Table 12*). None of the other variables predicted discontinuation, but the sample may have lacked sufficient power to detect predictors accurately.

Other secondary outcomes

Over 6 months, antidepressant withdrawal symptoms on the DESS scale were fewer in the intervention arm, although the overall difference, while statistically significant, was small [adjusted mean difference −1.56 points (95% CI −2.85 to −0.26; p = 0.018; *Appendix 5*, *Table 13*)]. It is interesting to note that the difference at 3 months was actually due to a drop in symptoms in the intervention group rather than an increase in the control. This may have been because the intervention group patients were made more aware of what symptoms might be due to withdrawal through the educational content of *ADvisor* and therefore did not report symptoms they thought were not due to withdrawal.

To look further into withdrawal, we carried out a post hoc analysis of the proportions of patients in each arm with significant withdrawal symptoms (defined as 4+ new symptoms on the DESS in the first 3 months). The proportions were 16.0% in the GP consultation-only control arm, and 7.1% in the intervention arm with internet and telephone support (odds ratio 0.26, 95% CI 0.09 to 0.81; p = 0.02), so the support reduced significant withdrawal symptoms by more than half.

Similarly, over 12 months, mental well-being scores on the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) were slightly better in the intervention arm [mean difference 2.17 points (95% CI 0.21 to 4.14; p = 0.030; *Appendix 5*, *Table 13*)]. The difference was due to scores worsening slightly in the control arm rather than improving in the intervention arm.

There were no significant differences in quality of life (QoL) on the EuroQol-5 Dimensions, five-level version (EQ-5D-5L) or Short Form questionnaire-12 items (SF-12) (see *Appendix 5*, *Table 13*). The QoL scores are discussed further in the section on the *Health economics evaluation* below. There were also no significant differences in anxiety on the Generalised Anxiety Disorder-7 (GAD-7), patient enablement on the Patient Enablement Instrument (PEI), or satisfaction with services on any of the Medical Informant Satisfaction Scale (MISS) satisfaction subscale scores (see *Appendix 5*, *Table 13*).

A total of 69 adverse events were experienced by 28 participants in the intervention arm (15.2%) and 22 in the control arm (15.0%): not significantly different rates. Eleven serious adverse events were recorded, for two intervention arm and five control arm patients: not significantly different. Nine of the 11 serious events were hospital admissions which were unrelated to the trial. The main types of adverse events reported by arm are shown in *Appendix 5*, *Table 14*.

There were two serious adverse reactions to coming off antidepressants. One intervention arm patient was admitted to a psychiatric unit for relapse of an anxiety disorder, and withdrew from the study. One control arm patient was referred urgently to psychiatric outpatients due to expressed suicidal ideas thought by the GP to represent high risk, but was not admitted, and remained in the study.

Quantitative process evaluation

There were no significant differences in patient outcomes in relation to their recorded use of the online intervention *ADvisor* (see *Appendix 5*, *Table 15*). The fidelity of PWP support calls to the guidance provided was generally high across all three calls, and maintained through the course of the study.

Patient interviews

A total of 39 qualitative interviews were carried out with patients in WS5: 25 intervention arm and 14 control. *Appendix 5*, *Table 16* shows the patients' characteristics.

Catherine Woods coded intervention arm transcripts and Ellen Van Leeuwen coded control arm transcripts. Catherine Woods was responsible for synthesising the coding for the themes shown in *Appendix 5*, *Table 17*.

Four themes were developed from the patient interviews:

1. *Intentions, stability and willingness to try discontinuation:* It was notable that success in discontinuing antidepressants was more likely if the invitation to try tapering them off came at a time when the person was feeling well and stable, and ready to try.
2. *Tapering experience:* Gradual tapering was highly valued, as was greater involvement of the GP in setting the tapering regimen and providing follow-up. Most patients experienced few withdrawal symptoms and proceeded to cessation, while others felt a relapse was impending and restarted their antidepressants. The latter stages of tapering down to low doses were identified as more problematic than the initial reductions.
3. *Engagement with the intervention components:* Most patients were positive about *ADvisor*, although it seemed most did not engage with it much after initial familiarisation with its content. The telephone support calls were generally highly valued, as patients felt they were being monitored and reassured during tapering. Some did not like the PHQ-9 questionnaire, regarding it as a tick-box exercise, and some wanted psychological therapy from the PWPs.
4. *Reflections and realisations from tapering:* All patients interviewed valued the opportunity to try to discontinue their antidepressants, even if they were not successful. Some suggested providing more information for patients on the possible harms of long-term antidepressants.

More details on each of the themes are presented in *Appendix 5*, *Table 17*, with illustrative quotes, and the outcome for those quoted (discontinued their antidepressant, reduced it, or remained on the original dose).

Practitioner interviews

Twenty-seven health professionals were interviewed: 23 GPs, 1 pharmacist, 1 mental health nurse (MHN) and 2 PWPs who provided support calls. Their characteristics are described in *Appendix 5*, *Table 18*. Unfortunately, seven GP interview recordings proved to be inaudible, but five of the GPs kindly agreed to be re-interviewed following the loss of the data, and one provided written responses to the interview schedule questions. The PWP interviews are reported separately as the questions, data and coding were dissimilar to those for the other HCPs.

Hannah Bowers coded intervention arm practitioner transcripts and Riya Tiwari coded controls. Hannah Bowers integrated the coding across arms and developed a thematic structure (focusing on the context, mechanisms and implementation of the intervention).[56]

Themes were also mapped onto NPT constructs[42] by Hannah Bowers and Carl May, to identify the process evaluation outcomes related to the four NPT implementation mechanisms. This was the first step towards achieving Objective 5 of the REDUCE programme, to build a translational framework addressing how to overcome practitioner and patient-related barriers, to facilitate the implementation of antidepressant cessation.

Five themes were developed from the practitioner interviews:

1. *Creating the opportunity to discuss discontinuation:* Responsibility to initiate discussions was often reported as shared, between a health practitioner's responsibility to offer reviews and a patient's responsibility to raise the topic too. (This had previously been identified as crucial in the WS1 qualitative synthesis and WS2 focus groups.)
2. *Slow tapering:* Two control and eight intervention arm GPs discussed slowly tapering medication. HCPs who used *ADvisorHP* often discussed the tapering regimens and their usefulness in informing slow tapering.
3. *Distribution of the workload:* GPs felt NPs, MHNs and pharmacists were well-placed to broach the idea of stopping antidepressants, conduct reviews and monitor patients who were tapering, while others who could follow up patients once tapering commenced included social prescribing practitioners and PWPs.
4. *Confidence and reassurance:* HCPs who had used *ADvisorHP* most frequently discussed how they had learnt to distinguish relapse and withdrawal and better understand patient perspectives.
5. *Variable engagement with intervention components:* Most HCPs found it useful to read *ADvisorHP* in one sitting at the start of the trial. Some referred back to it when consulting, while two did not look at it at all.

More details of each of the themes are presented in *Appendix 5*, *Table 19*, together with illustrative quotes.

Relation to the logic models for the interventions

In our logic model for the health professional intervention (see *Appendix 3*, *Figure 4*), we proposed mechanisms involving changes in the beliefs and behaviours of GPs. Of these, there was evidence from the interviews to support effects on *'improved knowledge of reduction schedules'*, *'improved self-efficacy'*, improved *'confidence to discontinue'* and an *'increase in GPs raising the topic of discontinuation with the patient'*.

There was limited evidence supporting effects on *'increased motivation to withdraw patients'*, *'better understanding of the patient's perspective'*, *'detachment from the serotonin hypothesis'*, *'discussion of withdrawal during the initial prescription of antidepressants'*, or *'being less likely to restart ADs in the face of mild and moderate withdrawal symptoms'*. There was no evidence to support *'not restarting antidepressants when faced with initial warning signs of relapse'*. HCPs did however report discussing withdrawal symptoms with the patient at the point of tapering as a way of managing expectations about the process, which had not been proposed within the logic model.

'GP raises the topic of discontinuation with the patient' was an inherent requirement in both trial arms, through checking the records searches and selecting patients who were well enough to stop antidepressants. The fact that patients and practitioners in both arms highlighted its importance suggests it may be a key mechanism supporting the relatively high discontinuation rates in both arms.

In our patient interviews, there did not appear to be a difference in recall of follow-up appointments between trial arms, so this is unlikely to have influenced the outcome, despite our expectation that intervention arm GPs would provide better follow-up following guidance in *ADvisorHP*. This was also supported in the health professional data. HCPs did not differ between arms in how they talked about the amount of follow-up – there was a mix in both arms of pre-arranged follow-up and leaving it up to the patient.

The importance of slow tapering was discussed in both arms, but more frequently highlighted in the intervention arm. Given that HCPs reported using the tapering regimens in *ADvisorHP*, it is possible that slower tapering in the intervention arm might explain the fewer reported withdrawal symptoms by intervention arm patients. However, this is uncertain as we did not have quantitative information on the tapering regimens recommended by the GPs for patients in each arm.

Mapping of themes to normalisation process theory

The mapping of themes to NPT constructs is shown in *Appendix 5*, *Table 20*, identifying how the process evaluation outcomes related to NPT implementation mechanisms, provide a translational framework to overcome barriers to implementing antidepressant discontinuation in practice beyond the trial.

Conclusions of the workstream 5 definitive randomised controlled trial

Rates of discontinuation of long-term antidepressants of more than 40% are achievable by enabling patients who are ready to consider reducing them to get tapering advice and support from their GP/NP. Relapse of depression is likely to occur in only a minority of patients in primary care, and, if it occurs, treatment can be quickly restarted if the process is being monitored. The REDUCE internet and psychologist telephone support may help protect patients tapering their treatment against depressive and withdrawal symptoms, and help conserve mental well-being. Adverse events are likely to be few, and usually not serious, so trying to help patients come off long-term antidepressants when appropriate is a relatively safe thing to do.

Health economics evaluation

The aim of the health economics evaluation was to assess the cost-effectiveness and cost–utility of the online and telephone interventions compared with usual care, from an NHS and Personal Social Service (PSS) perspective.

Details of the methods, including collection of data on medication and health service use from patients' medical records at the end of their 12-month involvement in the trial, are described in *Appendix 6*. Patient questionnaires were also used at 6 and 12 months to gather information on recalled medication and service use, which will be compared later with the medical record data to look at differences between them, but this was not a prime objective and the results are not reported here. However, the patient questionnaires also asked about out-of-pocket spending and sickness absence, to determine additional personal costs from a societal perspective, and these are reported here.

The economic analyses also followed the ITT principle. Unit costs for medications and health service use were derived from standard sources (see *Appendix 6*), adjusted for inflation to 2023–4 values. The cost of the online interventions was estimated to be £11 per patient which included only hosting and maintenance of the websites for 1 year, as their development was regarded as a research cost. The cost of an hour's PWP time in total for the three telephone calls was £14, giving an overall cost of £25 per patient for the combined interventions. No significant time was required to train the PWPs; the schedules were designed to be self-explanatory. They also did their own administration. However, a sensitivity analysis using a cost of £50 per patient was done to determine the sensitivity of the cost-effectiveness analysis to a greater cost for PWP time spent providing telephone support.

Quality of life was measured using both the EQ-5D-5L[57] and Medical Outcomes Study SF-12 questionnaire[58] at baseline, 3, 6, 9 and 12 months. Analyses of changes in QoL were adjusted for baseline values, sociodemographic factors, and practice as a random effect to take account of clustering. Quality-adjusted life-years (QALYs) were calculated using the area under the curve approach. As the trial period was limited to 12 months, no discounting rates were applied.

The primary outcome was cost–utility expressed as incremental cost per QALY gained. Base analyses were based on completed cases using utility scores generated by the EQ-5D-5L. Utility scores derived from the SF-12 were also analysed to compare cost–utility when changing the instrument. Multiple imputation by chained equation was used in sensitivity analyses to impute missing values for the QoL measures, to take account of loss to follow-up over the 12-month study period. An additional sensitivity analysis looked at the effect on cost–utility of a doubling in the cost of the intervention.

Bootstrapping with 1000 resamples with replacement was used to estimate incremental costs per point difference on the PHQ-9 depression questionnaire, and incremental costs per QALY gained. Incremental cost-effectiveness ratios (ICERs) were estimated through analysis of completed cases, and through multiple imputation sensitivity analyses, based on the EQ-5D-5L data. Cost-effectiveness acceptability curves (CEACs) were generated for a range of thresholds for societal willingness to pay per QALY, again based on both completed and imputed EQ-5D-5L analyses.

Results

Use of medication and GP and practice nurse contacts were greater in the intervention group, as expected, given the interventions were likely to involve more primary care contacts (see *Appendix 6*, *Table 21*). Total contacts with primary care were lower in the intervention arm, though not significantly (see *Appendix 5*, *Table 13*). Community, mental health service and general hospital contacts were similar in the two arms. The total mean cost per patient of NHS services used was £595.50 [standard deviation (SD) £1662.50] in the intervention arm, and £668.90 (SD £921.50) in the control arm. The unadjusted mean total cost per patient was therefore £73.40 lower in the intervention arm.

Mean values for the QoL measures improved slightly more in the intervention arm, on both the EQ-5D-5L and SF-12, although the differences were not statistically significant (see *Appendix 5*, *Table 13*). The adjusted mean difference in the EQ-5D-5L at 6 months was 0.049 (95% CI −0.002 to 0.099; $p = 0.057$) and at 12 months 0.022 (−0.030 to 0.075; $p = 0.363$). On the SF-12, the adjusted mean difference at 6 months was 0.041 (−0.012 to 0.093; $p = 0.119$) and at 12 months 0.010 (−0.060 to 0.080; $p = 0.736$). Therefore, the SF-12 did not prove to be more sensitive to change than the EQ-5D-5L.

The adjusted mean difference per 1-point improvement in depression score on the PHQ-9 questionnaire at 6 months in the intervention arm, computed using the bootstrapped method, was −£69 (95% CI −£77 to £207), meaning the intervention was dominant, being both cost saving and more effective than the control condition of unsupported GP review. The bootstrapped cost-effectiveness analysis gave an estimated mean saving of −£88 (95% CI −£652 to £382; *Appendix 6*, *Table 22*).

The bootstrapped cost–utility analysis gave an estimated mean incremental QALY gain based on completed EQ-5D-5L values at 12 months of 0.024 (0.023 to 0.059; *Appendix 6*, *Table 23*). The mean QALY gain estimated by the multiple imputation sensitivity analysis (to take account of missing EQ-5D-5L values at 12 months) was slightly greater at 0.035 (0.013 to 0.059; *Appendix 6*, *Table 24*). Corresponding values for the SF-12-based figures were all slightly lower.

The ICER for the completed EQ-5D-5L data was a mean saving of −£2839 per QALY gained (95% CI −£30,024 to £22,227; *Appendix 6*, *Table 23*), and for the imputed data −£4678 (−£11,265 to £8268; *Appendix 6*, *Table 24*). The sensitivity analysis with a doubling of the intervention cost from £25 to £50 per patient attenuated the ICERs to a mean saving of −£49 per point reduction on the PHQ-9, and −£1418 per QALY (−£28,295 to £23,974; *Appendix 6*, *Table 25*). The intervention therefore remained dominant in all the sensitivity analyses, with an ICER well below the NICE societal willingness-to-pay lower threshold of £20,000 per QALY.

The scatter plot of the bootstrapped sampling with replacement comparing the intervention with the control, based on QALYs from completed EQ-5D-5L values over 1 year, illustrates the uncertainty around the point estimate of the ICER with a 95% confidence ellipse (see *Appendix 6*, *Figure 10*).

Costs from a societal perspective including productivity loss due to patient or carer sickness absence, and out-of-pocket expenses, are shown in *Appendix 6*, *Table 26*. Sickness absence was reported by fewer than 10% of patients and out-of-pocket expenses by fewer than 15%, and there were no significant differences between intervention and

control groups, although there was a trend towards higher personal/societal costs in the intervention arm. Given the differences in mental health outcomes tended to favour the intervention arm, it is likely that the higher sickness absence was due to reasons other than mental health problems.

Sensitivity analyses including personal costs gave similar findings for the ICERs for depression score, completed QoL data and imputed QoL data, although the mean saving was reduced from −£69 to −£45 per patient (see *Appendix 6*, *Tables 27–29*).

Cost-effectiveness acceptability curves based on both completed and imputed EQ-5D-5L values are also shown in *Appendix 6*. For completed values, the probability of the intervention being cost-effective compared to usual care in the control group was 89% at both the lower and upper NICE thresholds for willingness to pay of £20,000 and £30,000 per QALY (see *Appendix 6*, *Figure 11*). For imputed values, the probability was 99% at both thresholds (see *Appendix 6*, *Figure 12*).

Conclusions and implications for the REDUCE programme

The intervention appeared highly likely to be cost-effective compared to usual care at both NICE thresholds for societal willingness to pay of £20,000 and £30,000 per QALY. This is an important prerequisite for the implementation of the intervention throughout the NHS. However, the findings are based on the single year of the trial's duration, and we will develop a decision-analytic model to extrapolate estimates of cost-effectiveness beyond the trial, in light of the risk of later recurrence of depression requiring further care and incurring further NHS costs.

Additional workstream: the REDUCE-Urdu study – October 2020–May 2022

Background

It is crucial that psychosocial interventions are made more accessible to people from minority ethnic communities.[59,60] Given the main study exclusion criteria included being a non-English speaker, the Programme Grants Board requested additional work to develop an intervention for a minority ethnic group. We summarise the workstream here; *Appendix 7* gives a fuller description.

Aim and objectives

The study aimed to develop a version of the *ADvisor* intervention for South Asian Urdu-speaking patients and test it using 'think-aloud' interviews. This was led by the team at the University of Liverpool.

There were three objectives:

- Phase 1 – REDUCE Urdu formative work
- Phase 2 – Developing the Urdu *ADvisor*
- Phase 3 – Piloting the Urdu *ADvisor*.

Phase 1 – REDUCE Urdu Formative work

The first phase explored Urdu-speaking people's views on mental health, on using and stopping antidepressants, and on a possible online intervention to help Urdu-speaking people come off antidepressants when appropriate. It involved three steps:

Step 1: Healthcare Professionals focus group
Step 2: Community Leaders focus group
Step 3: Urdu-speaking South Asian community focus groups

Through these focus groups, we explored barriers and facilitators to stopping antidepressants which were specific to Urdu-speaking people, and asked questions on the possible content and presentation of an online intervention, without showing them the *ADvisor* intervention.

Phase 2 – Developing the Urdu *ADvisor*

The Urdu intervention was developed on the basis of the focus groups, most significantly on the basis of the main result found, which was that most participants did not want an internet-based interactive digital intervention. The intervention we developed, therefore, consisted of online videos and a paper booklet, in both Urdu and English, which could be read or viewed together with family and friends, rather than an interactive website for an individual.

After a careful review of the first phase interviews, PBA analysis and *ADvisor* online intervention, we concluded the core structure, techniques and elements of the intervention were culturally compatible and did not require significant changes. However, subtle but critical adaptations were needed in the areas of language, persons, metaphor, content, concepts, methods and context.

The *ADvisor* content was first developed into an English booklet. This was translated into Urdu, considering conceptual equivalents, rather than word-for-word translation. Specialised terms and jargon were avoided. Links to online versions of the booklet in English and Urdu were created by the lead bilingual researcher Yumna Masood.

The final versions of the Urdu *ADvisor* booklets and online links were critically reviewed by the study research team, and an expert group (Yumna Masood and three Urdu-speaking PPI colleagues) who finalised the cultural adaptation of the intervention.

Phase 3 – Piloting the Urdu *ADvisor*

Think-aloud interviews were conducted with 10 Urdu-speaking people on long-term antidepressant treatment who fitted the study inclusion and exclusion criteria above, to enable iterative assessments and changes. Interviews continued until data saturation was reached, and no further changes were necessary according to the PBA.

Participants provided generally positive feedback on the Urdu booklet and video links which were seen as useful self-management tools for people wanting to discontinue antidepressants and also a way to increase the South Asian community awareness of discontinuation issues.

In light of the feedback, further adaptations to the Urdu *ADvisor* booklets were made. Due to logistical and time constraints, changes to the video links were not possible, but comments on these were documented, and could be implemented in future research.

Conclusion

Overall, the Urdu *ADvisor* development and refinement were successful. Feedback on the final version was positive, and it is now available for further evaluation. *Appendix 7* gives links to English and Urdu versions of online slideshows based on the booklet modules.

Public and patient involvement in the programme

We enlisted the help of PPI colleagues Sue Collinson, Bryan Palmer, and Margaret Bell, who confirmed the need for the proposed intervention and contributed to the study design. Sue is a very experienced service user, previously Chair of the Service Users in Research Advisory Board for the Mental Health Research Network, and a member of the McPin PPI Advisory Group (http://mcpin.org/; accessed 27 November 2024). Bryan convened the Southampton Depression Alliance group, including both people who were determined to continue taking antidepressants because they believed they kept them well, as well as people wanting support to discontinue. Margaret has personal experience of long-term antidepressant treatment, and indicated older, isolated patients in particular would need around-the-clock support. These colleagues had track records working with us on previous studies, and so were readily available to contribute to our ideas for developing this proposal.

We also had support for the proposal from the CEP, a self-help organisation of patients/service users, health professionals and academics (including co-applicant Joanna Moncrieff). CEP had a database of more than 700 people who have had problems with medication, and a website illustrating the difficulties people have withdrawing from antidepressants.

Bryan helped us set up a PPI advisory group of seven volunteers from Depression Alliance. They all agreed there was a need for greater monitoring and review of people taking antidepressants long term. They showed us that people taking them vary widely in their views about stopping, however, and we should not presume to know why that was, before carefully gathering patients' views.

Sue, Margaret and Bryan were invited to attend our monthly study group meetings, and we regularly had one or two of them present at each. They helped us prepare study documents, check patient information sheets and consent forms for readability and ease of understanding, and make suggestions for questions in topic guides for qualitative interviews in WS2–5. They helped review the themes and logic models developed in WS2, and Bryan helped organise patient interviews in Southampton. All three provided a PPI perspective on questions to be asked of participants, to ensure all relevant and important points were covered.

Sue and Margaret agreed to undergo pilot 'think-aloud' interviews in WS3, and Bryan helped provide interpretations of themes developed from WS2 to WS3 interviews which differed somewhat from the team's perspectives – for example, he reminded us that patients who try to come off antidepressants and do not manage it may have an altered view of themselves and their illness afterwards, which needs to be picked up by their GPs.

Bryan had more direct involvement in the WS4 qualitative work, carrying out interviews under the supervision of the research team, and contributing to analysis of interview transcripts, employed by the University of Southampton on a casual basis to do this, from September 2018 for 1 year. Bryan will also help publicise the results, through the Mind/Depression Alliance website and mailing list.

Equality, diversity and inclusion

Participant representation

Deprivation

Most of the patients and practitioners recruited for WS2 interviews and focus groups, and WS3 think-aloud interviews, were recruited from relatively affluent parts of the south of England, by the Southampton centre. The perspectives in this work may therefore not have represented broader experiences of antidepressant treatment nationally. While recruitment for the main WS5 trial extended into relatively deprived parts of North-West England, North Wales and East Yorkshire, two-thirds of participating practices were situated in less deprived areas with Index of Multiple Deprivation (IMD) scores above the median. The patients recruited were usually homeowners, either working or retired, and relatively well-educated.

The PHE national survey found antidepressant use increased from 14% of adults in the least deprived quintile of people up to 17% in the most deprived,[5] which may mean that our findings would not generalise readily to people living in areas with greater deprivation. Higher rates of antidepressant prescription are not entirely explained by the higher rates of depression in this group,[61] and qualitative research has shown that GPs view depression in more deprived areas as being driven by difficult life circumstances.[62] However, antidepressants may not be appropriate for those experiencing stressful life circumstances and instead further support may be needed to support the patient's circumstances via social prescribing and community services before considering discontinuation.[63] This is particularly important given that the findings from WS2 demonstrate that practitioners view stability in the patient's life as a key facilitator to successful discontinuation.

Gender

The majority of our participants in the WS2 qualitative work and WS3 think-aloud interviews were women. While this reflects greater antidepressant use among women, our qualitative findings may not have reflected men's views to an equivalent extent. Conversely, in the main WS5 trial, the ratio of women to men was 126/97 = 1.3. In the PHE national survey of antidepressant use, the ratio of women to men receiving antidepressants was 1.8,[5] so our quantitative findings may have under-represented women to an extent.

Age

The mean age of our WS5 trial participants, 54.0 years, was higher than the median age of people in the UK of 40.4 years in 2021 according to the Office for National Statistics. This is in keeping with the trend for antidepressant use found in the PHE survey however, which shows an overall increase of use with age, with peaks among people in their mid-40s and in over-65-year-olds.[5]

Ethnicity

In WS3, think-aloud interview participants were predominantly White British and may not have represented the views of all antidepressant users. In the WS5 trial, 98% of participants declared themselves White British, and only 2% were from other ethnic groups, much less than the 14% of people in England and Wales who declared themselves to be of black and minority ethnic groups in the 2011 census.[64]

Insisting that participants could read and write English to participate in the main programme was essential, to take part in interviews and use the interventions, but would have contributed to the lack of ethnic minority participants. It was for this reason that the Urdu study was carried out, so we did at least develop an alternative intervention for one major ethnic minority group.

Quantitative effects on the outcomes of our studies caused by the variable representativeness of different demographic groups are uncertain. In our WS5 trial, depressive symptoms and antidepressant discontinuation were not predicted by gender, age, ethnic group, or urban/rural location. However, our sample may have lacked sufficient power to determine the significance of these demographic factors in predicting outcomes.

Research team representation

Study team members ranged in gender, culture and ethnicity, including black and Asian ethnicities generally under-represented in healthcare research. Our team was a diverse group of academic and clinical researchers at different career stages, including research assistants, a PhD student, research fellows and professors. Development opportunities were provided for more junior members, some of whom left during the study to enrol for PhDs and clinical doctorates in psychology.

Reflections on what was and what was not successful in the programme

The programme was generally very successful. There were no significant alterations to the original aims or design, and up until the start of WS5, we achieved our milestones. The COVID-19 pandemic significantly delayed progress in recruiting sites and participants to WS5 during most of 2020, and so we had to request an extended end-date to enable completion, but achieved this at no extra cost.

We were unable in the event to carry out health economics decision-analytic Markov modelling during WS2, as the WS1 systematic review did not identify any health economics literature to inform the model. However, we can now produce a model to extrapolate estimates of cost-effectiveness beyond the trial period, in light of the known potential risk of later recurrence of depression.

Most importantly, we successfully achieved our objectives to develop and evaluate online interventions to support antidepressant withdrawal for both patients and practitioners, together with PWP telephone support to patients. The

interventions proved feasible, effective in protecting patients against depressive and withdrawal symptoms, beneficial to mental well-being, and cost-effective at the threshold for implementation in the NHS set by NICE.

We also developed an intervention for Urdu speakers, ready for further testing and implementation, subject to obtaining funding.

Limitations relating to the method or execution of the research

We identified a number of limitations in the execution of the programme. In our WS1 qualitative evidence synthesis, we deviated from our protocol due to time constraints. Instead of two researchers independently performing line-by-line coding to generate themes, this was performed by one researcher and further developed through discussion with two others. However, this method has been used in other published qualitative syntheses. Similarly, in the WS1 systematic review, one researcher performed study selection, data extraction and risk-of-bias assessment, which were checked by another experienced reviewer. This approach is time-efficient but may incur more errors than full data extraction by two reviewers.

The use of focus groups to elicit barriers and facilitators to discontinuation from health professionals in WS1 facilitated discussion and candid responses from participants. However, discussions can become polarised or influenced by dominant members in a group, and some participants' views may be less well represented. Giving participants opportunities to feed back on the findings might have provided greater representation.

The practitioners interested in participating in the REDUCE programme were interested in mental health research and may be more knowledgeable than practitioners generally. This may explain why some who participated in the WS3–5 interviews felt that much of the information provided in *ADvisorHP* was not new. However, they thought that it would be useful for GPs in training and doctors who are relatively new to UK practice.

The development work included only two NPs, both prescribers responsible for managing long-term antidepressant use in primary care, and this limited representation made it difficult to identify differences between GP and NP perspectives. Conducting more research with NPs and other HCPs who may support antidepressant discontinuation in future would help further understand how the interventions may need adaptation.

In the main WS5 trial, we did not quite achieve the revised target sample size of 360 participants, falling short by 30. We were confident we had sufficient power to address the primary outcome, having greater than the 80% follow-up anticipated at 6 months (83%). However, only 73% were followed up at 12 months which reduced the power of the sample to exclude differences in depression and discontinuation of antidepressants developing beyond 6 months. In the missing cases multiple imputation analysis, the apparent effect of the intervention on preventing depressive symptoms was slightly attenuated and while the non-inferiority conclusion remained, the intervention no longer appeared superior to the control.

The vetting by participating GPs of patient lists generated by the electronic medical records searches means there would have been selection bias, towards including people who were well and considered ready to try tapering by the GP, and excluding people who were considered to be at greater risk of relapse. This may explain why we found that more than 40% of people in each arm discontinued their antidepressants, a high rate given previous studies had suggested only 6–8% would succeed following a GP review of long-term antidepressant treatment.[12,23,24] The results may not generalise to an unselected sample of people on long-term antidepressants, many of whom might be at greater risk of relapse, particularly if they have had two or more episodes of depression.

Finally, we had no information on the number of patients in each arm who did not attempt to taper their antidepressant in the event, or embarked on tapering, but subsequently went back on the original dose. Quantitative exploration of the relation between attempted tapering and the development of depressive and withdrawal symptoms was therefore not possible. However, the qualitative interviews indicated some patients went quickly back on to their original dose of

antidepressant when new symptoms developed, and were not supported by their GPs to try and get through them by going back up in dose temporarily, and then trying to taper again subsequently.

Conclusions from the whole programme

We have demonstrated that rates of discontinuation of long-term antidepressants of more than 40% are achievable through enabling patients who are ready to consider reducing them to get tapering advice and support from their GPs or NPs, as was provided in both arms of our trial. Qualitative interviews with patients suggest that facilitating practitioner review was a major factor contributing to successful discontinuation. They further suggest that the invitation for a review of medication needs to come at the '*right time*' for a patient to consider tapering.

We can also conclude that the *ADvisor* and *ADvisorHP* online interventions, together with PWP telephone support, appear to help protect patients coming off long-term antidepressants against depressive and withdrawal symptoms, and conserve mental well-being, although the benefits are modest. This may be because most modules of the *ADvisor* patient intervention were completed by fewer than half of the participants, and might benefit from revision, working with patients to understand why. Qualitative interviews with patients and practitioners suggest that advice to taper slowly, and information on the difference between symptoms of relapse and withdrawal, were major factors contributing to the success of the interventions. We intend to learn how to improve the interventions from the results of the trial process evaluations, to produce better versions for dissemination within the NHS.

Adverse events from attempting discontinuation are likely to be few, and usually not serious, so trying to help patients come off long-term antidepressants when appropriate is a relatively safe thing to do. Relapse of depression is likely to occur in only a minority of patients in primary care, and if it starts to occur treatment can be quickly restarted with no negative outcome in most cases as long as patients are monitored. The qualitative interviews showed patients were often greatly reassured by being able to ask questions during the psychologist's telephone support calls.

Recommendations for future research

Future research should:

1. Try to engage a greater proportion of people taking antidepressants, including younger people, unemployed people, people from deprived areas and of ethnic minority groups. This may be achieved through co-production of research methods and materials with diverse and underserved populations to ensure the approach is more relevant, appropriate, and inclusive.[65] Our work with Urdu-speaking people in this programme is one example.
2. Follow people more closely through their attempts to taper antidepressants, record the development of depressive and withdrawal symptoms, distinguish where possible between withdrawal and relapse, and determine relationships between symptoms and progress in tapering.
3. Assess barriers and facilitators to wider implementation of support to practitioners and patients in clinical practice for antidepressant discontinuation.
4. Assess the potential for involvement in deprescribing of other HCPs besides GPs and NPs, in particular pharmacists, and mental health professionals.
5. Compare new interventions against best practice, that is active review of medication by HCPs, rather than usual care, which currently means no active review for many people taking long-term antidepressants.

Implications for practice and any lessons learnt

It may appear from the response and participation rates in our WS5 trial that only a small minority of people on long-term antidepressants may be willing to try to come off them at any one time. Even though the GPs had selected

patients who were well and stable for possible participation, only 8% of patients approached were willing to take part and only 5% consented and could be recruited.

A low rate of willingness to attempt antidepressant discontinuation was also found in a questionnaire survey carried out on a different sample of patients in Rachel Dewar-Haggart's PhD, related to the REDUCE programme, of people's intentions to discontinue antidepressants outside of the trial situation.[66] Among 277 people surveyed from 20 practices, with a median duration of antidepressant use of 10 years, 85% declared that continuing their antidepressant was necessary. Prescribing outcomes retrieved from 175 participants' medical records over 6 months following the survey found that 87% had not changed their antidepressant, while 8% had reduced the dose, only 1% had discontinued their antidepressant, and 4% had increased the dose.[66]

However, a relatively low response rate to cold-calling invitations is common in research trials, as understandably patients have worries about trying out untested interventions. Uptake in routine clinical practice outside the trial situation is likely to be higher once interventions have been demonstrated to be effective. This was found for a handwashing intervention to modify transmission of influenza-like illness and respiratory infection, despite major concerns about generalisability given a low uptake in the trial.[67,68] Our qualitative research suggests more patients will be encouraged to try discontinuing antidepressants in future, having shown a > 40% chance of succeeding if they are well and are actively supported by practitioners to taper slowly.

On the other hand, more than 50% of our trial patients did not discontinue their antidepressants. This may have been because in the event they did not try to start tapering after a discussion with their prescriber, or did try but restarted treatment when they felt they were starting to relapse. The placebo-controlled ANTLER trial found that more than 50% of people discontinuing antidepressants for recurrent depression relapsed within 12 months, although as in our trial, more than 40% were able to stay off them with a good QoL at 12 months follow-up.[16] In the primary care placebo-controlled trial in New Zealand, only 23% of the discontinuation group relapsed, and that sample included patients taking antidepressants for a first episode of depression, like ours.[34] In our trial, we did not find a relationship between successful discontinuation and the number of previous episodes of depression, but systematic reviews of relapse prevention suggest the risk is higher for people who have had two or more episodes,[15,69,70] and that practitioners should be particularly careful about monitoring people who want to try tapering antidepressants for recurrent depression, as opposed to those taking them long term for a first episode.

There does appear to be a relatively low risk of relapse of depression as long as patients are well at the start of tapering, and monitored for the early development of symptoms. This demonstration of the safety of attempting discontinuation should help tackle one of the main barriers identified in our qualitative work during all five workstreams of the REDUCE programme, namely the fear of relapse.

The other main barrier is the inertia found among both practitioners giving, and patients receiving, repeat prescriptions, which works against having a more proactive review of long-term antidepressants and more encouraging discussions about discontinuation.

Our trial process evaluation suggests that implementation methods need to include:

1. Creating opportunities for discussing antidepressant discontinuation (more active reviews of people on long-term treatment and fewer routinely repeated prescriptions).
2. Flagging the electronic records of patients who qualify for considering discontinuation.
3. Delegation of medication reviews and tapering support to other professionals besides GPs.
4. Making patients more aware of how withdrawal symptoms differ from relapse, and how to cope with them.
5. Adopting tapering regimens over months rather than weeks, to reduce the occurrence and severity of withdrawal symptoms, with flexibility to go back up in dose if necessary.
6. Proactive follow-up during tapering where possible, including brief telephone calls or text messages.
7. Embedding links to alternative treatment resources in the electronic patient record.

Challenges for the implementation of our interventions throughout the National Health Service

National Health Service policy is to expand NHS-accredited health apps/websites to support people in managing their own health, but progress on accrediting apps/websites has been slow, and online infrastructure is needed to signpost reliable resources. The Digital Technology Assessment Criteria for health apps [Using the NHS Digital Technology Assessment Criteria – AI regulation service – NHS (innovation.nhs.uk)] were produced to give staff and patients confidence that they meet clinical safety, data protection, accessibility and cyber security standards. However, meeting these criteria is difficult for research teams, requiring substantial additional investment of time beyond the scope of the original funding. This is in addition to licensing and technology transfer arising when staff contracts may be ending, and research teams may have limited capacity to complete these tasks.

We will explore funding for the costs of hosting the intervention to secure longer-term sustainability allowing content, infrastructure and format to be kept up to date. We would like to keep the intervention free from commercial influence, so it is a trusted resource, free to use. We would therefore like to maintain content control of the online interventions with a commitment to ensuring content remains evidence-based while disseminating it in partnership with NHS organisations and mental health charities to raise awareness.

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Other contributions

Simone Holley, Emma Hughes (medical student), Kirsty Hancock (medical student) and Imogen Fry (psychology student) collected quantitative data and/or collected and helped analyse qualitative data. Two other medical students, Megan

Warinton and Annabelle Hook, conducted secondary analyses of patient interviews from WS2 which are not reported here but were presented at the Royal College of General Practitioners Annual Scientific Meeting in Liverpool in 2019.

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Programme management

Wendy O'Brien (University of Southampton) was Programme Manager. Claire Chapman, Sophie Johnson, Sonja Poore (University of Southampton); Amy Porter, Amy Hindhaugh-Ness (University of Hull); and Dan Lawrence and Debbie Fisher (University of Liverpool) provided administrative support.

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Thanks to the Programme Steering committee (Trial Steering Committee) members who were: André Tylee (academic general practitioner and Chair); David Kessler (academic general practitioner and replacement Chair), Thomas Kabir (PPI representative); Debs Smith (PPI representative); Sally Kerry (statistician); and Isobel Cameron (academic psychologist).

Thanks also to the trial Independent Data Monitoring Committee members who were Roland Zahn (academic psychiatrist and Chair), Nicholas Turner (statistician), and Mark Ashworth (academic general practitioner).

Participants

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Abbeywell Surgery, Affinity Care Partnership, Aintree Park Group Practice, Andover Health Centre, Ashington House Surgery, Banbury Cross Health Centre, Bartholomew Medical Group, Bay Medical Group, Beaumont Street Surgery, Bicester Health Centre, Boathouse Surgery, Bodey Medical Centre, Bosmere Medical Practice, Bridge House Surgery (Cheadle Hulme Medical Centre), Brinnington Surgery, Brockwood Medical Practice, Brownlow Health Centre, Campden Surgery, Cartmel Surgery, Chawton Park Surgery, Church Street Practice, Church View Surgery, Clarence Medical Centre, Clevedon Medical Centre, Clifton Medical Centre, Concord Medical Centre, Corwen Family Practice, Cotswold Medical Practice, Darwen Healthcare, Denmead Health Centre, Diadem Medical Practice, Elm Tree Surgery, Elmwood Family Doctors, Eric Moore Partnership, Gosford Hill Medical Centre, Gratton Surgery, Heswall and Pensby Group Practice, Heworth Green Surgery, High Street Medical Centre, Highcliffe Medical Centre, Ide Lane Surgery, James Alexander Family Practice, Kensington Park surgery (Brownlow group), Kingswood Surgery, Mann Cottage Surgery, Marine Lake Medical Centre, Maywood Healthcare Centre, Mendip Vale Medical Practice, Mosborough Health Centre, My Health Stamford Bridge, My Health Strensall Health Care Centre, New Hall Surgery, Newland Medical Practice, Newton Place Surgery, Old Goole Surgery, Park and St Francis Surgery, Park Surgery Horsham, Park View Surgery, Pembroke Road Surgery, Pendle View Medical Centre, Pendleside Medical Practice, Phoenix Health Group, Pickering Medical Practice, Posterngate Surgery, Poundbury Doctors Surgery, Price's Mill Surgery, Queen Square Medical Practice, Regent Street Surgery, Rendcomb Surgery, Ringwood Medical Centre, Springhead Medical, St Augustine's Medical Practice, St Bartholomew's Medical Centre/South Oxford Health Centre, St Georges Medical Centre, Station House Surgery, Stewkley Road Surgery/Wing Surgery, Stockwood Medical Centre, Streamside Surgery, Summertown Health Centre, Swanage Medical Centre, The Burns Practice, The Family Practice, The Lennard Surgery, The Ridings Medical Group, The Scott Practice, The Wilson Practice, Tollerton Surgery, Trafalgar Medical Group Practice, Tyntesfield Medical Group, Vauxhall Medical Centre, Wareham Surgery, West Walk Surgery, White Horse Medical Practice, Whiteladies Medical Group, and Winchcombe Medical Practice.

Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

Data-sharing statement

No data will be shared prior to publication of the results of the study in peer-reviewed journals and the NIHR report. After that we will be open to applications for collaborations with other scientists to use the study quantitative data, as our research ethics permission is for use of the data by the research team only. Applications to use the quantitative data will need to be in the form of a peer-reviewed protocol, and will be considered by the three lead investigators, Tony Kendrick at Southampton (ark1@soton.ac.uk), Una MacLeod at Hull, and Mark Gabbay at Liverpool, in the first instance, before a decision on data sharing will be taken by the rest of the co-applicants. Qualitative data will not be shared, due to the relatively high risk of breaches of confidentiality arising from the nature of qualitative interviews, which are difficult to make completely anonymous.

Ethics statement

This study was conducted in compliance with the ethical principles of the Declaration of Helsinki and in compliance with all International Council for Harmonisation Good Clinical Practice guidelines. Study protocols were reviewed and approved by the Sponsor, the University of Southampton, and the independent NHS Research Ethics Committees (RECs) listed below. All participants provided written informed consent.

Workstream 2

Dates of study: 7 October 2017–30 June 2017.

REC: Berkshire B; reference number: 16/SC/0472; date of approval: 7 October 2016.

Integrated Research Application System (IRAS) approval for health and social care/community care research in the UK (IRAS) reference: 212209.

Workstream 3

Dates of study: 10 July 2017–30 September 2018.

REC: Oxford B; reference number: 17/SC/0457; date of approval: 21 September 2017.

IRAS reference: 231064.

Workstream 4

Dates of study: 1 September 2018–30 June 2020.

REC: West of Scotland; reference number: 18/WS/0143; date of approval: 21 September 2018.

IRAS reference: 247830.

International Standardised Randomised Controlled Trial Number (ISRCTN) registration number: 15036829.

Workstream 5

Dates of study 1 November 2019–30 June 2023.

REC: North of Scotland; reference number: 19/NS/0144; date of approval: 10 September 2019.

IRAS reference: 266517.

ISRCTN registration number: 12417565.

REDUCE-Urdu Study

Dates of study 17 November 2020–31 May 2022.

REC: Health and Social Care Research Ethics Committee B, Lisburn, Northern Ireland; reference number: 20/NI/0144.

IRAS reference: 283476.

Information governance statement

The University of Southampton is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, the University of Southampton is the Data Controller, and information on how we handle personal data, including how participants can exercise their individual rights, is available from our Data Protection Officer, whose contact details are at: www.southampton.ac.uk/hr/services/data-protection/data-protection.page

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/BTBL3945.

Primary conflicts of interest: Tony Kendrick, Beth Stuart, Christopher Dowrick, Michael Moore, Mark Gabbay, Geraldine Leydon, Guiqing Lily Yao, Shihua Zhu, Paul Little, Gareth Griffiths, Glyn Lewis, Carl May, Joanna Moncrieff, Una MacLeod, Simon Gilbody and Adam WA Geraghty have received grant funding to their employer universities from the National Institute for Health and Care Research (NIHR) to carry out this study and other research.

Tony Kendrick has been a member of the NHS England Quality Outcomes Framework (QOF) Advisory Committee 2009–14, NICE Quality Indicators Advisory Committee 2015–8, NICE Depression Guideline Update Committee 2015–22, NHS England Improving Access to Psychological Therapies Expert Advisory Committee 2020–4, member of the NICE Committee on Quality Standards in Depression 2021–4, and HTA Commissioning Committee 2023–4.

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Christopher Dowrick chaired the WONCA Working Party on Mental Health 2016–21.

Beth Stuart is Director of the Queen Mary's University of London Pragmatic Clinical Trials Unit (part-funded by the NIHR), and a member of the HTA Commissioning Committee.

Guiqing Lily Yao is a member of the NICE Public Health Committee.

Mark Gabbay was a member of the HTA IP Panel 2016–8 and HTA Prioritisation Committee B (In hospital) 2016–20. He is part funded by the NIHR ARC NWC. He has received consultancy fees from Spectrum Learning and Development as a board member for substance misuse training courses, and has grant funding from the UKRI. He is Provost of the RCGP NEW Faculty, and has stock options at Lloyds Bank, Aviva, and ABRDN.

Paul Little was Director of the NIHR Programme Grants for Applied Research Board for 6 years and a member of the Board of the NIHR Journals Library.

Chris Johnson has received funding from The Scottish National Forum on Drug-Related Deaths, Pharmacy Management group, and NHS Education Scotland. He has participated in advisory groups in 2015 for Lundbeck and in 2011 for Astra Zeneca.

Glyn Lewis was a member of the NIHR EME Funding Committee and has received grant funding from the NIHR, the UCLH BRC, the MRC, ESRC and Wellcome Trust.

Gareth Griffiths is Director of the Southampton Clinical trials Unit (part-funded by the NIHR). He has received funding from Janssen-Cilag, AstraZeneca, Novartis, Astex, Roche, Heartflow, Celldex, BMS, BioNTech, Cancer Research UK, the NIHR, Asthma and Lung UK, UKRI, Unitaid, and GSK for unrelated academic clinical trials and programme funding, has received personal payments from AZ and AbbVie for delivering CPD training courses, and honoraria from the Irish Cancer Society.

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Joanna Moncrieff has received lecture fees from Alberta Psychiatric Association, the British Psychological Association, Université de Sherbrooke, University of Vancouver, Case Western Reserve University, and the University of Basle. She is an unpaid board member of the non-profit Council for Evidence-based Psychiatry, and Co-Chair of the Critical Psychiatry Network.

Simon Gilbody has received grant funding from the NIHR and was previously Deputy Chair of the NIHR HTA Funding Committee. He has been a member of committees for HTA Efficient Study Designs – 2 Calibri (Body) 2015–6, HTA End of Life Care and Add-on Studies to 2015–6, HTA Funding Teleconference Members 2015–6, HTA Post-Funding Committee teleconference (POC members to attend) 2017–20, HTA Funding Committee Policy Group (formerly CSG) 2017–20, HTA Clinical Evaluation and Trials Committee 2008–14, and HTA Commissioning Committee 2016–20. He is Editor of the Cochrane Common Mental Disorders Group, and a member of the Editorial Board for the British Journal of Psychiatry.

Tony Kendrick, Glyn Lewis, Michael Moore, Paul Little, Gareth Griffiths, Simon Gilbody, Guiqing Lily Yao and Beth Stuart have been members of trial steering committees for other NIHR-funded studies.

Marta Glowacka declares that the University of Southampton received grant funding for her employment and received a grant which covered funding for her to attend meetings in Plymouth in March 2018 and Dublin in April 2018.

Adam WA Geraghty declares the following grant funding: a NIHR Programme Development Grant PDG NIHR 203688: 2021–3; Geraghty Co-App: Developing a patient-centred evidence-based intervention to address distress in the context of chronic MSK pain. Versus Arthritis. 2021–4; Geraghty CI: Understand patients experiences of

self-management interventions for Chronic Widespread Pain including Fibromyalgia: A systematic review and thematic synthesis. SPCR. 2022–3.

All the other authors declared no relevant interests.

Publications

Papers published in peer-reviewed journals

[1] Kendrick T. Strategies to reduce use of antidepressants. *Br J Clin Pharmacol* 2020;1–11. https://doi.org/10.1111/bcp.14475

[2] Maund E, Stuart B, Moore M, Dowrick C, Geraghty A, Dawson S, Kendrick T. Managing antidepressant discontinuation: a systematic review. *Ann Fam Med* 2019;**17**:52–60. https://doi.org/10.1370/afm.2336

[3] Maund E, Leydon G, Williams S, Geraghty A, Bowers H, May C, Kendrick T. Barriers and facilitators to discontinuing antidepressant use: a systematic review and thematic synthesis. *J Affect Disord* 2019;**245**:38–62. https://doi.org/10.1016/j.jad.2018.10.107. The author's accepted manuscript is freely available at: https://eprints.soton.ac.uk/425405/ (accessed 27 November 2024).

[4] Bowers HM, Williams SJ, Geraghty AWA, Maund E, O'brien W, Leydon G,. Helping people discontinue long-term antidepressants: views of health professionals in UK primary care. *BMJ Open* 2019;**9**:1–8. [e027837]. https://doi.org/10.1136/bmjopen-2018-027837

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[6] Bowers H, Kendrick T, van Ginneken N, Glowacka M, Williams S, Leydon GM, *et al*. A digital intervention for primary care practitioners to support antidepressant discontinuation (*ADvisor* for Health Professionals): development study. *J Med Internet Res* 2021;**23**:e25537. http://dx.doi.org/10.2196/25537

[7] Kendrick T, Geraghty AWA, Bowers H, Stuart B, Leydon G, May C, *et al*. REDUCE (Reviewing long-term antidepressant use by careful monitoring in everyday practice) internet and telephone support to people coming off long-term antidepressants: protocol for a randomised controlled trial. *Trials* 2020;**21**:419. https://doi.org/10.1186/s13063-020-04338-7 (accessed 27 November 2024).

[8] Kendrick T, Stuart B, Bowers H, Haji Sadeghi M, Page H, Dowrick C, *et al*. Internet and telephone support for discontinuing long-term antidepressants: the REDUCE cluster randomized trial. *JAMA Network Open* 2024;**7**. https://doi.org/10.1001/jamanetworkopen.2024.18383

The qualitative synthesis [3] above was updated, specifically in relation to health professionals, as:

[9] Van Leeuwen E, Maund E, Woods C, Anthierens S, Bowers H, Kendrick T, Christiaens T. Health Care Professional barriers and facilitators to discontinuing antidepressant use: a systematic review and thematic synthesis. *J Affect Disord* 2024;**356**:616–627. https://doi.org/10.1016/j.jad.2024.04.060. The author's accepted manuscript is freely available at: https://eprints.soton.ac.uk/cgi/request_doc?docid=3813259 (accessed 27 November 2024).

In addition, information from the WS1 systematic review [2] above was included in:

Van Leeuwen E, Van Driel ML, Horowitz MA, Kendrick T, Donald M, De Sutter AI, *et al.* Approaches for discontinuation versus continuation of long-term antidepressant use for depressive and anxiety disorders in adults. *Cochrane Database Syst Rev* 2021. https://doi.org/10.1002/14651858.CD013495.pub2 (accessed 27 November 2024).

Five more papers are currently planned on:

[10] The health economics evaluation of the trial in WS5.

[11] The qualitative interviews with patients in WS5.

[12] The qualitative interviews with practitioners in WS5.

[13] The development of the intervention for Urdu-speaking patients.

[14] The implementation framework derived from NPT.

Peer-reviewed presentations at international, national and local conferences

International

1. Glowacka M. *The Role of Health Professionals' Involvement in the Development of the ADvisor Intervention to Support Practitioners Withdrawing Patients from Long-Term Antidepressant Use*. 5th ESRII Conference, Dublin, April 2018.

2. Yao GL. *Economic Evaluation Alongside Randomized Controlled Trials. Case Study: Antidepressant Use*. 5th ESRII Conference, Dublin, April 2018.

3. Yao GL. *Economic Evaluation Alongside Randomized Controlled Trials. Case Study: Antidepressant Use*. International Health Economics Conference, Beijing, August 2018.

4. Yao GL. *Economic Evaluation Alongside Randomized Controlled Trials. Case Study: Antidepressant Use*. International Health Economics Conference, Fujian Medical School, China, November 2019.

5. Reidy C. *Patient and Health Professional Experiences of Reducing Antidepressant Medication within the REDUCE WS4 Feasibility RCT*. 34th Annual Conference of the European Health Psychology Society, Southampton, August 2020.

6. Haji Sadeghi M. *Strategies to Increase Retention of Participants in a Definitive RCT: Aiming to Retain Power in a Study Impacted by COVID-19*. International Clinical Trials Methodology Conference, Harrogate, October 2022.

7. Kendrick T. *REDUCE (REviewing long term antiDepressant Use by Careful monitoring in Everyday practice) Programme*. WONCA Europe Annual Scientific Meeting, Brussels, June 2023.

8. Kendrick T. *REDUCE (REviewing long term antiDepressant Use by Careful monitoring in Everyday practice) Programme*. North American Primary Care Research Group (NAPCRG) Conference, San Francisco, October 2023.

9. Kendrick T. *REDUCE (REviewing long term antiDepressant Use by Careful monitoring in Everyday practice) Programme*. International Society for Affective Disorders (ISAD) conference, Milan, December 2023.

National

1. Kendrick T. *REDUCE Programme to Help People Withdraw from Inappropriate Long-Term Antidepressant Treatment*. Society for Academic Primary Care Annual Scientific Meeting, London, July 2017.

2. Maund E. *Barriers and Facilitators to Discontinuing Antidepressant Use: A Systematic Review and Thematic Synthesis*. SW Society for Academic Primary Care Annual Scientific Meeting, Plymouth, March 2018.

3. Williams S. *Barriers and Facilitators to Discontinuing Antidepressants: Patient and Health Professional Views in UK Primary Care*. SW Society for Academic Primary Care Annual Scientific Meeting, Plymouth, March 2018.

4. Bowers HB. *Development of the ADvisor Intervention to Support Patients Withdrawing from Long-Term Antidepressant Use (Work Stream 3 of the REDUCE Programme)*. SW Society for Academic Primary Care Annual Scientific Meeting, Plymouth, March 2018.

5. Glowacka, M. *The Role of Health Professionals' Involvement in the Development of the ADvisor Intervention to Support Practitioners Withdrawing Patients from Long-Term Antidepressant Use*. SW Society for Academic Primary Care Annual Scientific Meeting, Plymouth, March 2018.

6. Kendrick T. *REDUCE Programme to Help People Withdraw from Inappropriate Long-Term Antidepressant Treatment*. Primary Care Mental Health Conference, Southampton, March 2018.

7. Kendrick T. *Long-Term Antidepressant Prescribing in Primary Care and What Should Be Done about It*. Royal College of Psychiatrists, London, October 2018.

8. Kendrick T. *REviewing Long term Anti-depressant Use by Careful Monitoring in Everyday Practice (REDUCE) Programme*. NIHR School for Primary Care Research Showcase, Oxford, November 2018.

9. Warinton M, Hook A. *Achieving Equilibrium: Patient Perspectives on Feeling Ready to Withdraw from Long-Term Antidepressants*. Royal College of General Practitioners Annual Scientific meeting, Liverpool, October 2019.

10. Kendrick T. *Strategies to Reduce Use of Antidepressants*. Royal College of Physicians, London, November 2019.

11. Kendrick T. *REDUCE Antidepressant Reduction Programme: Work Stream 4 Feasibility RCT*. SW Society for Academic Primary Care Annual Scientific Meeting, Bristol, March 2020.

12. Williams S. *REDUCE Antidepressant Reduction Programme: Work Stream 4 Qualitative Interviews with Patients*. SW Society for Academic Primary Care Annual Scientific Meeting, Bristol, March 2020.

13. Reidy C. *REDUCE Antidepressant Reduction Programme: Work Stream 4 Qualitative Interviews with Health Professionals*. SW Society for Academic Primary Care Annual Scientific Meeting, Bristol, March 2020.

14. Van Leeuwen E. *Health Professionals' Views on Discontinuation of Long-Term Antidepressants: A Systematic Review and Thematic Synthesis*. British Journal of General Practice Research Conference, London, March 2023.

15. Kendrick T. *Keynote: Main Findings of the REDUCE Programme to Help People Withdraw from Inappropriate Long-Term Antidepressant Treatment*. Society for Academic Primary Care Primary Care Mental Health Conference, Bristol, May 2023.

16. Bowers HB. *What Were Health Professionals' Perspectives of Antidepressant Discontinuation During the REDUCE Trial?* Society for Academic Primary Care Annual Scientific Meeting, Brighton, July 2023.

17. Van Leeuwen E. *Health Care Professionals' Barriers and Facilitators to Discontinuing Antidepressant Use: Systematic Review and Thematic Synthesis*. Society for Academic Primary Care Annual Scientific Meeting, Brighton, July 2023.

Local

1. Bowers HB. *Development of the ADvisor Intervention to Support Patients Withdrawing from Long-Term Antidepressant Use (Work Stream 3 of the REDUCE Programme)*. Medical and Health Research Conference, University Hospital Southampton, February 2018.

2. Glowacka M. *The Role of Health Professionals' Involvement in the Development of the ADvisor Intervention to Support Practitioners Withdrawing Patients from Long-Term Antidepressant Use*. Medical and Health Research Conference, University Hospital Southampton, February 2018.

3. Kendrick T, Bowers HB. *REDUCE Work Stream 4. Feasibility RCT*. Wessex CRN Research Scheme Initiative practices meeting, Romsey, October 2019.

4. Tiwari R. *REDUCE Programme Work Stream 5: RCT*. Wessex CRN Research Scheme Initiative practices meeting, Southampton, October 2020.

5. Tiwari R. *Patient and Health Professional Experiences of Reducing Antidepressant Medication as Part of the REDUCE Feasibility RCT*. Faculty of Medicine Conference, University of Southampton, June 2021.

6. Bowers HB. *REDUCE Antidepressant Reduction Feasibility RCT*. Faculty of Medicine Conference, University of Southampton, June 2021.

7. Woods CJ. *What Are the Individual and Contextual Factors That Support Antidepressant Cessation for Adult Patients? A Qualitative Process Evaluation of Patient Experiences within a Large RCT*. Faculty of Medicine Conference, University of Southampton, June 2023.

8. Bowers HB. *What Were Health Professionals' Perspectives of Antidepressant Discontinuation During the REDUCE Trial?* Faculty of Medicine Conference, University of Southampton, June 2023.

9. Haji Sadeghi M. *REDUCE (REviewing long term antiDepressant Use by Careful monitoring in Everyday practice) Programme*. Allam Lecture, University of Hull, May 2023.

National and international media reports

BBC Radio 4, March 2016: BBC Radio 4 – Inside Health, Dementia advice, Antidepressants, Transplant organs, Vaginal seeding.

Mad in America, August 2016: Interview: Researcher Runs Trial on Antidepressant Withdrawal – Mad In America.

The New York Times, August 2018: Psychiatric meds withdrawal: Many people trying to quit antidepressants discover they can't – Health and Wellness – Sott.net.

Sky News, March 2019: Long-term use of antidepressants could cause permanent damage, doctors warn | UK News | Sky News.

The Naked Scientist (podcast), January 2020. Coming off antidepressants | Podcasts | Naked Scientists (thenakedscientists.com).

BBC Panorama, June 2023: BBC One – Panorama, The Antidepressant Story.

The trial results, published in *JAMA Network Open*, were reported by 71 media outlets in July 2024, including 34 newspapers and 37 TV and radio stations, across the UK, USA, Europe, China, Australia and India, including *The Times*, *Guardian*, Sky News, ITV News, LBC Radio, and *ITV's This Morning* (the last two including interviews with Tony Kendrick).

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Appendix 1 Workstream 1

TABLE 2 Barriers and facilitators to discontinuing antidepressants emerging from the WS1 systematic review and qualitative synthesis of patient and professional views

Themes	Barriers (subthemes)	Facilitators (subthemes)
1. Psychological and physical capabilities	Dependence	Confidence in capability to discontinue
	Experience of problematic discontinuation attempts	Coping strategies effective
	Life circumstances difficult	Life circumstances stable
	Routine	Acceptable experience of dose reduction
	Intermittent need	Knowledge to taper
	Coping strategies ineffective	
2. Perception of antidepressants	Positive effect	Ineffectual
	Natural/benign characterisation	Experience of unacceptable side effects
	Lack of concern over side effects	Negative/unnatural characterisation
		Unhappy about long-term use
3. Fears	Fear of relapse	Fear of addiction
	Fear of withdrawal effects	Fear of potential side effects
	Fear – miscellaneous	
4. Intrinsic motivators and goals	Self-identity (disabled, 'good mother/daughter', old)	Self-identity (healthy, true-self, 'good mother/daughter')
	Threat to stability	Desire to function without antidepressants
	Irrational	Feeling better
	Goal priority is benefit of continuing to significant others	Self-stigma of taking antidepressants
	Goal is management rather than cure	
5. The doctor as a navigator to maintenance or discontinuation	Doctor's work practices	Doctor's support/guidance
	Doctor's work issues – lack of time	Doctor recommends/approves discontinuation
	Doctor recommends continuation	
	Doctor's responsibility to initiate discussions about discontinuation	
	Lack or inadequacy of doctor support/guidance	
6. Perceived cause of depression	Long-term condition and treatment	Aetiology – life circumstances, seasonal
	Aetiology – biochemical	
7. Aspects of information that support decision-making	Incongruent information about discontinuation of antidepressants	Information on how to discontinue and what to expect

continued

TABLE 2 Barriers and facilitators to discontinuing antidepressants emerging from the WS1 systematic review and qualitative synthesis of patient and professional views (*continued*)

Themes	Barriers (subthemes)	Facilitators (subthemes)
	Insufficient information on how to discontinue, and of risks and benefits of discontinuation	
8. Significant others – a help or a hindrance	Pressure to continue	Pressure to discontinue
		Support/guidance
9. Support of other health professionals	*No subthemes*	Support

Appendix 2 Workstream 2

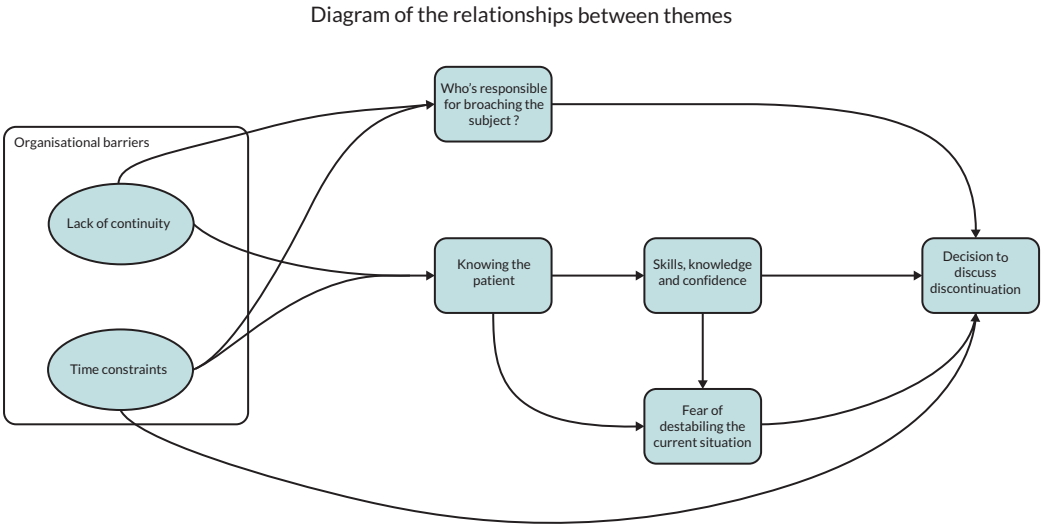

FIGURE 2 Interactions between barriers and facilitators to discontinuation from WS2 health professional focus groups and interviews. Note: This figure was published in Bowers *et al.*[43] https://bmjopen.bmj.com/content/9/7/e027837 © 2019 *British Medical Journal* Publishing Group. This is an open access article under the terms of the Creative Commons Attribution 4.0 International License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

Appendix 3 Workstream 3

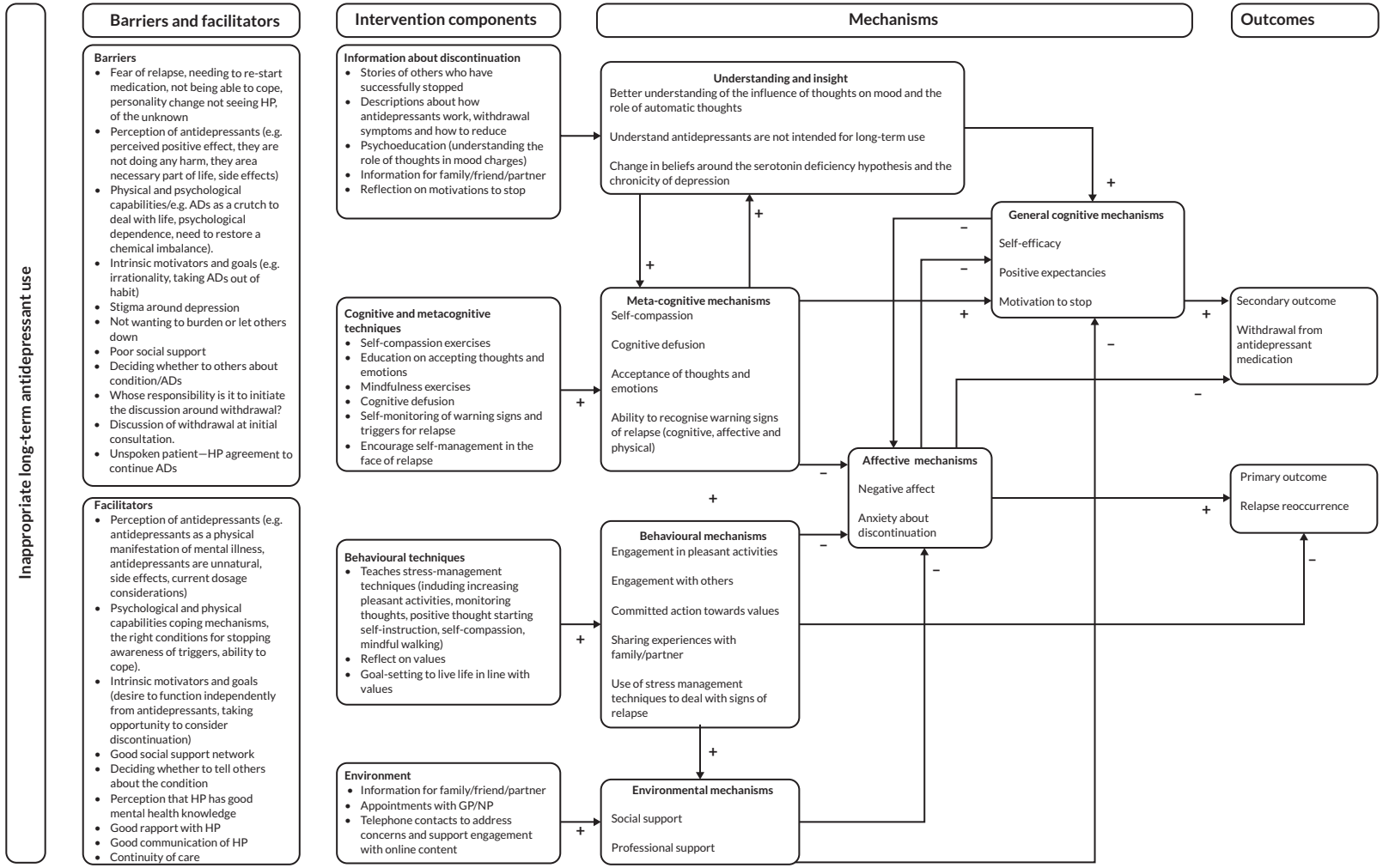

FIGURE 3 Logic model for WS3 development of patient online intervention (*ADvisor*).

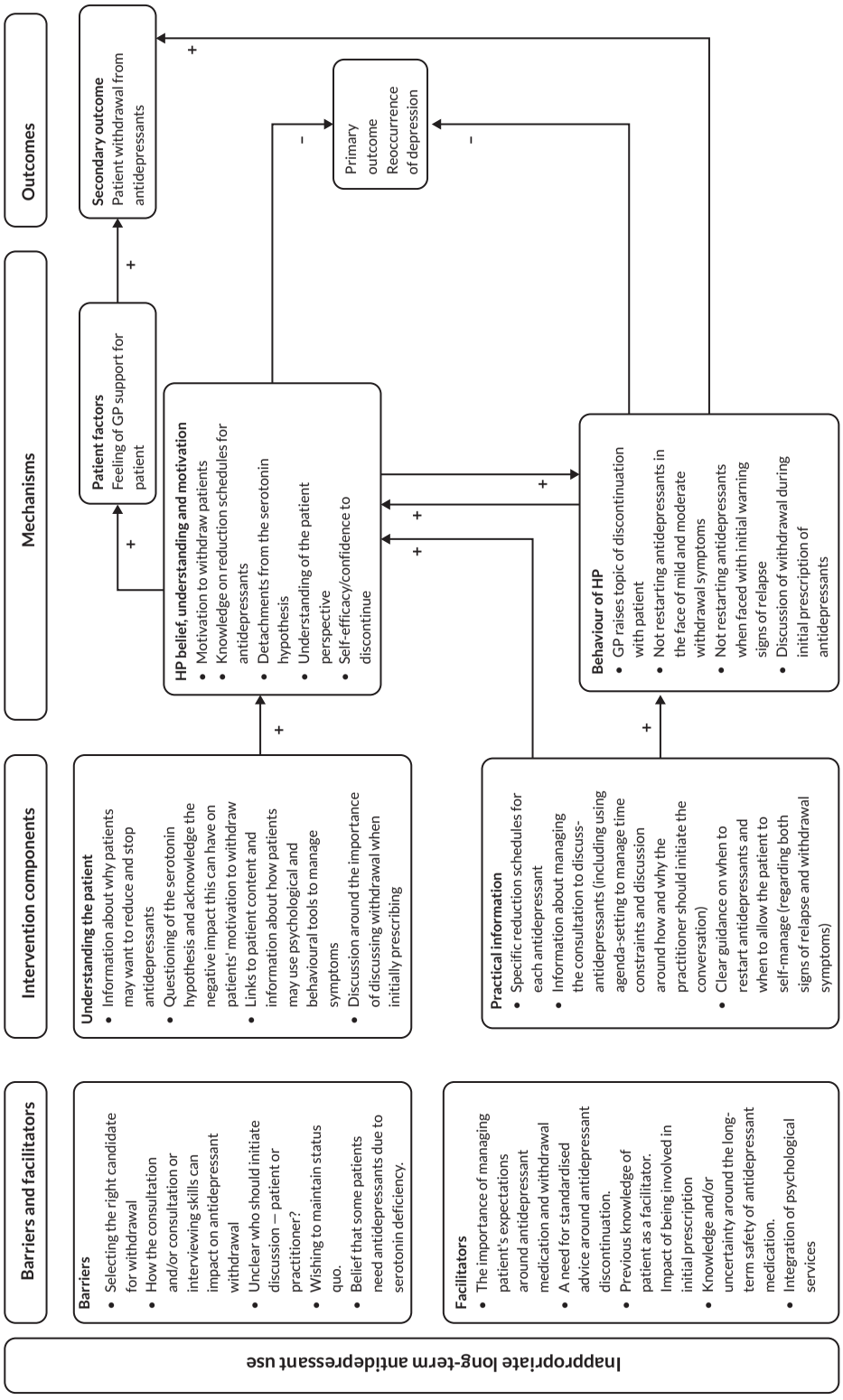

FIGURE 4 Logic model for WS3 development of health professional online intervention (*ADvisorHP*).

TABLE 3 Outline of content of the patient online intervention (*ADvisor*) including supporting evidence and theory

Intervention module	Page	Content	Evidence: Importance of barrier/facilitator content targets OR evidence for effectiveness of content	BCW construct	BCW function	BCTs (taxonomy V1) techniques broadly applied across content sections	SCT construct constructs applied across content sections	NPT construct constructs applied across content sections
Reducing and stopping antidepressants	Welcome							
	Why should I reduce and stop?	Foster a motivation to withdraw through discussion of benefits, reduction of side effects, potential for increase in agency, potential for effective use of alternatives to medication	Bosman *et al*. (2016); Dickinson *et al*. (2010); Verbeek-Heida and Mathot (2006); Iden *et al*. (2011); Karp (1993); Knudsen *et al*. (2002); Eveleigh (2015); Gibson (2016); Schofield (2011)	Reflexive motivation	Enablement; training; education	9.1 Credible source 9.2 Pros and cons 5.2. Persuasion about capability 3.2 Framing-reframing	Knowledge; social outcome expectations; physical outcomeexpectations; self-efficacy (somatic and emotional states)	Coherence: Individual specification Cognitive participation: Initiation
	The downsides	Reflection on the side effects of antidepressants as a means to foster motivation to withdraw		Reflexive motivation	Enablement; training; education			
	When should I reduce and stop?	Highlighting that it is best to start withdrawal at a stable time in life		Psychological capability	Enablement; training; education			
	What to expect	Outline the discontinuation process: that the will provide a schedule, that this is flexible and that there may be side effects but there are ways to manage these and they are often short-lived.		Psychological capability	Enablement; training; education			
	Addressing concerns	Briefly acknowledges that many people have concerns about withdrawal but that there are techniques for dealing with this in		Psychological capability	Enablement; training; education			
	How can my help?	Outline the role of the in discontinuation, when to go to the for support.	Bosman *et al*. (2016); Dickenson *et al*. (2010); Grime and Pollock (2003); Verbeek-Heida and Mathot (2006); Eveleigh (2015); Gibson (2016); Leydon *et al*. (2007); Cartwright (2016)	Physical capability	Enablement; training; education			
	Planning ahead	Overview of the process: will give schedule and, as one tapers, there is support in that can be used		Reflexive motivation	Enablement; training; education			
	Support from family and friends	Highlight how friends and family members can play an important role	Bosman *et al*. (2016); Cromartry (2011); Verbeek-Heida and Mathot (2006); Eveleigh (2015)	Social opportunity	Enablement; training; education	3.1 Social support 3.3 Social support (emotional)		

TABLE 3 Outline of content of the patient online intervention (*ADvisor*) including supporting evidence and theory (*continued*)

Intervention module	Page	Content	Evidence: Importance of barrier/facilitator content targets OR evidence for effectiveness of content	BCW construct	BCW function	BCTs (taxonomy V1) techniques broadly applied across content sections	SCT construct constructs applied across content sections	NPT construct constructs applied across content sections
How to reduce antidepressants	How to reduce	Practical information about tapering schedules		Physical capability	Enablement; training; education	4.1 Instructions on how to perform behaviour 6.1 Demonstration of behaviour (modelling)	Self-efficacy (mastery experiences/ vicarious experiences)	Coherence: Individual specification
	How to reduce (2)	Highlight that there is unlikely to be a need for liquid formulations or pill cutters but, if needed, the can offer some guidance (perhaps via community pharmacist)		Physical capability	Environmental restructuring; Enablement; training; education			
	When to reduce	Reiterate that there are ideal times to begin tapering, such as when no major life events are expected		Psychological capability	Enablement; training; education			
Thinking about antidepressants	What are antidepressants?	Briefly explains what antidepressants are used for. Highlights that while it was believed they work through increasing serotonin, we now know it is more complex than that	Bosman *et al*. (2016); Dickenson *et al*. (2010); Grime and Pollock (2003); Verbeek-Heida and Mathot (2006); Karp (1993); Knudsen *et al*. (2002); Eveleigh (2015); Gibson (2016); Cartwright (2016); Leydon *et al*. (2007)	Reflexive motivation	Enablement; training; education	13.2 Framing/ reframing 15.2. Persuasion about capability	Social outcome expectations; knowledge; physical outcomeexpectations	Coherence: Internalisation
	Can I stop taking them?	Key point: even though we don't know exactly they work, we do know that many people can successfully discontinue		Reflexive motivation	Enablement; training; education			
	Other forms of 'antidepressant'	There are things other than medication which can improve mood. The relationship between brain and behaviour is highlighted through a study which shows that can result in changes in the brain		Reflexive motivation	Enablement; training; education			
	How do antidepressants work	Highlights again that we don't know exactly how they work but we do know: antidepressants help some people and not others and many people can successfully stop		Reflexive motivation	Enablement; training; education			

continued

TABLE 3 Outline of content of the patient online intervention (*ADvisor*) including supporting evidence and theory (*continued*)

Intervention module	Page	Content	Evidence: Importance of barrier/facilitator content targets OR evidence for effectiveness of content	BCW construct	BCW function	BCTs (taxonomy V1) techniques broadly applied across content sections	SCT construct constructs applied across content sections	NPT construct constructs applied across content sections
I'm worried about stopping	I'm worried about stopping	Highlight that many people have concerns about stopping and this is understandable and does not mean you won't be able to discontinue	Bosman *et al.* (2016); Dickinson *et al.* (2010); Verbeek-Heida and Mathot (2006); Iden *et al.* (2011); Karp (1993); Knudsen *et al.* (2002); Eveleigh (2015); Gibson (2016); Schofield (2011); Leydon *et al.* (2007)	Psychological capability	Enablement; training; education	13.2 Framing/ reframing 15.2. Persuasion about capability	Knowledge Self-efficacy (mastery experiences vicarious experiences) Social outcome expectations Knowledge; physical outcome expectations	Cognitive participation: Initiation Cognitive participation: Activation
	Successful stopping	Indicate that many people stop SD without problems, and those who are worried can overcome their concerns		Psychological capability	Enablement; training; education			
	Concerns about stopping	Patients will be given a selection of options to click on to read more about specific concerns		Psychological capability	Enablement; training; education			
	How will I cope if something big happens?	Reassure that *ADvisor* has guidance on managing stress in difficult situations. Signpost to Moving Forward module.		Psychological capability	Enablement; training; education			
	What if I go back to how I was before?	Reassure that *ADvisor* has guidance on preventing relapse and signpost to Keeping Well module.		Psychological capability	Enablement; training; education			
	What if I have to start taking antidepressants again?	Reassure that hopefully this won't be necessary because they will learn how to prevent relapse, but if it is, they can try withdrawing again in future		Psychological capability	Enablement; training; education			
	How will I manage my responsibilities?	Guidance on planning activities and highlight the importance family support as well as the timing of the tapering process		Psychological capability	Enablement; training; education			
	Dealing with worries	Reflecting on the motivations to discontinue and weighing these up against concerns.		Reflexive motivation	Enablement; training; education			

TABLE 3 Outline of content of the patient online intervention (*ADvisor*) including supporting evidence and theory (*continued*)

Intervention module	Page	Content	Evidence: Importance of barrier/facilitator content targets OR evidence for effectiveness of content	BCW construct	BCW function	BCTs (taxonomy V1) techniques broadly applied across content sections	SCT construct constructs applied across content sections	NPT construct constructs applied across content sections
Keeping well	Keeping well	Introduce to the idea of relapse prevention	Kuyken (2008); Allen (2009); Kuyken (2010); Fava (1998); Cromarty (2011); Otto (2010)	Psychological capability	Enablement; training; education	11.2 Reduce negative emotions 13.2 Framing/ reframing 6.1 Demonstration of behaviour 4.3 Reattribution	Knowledge Goals Self-efficacy (Mastery experiences vicarious experiences) Social outcome expectations Knowledge; physical outcome expectation	Cognitive participation: Activation
	Automatic pilot	Define running on autopilot and explain negative automatic thoughts		Psychological capability	Enablement; training; education			
	The power of thoughts	Explain how the way we think impacts mood and teach cognitive defusion (thoughts are not facts)		Psychological capability	Enablement; training; education			
	Let it be	Defining the term 'acceptance' and why it is useful in dealing with difficult thoughts and feelings		Psychological capability	Enablement; training; education			
	Recognising warning signs	Explaining and reflecting on what thoughts and physical sensations might be indicators of relapse		Psychological capability	Enablement; training; education			
	Recognising triggers	Reflecting on situations that might trigger a relapse		Psychological capability	Enablement; training; education			
	Recognising relapse	Writing down warning signs and triggers and saving these to view later		Psychological capability	Enablement; training; education			
	Responding differently	Highlight that you cannot change thoughts or the things that happen in life, but you have a choice how to respond to these. Responding in more helpful ways can prevent relapse		Psychological capability	Enablement; training; education			
	Preventing relapse	1. Take a breath 2. Make a decision on how to act 3. Take action		Psychological capability	Enablement; training; education			

continued

TABLE 3 Outline of content of the patient online intervention (*ADvisor*) including supporting evidence and theory (*continued*)

Intervention module	Page	Content	Evidence: Importance of barrier/facilitator content targets OR evidence for effectiveness of content	BCW construct	BCW function	BCTs (taxonomy V1) techniques broadly applied across content sections	SCT construct constructs applied across content sections	NPT construct constructs applied across content sections
Thinking about what you value	What are values	Defines values as like a compass point providing direction for our lives.	Swain *et al.* (2013); Powers *et al.* (2009)	Psychological capability	Enablement; training; education	11.2 Reduce negative emotions 13.2 Framing/ reframing 6.1 Demonstration of behaviour 4.3 Reattribution	Knowledge, goals	Coherence: Internalisation
	What do I value?	Provides a space to write down what they value		Psychological capability	Enablement; training; education			
	Goals	Explaining the need to set goals in order to act in line with our values		Psychological capability	Enablement; training; education			
	Setting goals	Guidance and space to write goals		Psychological capability	Enablement; training; education			
	Meeting goals	Reminds users to revisit this section to review their goals and see if they have met them		Psychological capability	Enablement; training; education			
Dealing with withdrawal symptoms	What are withdrawal symptoms?	Describes what they are and that they are a consequence of the brain and body adapting to the change in medication	Bosman *et al.* (2016); Dickinson *et al.* (2010); Verbeek-Heida and Mathot (2006); Iden *et al.* (2011); Karp (1993); Knudsen *et al.* (2002); Eveleigh (2015); Gibson (2016); Schofield (2011); Leydon *et al.* (2007)	Psychological capability Physical capability	Enablement; training; education	13.2 Framing/ reframing 6.1 Demonstration of behaviour 4.3 Reattribution	Social outcome expectations	Cognitive participation: Activation
	Recognising withdrawal symptoms	This page highlights that there are different symptoms that might be physical or mental. Specific details of what symptoms may occur are not given	Psychological capability	Psychological capability Physical capability	Enablement; training; education			
	Thinking about withdrawal symptoms	Explains that the way we think about symptoms can change how much impact they have (e.g. if you mistake a withdrawal symptom for relapse, it may be harder for the symptom to pass)		Psychological capability Physical capability	Enablement; training; education			
	Knowing the difference	Details about the differences between withdrawal symptoms and relapse		Psychological capability Physical capability	Enablement; training; education			

TABLE 3 Outline of content of the patient online intervention (*ADvisor*) including supporting evidence and theory (*continued*)

Intervention module	Page	Content	Evidence: Importance of barrier/facilitator content targets OR evidence for effectiveness of content	BCW construct	BCW function	BCTs (taxonomy V1) techniques broadly applied across content sections	SCT construct constructs applied across content sections	NPT construct constructs applied across content sections
	Dealing with withdrawal symptoms	Mild symptoms can be tolerated and will pass, moderate symptoms can be treated by a doctor, and severe symptoms may indicate a slower taper is needed		Psychological capability Physical capability	Enablement; training; education			
	Accepting withdrawal symptoms	Guidance on accepting/tolerating symptoms based on acceptance and commitment exercises used with chronic physical symptoms		Psychological capability Physical capability	Enablement; training; education			
Moving forward	Healthy Paths Through Stress intervention (Healthy Paths). See Geraghty *et al.* (2017) for full description	This module is based on an intervention aimed at managing life stresses. The modules have been developed as part of a separate project and their content will be incorporated into *ADvisor*. This section will include guidance on mindfulness practices and behavioural activation	Muñoz *et al.* (2005); Geraghty *et al.* (2016)	Psychological capability	Enablement; training; education	11.2 Reduce negative emotions 13.2 Framing/ reframing 6.1 Demonstration of behaviour 4.3 Reattribution	Knowledge Goals Self-efficacy (mastery experiences vicarious experiences) Social outcome expectations Knowledge; physical outcome expectations	Coherence: Individual specification Coherence: Internalisation Cognitive participation: Initiation Cognitive participation: Activation

BCW, behaviour change wheel;[47] BCT, behaviour change technique;[71] SCT, social cognitive theory;[72] NPT, normalisation process theory.[42]

TABLE 4 Outline of content of the health professional online intervention (*ADvisorHP*) plus supporting evidence and theory

Intervention module	Page	Content	Evidence	NPT construct	BCW construct
Why reduce and discontinue antidepressants?	Who is eligible to discontinue?	A bullet point list of criteria a patient should meet to be considered eligible to discontinue treatment, based on NICE guidelines	During focus groups, practitioners reported wanting more information about assessing who would be suitable to discontinue and that they would like information from existing guidelines to be presented more clearly and accessibly	Individual specification	Psychological capability
	Why reduce and stop antidepressants?	Provides a rationale for discontinuation by highlighting that many patients would rather not take antidepressants if they can stay well, and that many people won't relapse if they discontinue	Using NPT, primary qualitative work with health professionals indicates that evidence that the intervention can benefit patients is important with regards to encouraging the practitioners to engage with the intervention	Enrolment, systematisation, Internalisation	Reflective motivation
	Patient problems from taking antidepressants long term	Highlights the problems encountered by patients such as side effects, which worsen with the length of treatment	Primary qualitative work with practitioners indicates that they would like information about the long-term safety of antidepressants and that this would be beneficial in engaging practitioners in the intervention	Enrolment, internalisation, communal specification	Reflective motivation
	Guidelines for using antidepressants	Summarises the NICE guidance on prescribing antidepressants, including for how long they should be prescribed	Focus groups with health professionals suggest that there is a need for the information around discontinuation in existing guidance to be highlighted and made more accessible	Individual specification	Psychological capability
	Research on relapse rates	Summary of research on relapse rates in patients who withdrew from antidepressants by taking a placebo	Think-aloud interviews and focus groups suggest that practitioners are fearful of destabilising currently well patients and may need reassuring that many patients will continue to feel well after discontinuation	Systematisation	Reflective motivation
	Alternatives to antidepressants	Provides evidence that psychological methods can also prevent relapse	Practitioners in the focus groups report that they would like an intervention to be evidence-based and that this would help them to engage with the intervention.	Enrolment	Reflective motivation
	Why reduce and stop antidepressants (2)	Highlights patient experiences with side effects and that psychological support can be helpful in preventing relapse.	Focus groups with health professionals indicate that practitioners are not always aware of reasons why the patient may want to discontinue.		Reflective motivation
Broaching the subject	Broaching the subject	Summary of module content	Primary qualitative work suggests that practitioners disagree about whether the responsibility for raising the possibility of discontinuation lies with the practitioner or patient. Many agreed that it should be a shared decision. This module therefore highlights this issue to practitioners, along with evidence that many patients feel it is the practitioner's responsibility to initiate the discussion around withdrawal	Legitimation, skill-set workability	Social opportunity
	Who should initiate the conversation?	Highlights conflicting views between patients and practitioners about who should raise the issue		Skill-set workability	Reflective motivation, social opportunity

TABLE 4 Outline of content of the health professional online intervention (*ADvisorHP*) plus supporting evidence and theory (*continued*)

Intervention module	Page	Content	Evidence	NPT construct	BCW construct
	The role of the GP	Highlights what patients expect from their GP with regards to managing discontinuation		Skill-set workability	Social opportunity
	Patient perspectives	Acknowledge that patients may have understandings of antidepressants that do not facilitate discontinuation (e.g. seeing depression as a lifelong condition caused by low serotonin levels)	As there are a number of conflicting ideas about how antidepressants work, and belief in the serotonin hypothesis is considered a barrier to withdrawal for patients (according to the primary qualitative work and the qualitative synthesis), this information was included to ensure all practitioners provide information that is consistent with the information given to patients regarding how antidepressants work	Communal specification, internalisation	Psychological capability
	Talking to the patient	Highlights the importance of stating clearly that you plan to discuss antidepressant withdrawal. Explains that patients may need reassuring that they can come off and stay well. Agreeing a time to start tapering	Practitioners reported that both time constraints in consultations and confidence to de-prescribe were important in terms of being able to support patients through discontinuation. Providing information on how to have these initial discussions may build confidence and will also help practitioners to manage their limited time	Legitimation	Physical capability, psychological capability
	Reassurance and addressing concerns	Ask about patient's concerns and offer reassurance. Asking about additional concerns earlier in the consultation will help to address these concerns and manage time in consultation	Practitioners reported that both time constraints in consultations and confidence to de-prescribe were important in terms of being able to support patients through discontinuation. Providing information on how to have these initial discussions may build confidence and will also help practitioners to manage their limited time	Legitimation	Physical capability, psychological capability
When to start tapering	Dealing with relapse	Summary of module content	Practitioners stated during focus groups that an ideal intervention would contain information about when to consider discontinuation and reported that ability to assess the 'ideal' patient could be a facilitator to withdrawing	Internalisation	Psychological capability
	The patient has responded to treatment	Patients who have responded to antidepressants and have few residual symptoms are suitable for tapering		Internalisation	Psychological capability
	Things to consider	Those who are currently at high risk of relapse, currently experiencing major life events, do not have adequate support may not be suitable to withdraw. Time of year should also be considered		Internalisation	Psychological capability

continued

TABLE 4 Outline of content of the health professional online intervention (*ADvisorHP*) plus supporting evidence and theory (*continued*)

Intervention module	Page	Content	Evidence	NPT construct	BCW construct
	Research on residual symptoms	Evidence that many patients have some residual symptoms and that limiting withdrawal to only those with no symptoms would result in very few patients being offered to discontinue	Evidence base for considering patients for discontinuation	Internalisation	Reflective motivation
Antidepressant reduction schedules	Antidepressant reduction schedules	Summarises four plans for withdrawal depending on characteristics of the patient and their treatment	When asked about what information would support them when helping a patient to discontinue ADs, practitioners reported that specific guidance on tapering and information about particular types of ADs is needed	Internalisation, activation	Psychological capability
	Plan A	Schedules for patients with few problems, no history of distressing withdrawal and no fear of withdrawal over 4–6 weeks		Internalisation, activation	Psychological capability
	Plan B	Schedules for patients taking antidepressants associated with more withdrawal symptoms		Internalisation, activation	Psychological capability
	Plan C	Schedules for patients with a difficult history of withdrawal or a fear of withdrawing over 6 weeks or less		Internalisation, activation	Psychological capability
	Plan D	Schedules for patients taking tricyclic antidepressants, in particular older patients at risk of cholinergic rebound		Internalisation, activation	Psychological capability
Dealing with withdrawal symptoms	Withdrawal symptoms (1)	Summary of information in this module	When asked what information needed to be available in the intervention, practitioners reported the need for information around discontinuation effects		Psychological capability
	Withdrawal symptoms (2)	Provides a list of possible symptoms but explains that it may be best to explain to patients only the common symptoms so as to avoid expectations influencing symptoms		Individual specification	Psychological capability
	Distinguishing relapse from withdrawal	Information about the differences between withdrawal and relapse		Individual specification, differentiation	Psychological capability
	Guidance for dealing with withdrawal symptoms	Guidance on dealing with mild, moderate and severe withdrawal symptoms as well as guidance on dealing with patients who report suicidal thoughts		Individual specification	Psychological capability

TABLE 4 Outline of content of the health professional online intervention (*ADvisorHP*) plus supporting evidence and theory (*continued*)

Intervention module	Page	Content	Evidence	NPT construct	BCW construct
Dealing with relapse	Dealing with relapse	Summary of module content	Practitioners suggested that relapse prevention planning tools should be provided for both practitioners and patients. While patients receive information about how to self-manage through identifying their warning signs and triggers, practitioners are provided with links to this patient information as well as guidance on dealing with and preventing relapses with patients		Psychological capability
	Distinguishing relapse from withdrawal	Information about the differences between relapse and withdrawal		Individual specification, differentiation	Psychological capability
	ADvisor to help patients prevent relapse	A summary of how the patient digital intervention, '*ADvisor*', can support patients in recognising warning signs and managing stress in order to help prevent relapse		Internalisation	Psychological capability
	Treating relapse	A summary of when it might be advisable to reinstate their antidepressants (symptoms of relapse not caused by withdrawal, not helped by relapse prevention techniques and not helped by techniques for dealing with difficult life events)		Individual specification	Psychological capability
ADvisor for patients		This section gives a brief overview of the content in patient intervention	Practitioners report time constraints as a barrier to managing withdrawal. By allowing practitioners to view and recommend content for patients to look at outside of the consultation, this may help practitioners to support patients within their time constraints	Communal specification	Physical capability
Printable pages		This section provides a page that can be printed and given to the patient	GPs reported that the physical act of handing a patient a piece of paper can have therapeutic value in a consultation	Differentiation	Physical capability
Resources		Links to relevant papers and guidelines	Practitioners reported during focus groups that they had difficulty with accessing current guidelines and did not always know where to find these	Relational integration	Psychological capability

Note
Participating practitioners in intervention arm practices were given login details to access *ADvisorHP*, a digital intervention for practitioners. Once logged in, practitioners could access any intervention module in any order.

FIGURE 5 Screenshot of opening page of *ADvisor* online intervention for patients. Reproduced from Kendrick,[1] with permission from John Wiley & Sons on behalf of the British Pharmacological Society.

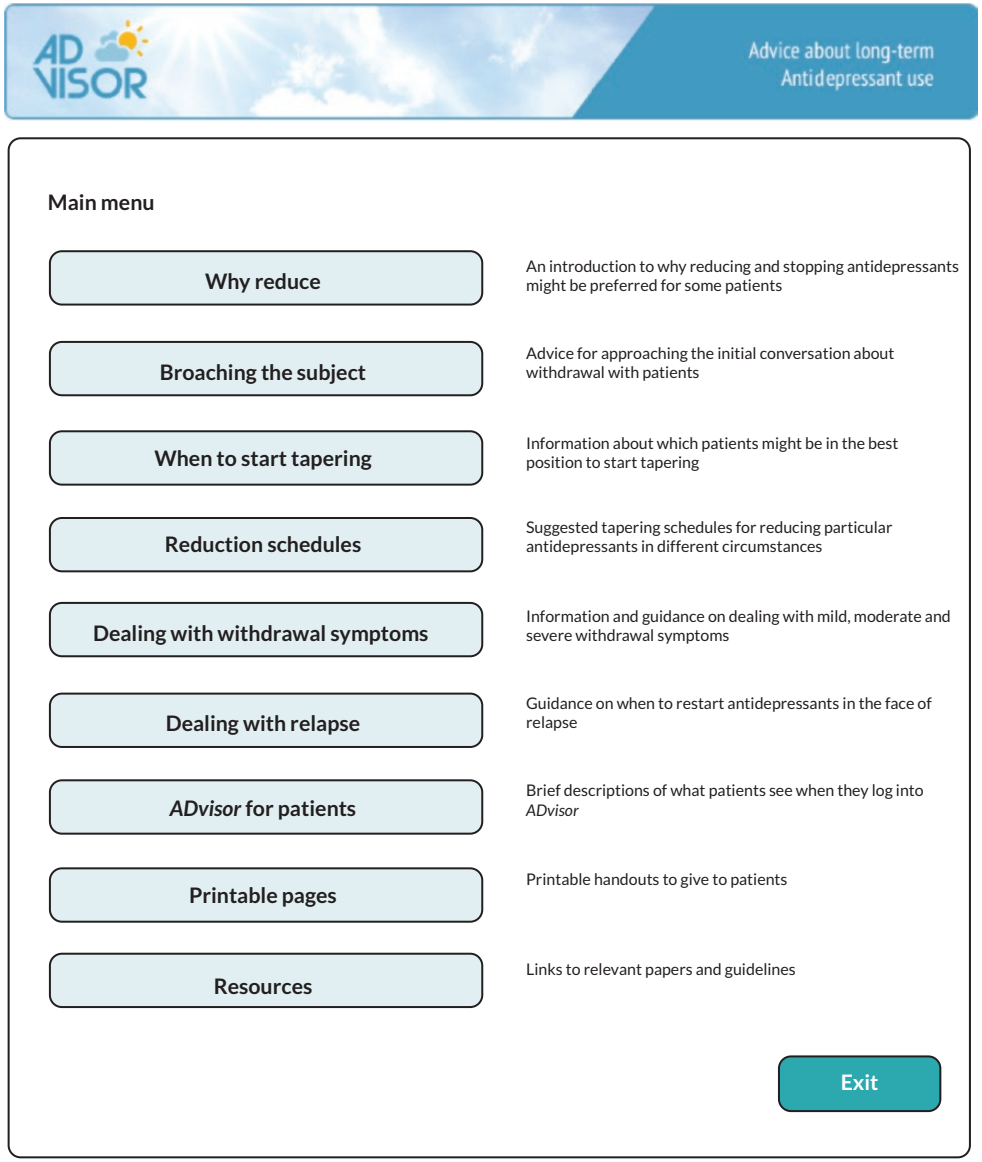

FIGURE 6 Screenshot of opening page of *ADvisorHP* online intervention for health professionals. Reproduced from Kendrick, with permission from John Wiley & Sons on behalf of the British Pharmacological Society.

Appendix 4 Workstream 4

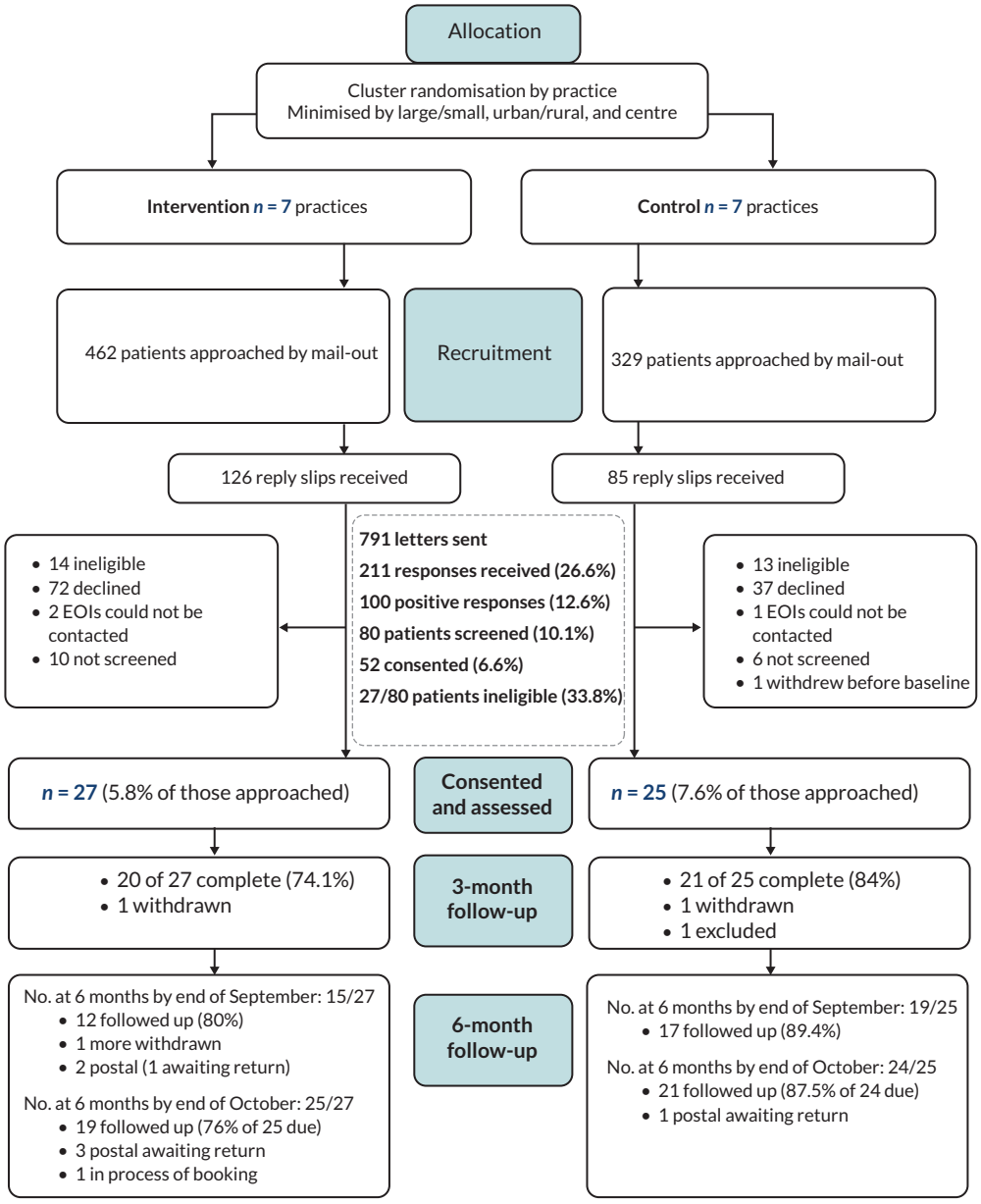

FIGURE 7 REDUCE WS4 feasibility RCT CONSORT diagram.

TABLE 5 REDUCE WS4 qualitative analysis of practitioner interviews using NPT

Constructs	Components	Themes	Subtheme
1.1 Coherence	1.1 Differentiation	1.1.1 Current role	
		1.1.2 Current perceived knowledge	
		1.1.3 Changes in practice	
		1.1.4 Aligning with current practice or priorities	
	1.2 Communal specification	1.2.1 Discussions within general surgery meetings impacted on taking part	1.2.1.1 Good previous experience of the earlier parts of the study (establishing networks)

TABLE 5 REDUCE WS4 qualitative analysis of practitioner interviews using NPT (*continued*)

Constructs	Components	Themes	Subtheme
			1.2.1.2 Ascertaining the fit of the study within the surgery through team discussions
	1.3 Individual specification	1.3.1 The GP role to support people to come off of antidepressants	
		1.3.2 While some 'cannot cope' without antidepressants	
		1.3.3 There is a lot of pressure on GPs to make the right decision about antidepressants	
	1.4 Internalisation	1.4.1 Guidelines	
		1.4.2 Approach to medication review	
		1.4.3 Wary about impacting on a patient's 'other' health issues	
		1.4.4 Patients need more holistic support	
		1.4.5 *AdvisorHP* contributes to educational development	
2. Cognitive participation	2.1 Initiation	2.1.1 Key staff members pushing the study forward	
		2.1.2 Study of interest to patient population	
		2.1.3 Active encouragement to patients to take part	
		2.1.4 Realistic recruitment targets	
		2.1.5 Desired more reassuring data around tapering off of antidepressants	
		2.1.6 Refresher training required	
		2.1.7 Relied on more 'motivated' GPs to remember to recruit for REDUCE	
		2.1.8 Normalisation of research study through team discussions	
	2.2 Enrolment	2.2.1 Protected time for research	2.2.1.1 Dedicated research time
			2.2.1.2 Support required within surgery
		2.2.2 Involvement from fellow practitioners	2.2.2.1 Getting as many practitioners involved as possible
			2.2.2.2 Need to renegotiate roles within a surgery
		2.2.3 Considered intervention as part of continuing professional development/continuing professional education	
		2.2.4 Approaches to keep up motivation, prioritisation and ease of access	2.2.4.1 Reminders and retraining
			2.2.4.2 Research team need to adapt to the surgeries
			2.2.4.3 Saving intervention under favourites

continued

TABLE 5 REDUCE WS4 qualitative analysis of practitioner interviews using NPT (*continued*)

Constructs	Components	Themes	Subtheme
	2.3 Legitimisation	2.3.1 Lack of investment from practitioner colleagues	
		2.3.2 For more unusual circumstances/antidepressants the intervention could be considered useful	
		2.3.3 Provides confirmation of what the GP is 'already doing'	
		2.3.4 REDUCE seems like a useful intervention	
		2.3.5 Fits into GP roles so straight forward to recruit	
		2.3.6 Flexible study procedures	
	2.4 Activation	2.4.1 Actively checking in with patients	
		2.4.2 Difficulty remembering passwords	
		2.4.3 Need protected research time and appointments	
		2.4.4 Need reminders and retraining	
3. Collective action	3.1 Interactional workability	3.1.1 Streamlined appointment systems	
		3.1.2 Problems with the technology used for implementing the inclusion and exclusion criteria within surgeries	
		3.1.3 Communication with other surgeries/shared practice	
	3.2 Relational integration	3.2.1 Gaining comprehension of the website before sharing with other patients	
		3.2.2 Need for regular communication, prompts and updates from study team	
	3.3 Skill-set workability	3.3.1 Clear roles (research coordinator/mental health specialist GPs) within GP surgeries helped manage the study and participants	
		3.3.2 Collective action and understanding within surgeries	
		3.3.3 Smaller patient lists meant surgeries could manage patient lists with confidence	
		3.3.4 Time limits and lack of staff	
	3.4 Contextual integration	3.4.1 Need for clear research procedures	
		3.4.2 Sending reminders to patients	
		3.4.3 Utilising different mediums to spread the word about the study	
		3.4.4 Undertaking the searches in batches rather than the entire patient population	

TABLE 5 REDUCE WS4 qualitative analysis of practitioner interviews using NPT (*continued*)

Constructs	Components	Themes	Subtheme
4. Reflexive monitoring	4.1 Systematisation		
	4.2 Communal appraisal		
	4.3 Individual appraisal		
	4.4 Reconfiguration		

Note
Analysis of the practitioner qualitative interviews was carried out using NPT constructs and components as a framework, combined with thematic analysis under the NPT elements. Claire Reidy led on this analysis.

Coherence

The sense-making work that people do individually and collectively when they are faced with the problem of operationalising some set of practices.

1.1 Coherence – differentiation

To understand how agents understand that a set of practices and their objects are different from each other.

1.1.1 Current role

- Current role is to provide knowledge about the medications and review patients they put on antidepressants.

1.1.2 Current perceived knowledge

- Many GPs felt that they already knew all about antidepressant tapering and did not need guidance, while others sought guidance and appreciated having it all in one place.
- Or new information but which is uncomfortable 'it does mention about swapping to another medication, which I – I don't know. I think I've not been so comfortable with doing that'. Some said 'gave ideas for the future'. The information can be comforting and confirmatory/legitimise current practice.
- Some did not appreciate new suggestions for tapering than that which they already undertook with patients.
- Others said it gave ideas for the future, and the information could be confirmatory and legitimise current practice.
- Said people need easy access to psychological support and life coaching, counselling, and support to manage their mental health.
- Some say there is a lack of guidance about what GPs should do to support people to come off.
- GPs will use guidelines if they are easy to access.

1.1.3 Changes in practice

- Happy to take part in the study because it would not be 'opening up the floodgates' and that they think most patients are happy with how they are feeling so do not want or need to come off.
- They did also recognise that the invitation to the study presents a new opportunity to come off, provides a thinking point.
- Some acknowledged that most of these patients are not reviewed at all, largely due to lack of time.

1.1.4 Aligning with current practice or priorities

- Like giving print offs to patients and *AdvisorHP* allows for that so more likely to use it this way as fits into how they do consultations.
- Some GPs discussed this study coinciding with their active review of medication in trying to reduce patients off meds they do not need, so it fit in with their priorities, as well as the opportunity to provide useful extra psychological support.

1.2 Coherence – communal specification

Sense-making relies on people working together to build a shared understanding of the aims, objectives and expected benefits of a set of practices.

1.2.1 Discussions within general surgery meetings impacted on taking part

1.2.1.1 Good previous experience of the earlier parts of the study (establishing networks)

- Where the surgery had good previous experience being involved in earlier parts of the study, and acknowledged that a lot of their patients are on antidepressants it meant that taking part in the feasibility study was a good move for them (will add quotes – CR).

1.2.1.2 Ascertaining the fit of the study within the surgery through team discussions

- The study fit with the patient population.
- They discussed it collectively and it fit with their capabilities as a surgery.
- They now have a research clinic so it is easier to take part.
- Decided as it was a small recruitment size they could take part.
- Agreed it provided an opportunity for a nudge for patients to try to come off of antidepressants.
- Where there were uncertainties about taking part, it relied on key GP members to agree to take part in the study.
- If it had not formally been discussed with them there was confusion over roles and tasks.
- General team meetings help the dissemination and discussion around the website and study (intervention). All GPs are involved in trials (normalised).

1.3 Coherence – individual specification

Sense-making has an individual component too. Here, participants in coherence work need to do things that will help them understand their specific tasks and responsibilities around a set of practices.

1.3.1 The general practitioner role to support people to come off of antidepressants

- Some GPs said that they felt people get put on medications and get stuck on them, and then do not question what their doctor is prescribing, so need a nudge need to be asked the question, and then support them through it, so the study enables this to occur: Understanding the importance of people coming off of antidepressants is useful to learn for the GP role and to drive forward from the study team – some GPs felt it was important for people to come off of antidepressants, and some did not agree with this (yet were surprised with the results).

1.3.2 While some 'cannot cope' without antidepressants

- Where practitioners felt that some patients could not cope without antidepressants, and have had bad experiences of people trying to come off of antidepressants and not coping without them, they were wary about the study, and needed to consider more vulnerable patients.

1.3.3 There is a lot of pressure on general practitioners to make the right decision about antidepressants

- There is a lot of pressure on GPs, and a lack of guidance, and time to explore issues with the patients, and yet a lot of trust goes into the practitioner's judgement on antidepressant use and tapering.

1.4 Coherence – internalisation

Sense-making involves people in work that is about understanding the value, benefits and importance of a set of practices.

1.4.1 Guidelines

- Some say there is a lack of guidance about what GPs should do to support people to come off.
- GPs will use guidelines if they are easy to access, and so this study could provide that support.
- Current role is to provide knowledge about the medications and review patients they put on antidepressants.

1.4.2 Approach to medication review

- GPs state that they follow up patients but also that they tend to leave people on their own to stop, presuming they would have come to them if they wanted to come off. And that patients are more passive and trust their doctor to review things. People get stuck on medications – do not get reviewed. People do not question what the doctor is prescribing.
- Some declare their current process is patient centred and they allow the patient to come to them to come off and decide for themselves, and that they do not consider antidepressants dangerous to stay on.
- One GP was surprised at some patients coming off that they would not have expected to.
- In an ideal world, they would be actively reviewed.
- Some GPs are wary about approaching patients who have been on them for a long time and who they do not know at all, so these patients can get left. They try to gauge the history of these patients from the notes but what actually happens to these patients were not really covered.
- Much more proactive with those they put on antidepressants and are followed up soon after. If it is currently 'not the right time', then there was not much mention of those who get passed that stage.
- Forgetting to let people know that once they go on meds, they will try and get them off them again once they are 'better'.

1.4.3 Wary about impacting on a patient's 'other' health issues

- If someone has a lot of health issues, you do not want to add to their burden (by taking them off antidepressants).

1.4.4 Patients need more holistic support

- Some GPs express feeling people need more holistic support.

1.4.5 *AdvisorHP* contributes to educational development

- And some felt that *AdvisorHP* contributes to educational development.

Cognitive participation

Cognitive participation is the relational work that people do to build and sustain a community of practice around a new technology or complex intervention.

2.1 Cognitive participation – initiation

When a set of practices is new or modified, a core problem is whether or not key participants are working to drive them forward.

2.1.1 Key staff members pushing the study forward

- Key members of the GP surgery pushing the study forward and encouraging others to get involved.

2.1.2 Study of interest to patient population

- Felt the study was of interest to their patient population.

2.1.3 Active encouragement to patients to take part

- Actively encouraging the patients to look at the Advisor website, or asking them about their contact with the PWP.
- Realistic to recruit for, and has protected research time to undertake this.

2.1.5 Desired more reassuring data around tapering off of antidepressants

- Some GPs felt that they would have understood the study better, prioritised it more or worked harder on the study if they had more 'reassuring' data.

2.1.6 Refresher training required

- It was suggested that refresher training would be beneficial for sites to address the inevitable big gap between SIV and patients starting the trial.

2.1.7 Relied on more 'motivated' general practitioners to remember to recruit for REDUCE

2.1.8 Normalisation of research study through team discussions

- Useful to normalise discussion of research projects at site meetings and all GPs being involved in trials at sites.

2.2 Cognitive participation – enrolment

Participants may need to organise or reorganise themselves and others in order to collectively contribute to the work involved in new practices. This is complex work that may involve rethinking individual and group relationships between people and things.

2.2.1 Protected time for research

Some GP surgeries had protected time for research which they felt helped them take part and study *AdvisorHP*

2.2.1.1 Dedicated research time

- Dedicated research time and research roles and time slots (mornings).

2.2.1.2 Support required within surgery

- Had some support from the study team, but needed more (either internally or main research team).

2.2.2 Involvement from fellow practitioners

2.2.2.1 Getting as many practitioners involved as possible

- Put work into getting as many GPs involved as possible – investment into research from surgery – all doing the same thing and providing a consistent service.

2.2.2.2 Need to renegotiate roles within a surgery

- Renegotiating roles within the surgery to support recruitment – such as involving prescribing nurses.

2.2.3 Considered intervention as part of CPD/CPE

- Considered intervention as part of CPD/CPE and so it aligned with priorities in job role.

2.2.4 Approaches to keep up motivation, prioritisation

2.2.4.1 Reminders and retraining

- Need reminders and retraining to keep motivation up and prioritisation of the study within the surgery.

2.2.4.2 Research team need to adapt to the surgeries needs

- Research team need to adapt to GP's needs and spoon-feed them or drip-feed information so they are not overwhelmed, as well as providing flow charts and checking back for support.

2.2.4.3 Saving intervention under favourites

- Saving *AdvisorHP* under favourites would have helped access to the intervention for practitioners.

2.3. Cognitive participation – legitimation

An important component of relational work around participation is the work of ensuring that other participants believe it is right for them to be involved, and that they can make a valid contribution to it.

2.3.1 Lack of investment from practitioner colleagues

2.3.2 For more unusual circumstances/antidepressants, the intervention could be considered useful

- One GP said that the study participants have been on 'easier' drugs to reduce, but if patients are on more difficult drugs to taper off of, the intervention could be useful to the GP.
- However, for some, it may have additional information on there too, to what they already knew. And sometimes expectations of what is on there can be 'too high'.

2.3.3 Provides confirmation of what the general practitioner is 'already doing'

- For some, it 'confirms' what the GP 'is already doing', but also that it is important to get people off of antidepressants (due to side effects and psychological dependence).

2.3.4 REDUCE seems like a useful intervention

- A cost-effective and quick therapy, web-based and telephone support, and also holistic therapy (like REDUCE) was seen as valuable.

2.3.5 Fits into general practitioner roles, so straightforward to recruit

Also thinking that it is possible to recruit for, as it is straightforward and fits into GP roles – so not having to do extra

2.3.6 Flexible study procedures

- There was a lot of variability and no right or wrong answers – found this reassuring.

2.4 Cognitive participation – activation

Once it is underway, participants need to collectively define the actions and procedures needed to sustain a practice and to stay involved.

2.4.1 Actively checking in with patients

- Some GPs have, at times, been attempting to check in with patients to see if they are using the web-based or telephone intervention.
- Some GPs were more proactive with these patients – feeling they might be less well than people they would usually approach so would ask them to come back for review, unlike their usual care.

2.4.2 Difficulty remembering passwords

- Difficulty remembering the passwords, this can be a barrier – so some GPs suggest having no password for the intervention.
- Saving the website as a favourite on your computer means it is easier to access as a reference point for providing advice to patients.

2.4.3 Need protected research time and appointments

- In addition to no password, a useful procedure for accessing *AdvisorHP* would be to have protected research time.
- To avoid confusion for patients, have protected GP time with protected appointments that patients can be booked into – so that they get appointments straight away rather than having to wait.

2.4.4 Need reminders and retraining

- Reminders/retraining would have been useful moving forward with the study as there was quite a big gap between the SIV and patient recruitment/GP appointment for tapering.
- If the process was not completely clear to GPs, then they, at times, tried to recruit patients opportunistically without giving them an opportunistic pack – so these participants did not get enrolled onto the study. This was the case for complicated paperwork too.
- However, the opportunistic packs were also used correctly handed out – although perhaps not with the full inclusion/exclusion criteria applied. But this was backed up by the screening process within the study, as a safety net.

Collective action

Collective action is the operational work that people do to enact a set of practices, whether these represent a new technology or complex healthcare intervention.

3.1 Collective action – interactional workability

This refers to the interactional work that people do with each other, with artefacts, and with other elements of a set of practices, when they seek to operationalise them in everyday settings.

3.1.1 Streamlined appointment systems

- Working out streamlined appointment system with colleagues/in the clinic is useful to ensure that the patients are referred to a GP who knows about the study.

3.1.2 Problems with the technology used for implementing the inclusion and exclusion criteria within surgeries

- Education Management Information System (EMIS) or other systems used for searching patient records in GP surgeries were frequently raised as areas where the surgery either did not know how to manipulate the system well

enough to get the necessary information about patients (in terms of inclusion and exclusion) or flourished because they did have someone in the surgery who did know a lot about EMIS.
- And the lack of uncertainty about whether they do indeed know if a patient has continued or stopped antidepressants.

3.1.3 Communication with other surgeries/shared practice

- Some surgery teams spoke to other surgery teams and discovered that they could have pooled resources, or that the central research team could have shared searches between surgeries rather than them all having to work individually all undertaking the same work, rather than sharing it.

3.2 Collective action – relational Integration

Knowledge work that people do to build accountability and maintain confidence in a set of practices and in each other as they use them.

3.2.1 Gaining comprehension of the website before sharing with other patients

- Some GPs tried to understand the website fully with one patient before seeing further patients.

3.2.2 Need for regular communication, prompts and updates from study team

- Wanted updates or communication, such as refresher training, due to the gap between site set-up and recruitment.
- And clear communication of all the steps and procedures in the first place from the central research team.
- As well as prompts form the researchers to remind surgeries about the study.

> *So maybe once in a while a call from the study team just to check how they're getting on. I think you are doing that anyway on the study arm, so I'm sure that sort of thing does help. I think those are the most important things. I was tempted to say incentives, but then I'm not entirely convinced incentives.*
>
> *01006GP001*

3.3 Collective action – skill-set workability

Allocation work that underpins the division of labour that is built up around a set of practices as they are operationalised in the real world.

3.3.1 Clear roles (research co-ordinator/mental health specialist general practitioners) within general practitioner surgeries helped manage the study and participants

- Had a research co-ordinator to undertake the searches, and then have the searches checked by the relevant GPs, which worked well – not too onerous. If someone is co-ordinating the searches and study, then it means other GPs can access study information that has been clearly labelled and organised by one central colleague.

> *sort of overlapped lots of people. And actually when I did a search and then I unpicked some of the exclusions … I actually had about 400 patients or something to look at, but actually … by the time I sort of got most of the way through screening the list then sort of sent the e-mail in and then got told, oh no, we've shut it now.*
>
> *01008NP001*

- *This includes the staff working on reception.*
- *Or allocating patient searches to admin/non-clinical staff.*
- Or surgeries with GPs with specialist interests or skills to see patients with mental health needs.

3.3.2 Collective action and understanding within surgeries

And as many GPs involved as possible.

3.3.3 Smaller patient lists meant surgeries could manage patient lists with confidence

- Small surgeries with smaller lists had the potential benefit of knowing their patients more and more quickly being able to identify suitable patients when going through the final screening process.

3.3.4 Time limits and lack of staff

- Time limits and lack of staff in some surgeries were cited as barriers to opportunistic recruitment.

3.4 Collective action – contextual integration

Resource work – managing a set of practices through the allocation of different kinds of resources and the execution of protocols, policies and procedures.

3.4.1 Need for clear research procedures

- Clear procedures needed – for example some GPs were not aware that they had to send a referral for the telephone support element of the intervention.

3.4.2 Sending reminders to patients

- Suggestions that reminders are sent to patients to invite them to take part in the study – might catch them at a more opportune moment.

3.4.3 Utilising different mediums to spread the word about the study

- A means to spread the work about the study could be through a variety of mediums, including CCG 'Hot topics' talks which occur yearly, directed e-mails and presenting in GP surgery general meetings.

3.4.4 Undertaking the searches in batches rather than the entire patient population

- Undertaking the searches in smaller batches of say 20–50 at a time, instead of searching through the entire patient list meant that practices could still undertake a comprehensive search of their patient list but limit the amount of time needed to go through a list – especially with only small recruitment number required.

Reflexive monitoring

Reflexive monitoring is the appraisal work that people do to assess and understand the ways that a new set of practices affect them and others around them.

4.1 Reflexive monitoring – systemisation

Participants in any set of practices may seek to determine how effective and useful it is for them and for others, and this involves the work of collecting information in a variety of ways.

4.2 Reflexive monitoring – communal appraisal

Participants work together – sometimes in formal collaboratives, sometimes in informal groups to evaluate the worth of a set of practices. They may use many different means to do this drawing on a variety of experiential and systematised information.

4.3 Reflexive monitoring – individual appraisal

Participants in a new set of practices also work experientially as individuals to appraise its effects on them and the contexts in which they are set. From this work stem actions through which individuals express their personal relationships to new technologies or complex interventions.

4.4 Reflexive monitoring – reconfiguration

Appraisal work by individuals or groups may lead to attempts to redefine procedures or modify practices – and even to change the shape of a new technology itself.

TABLE 6 Themes and subthemes identified from WS4 qualitative interviews with patients

Contextual/background	Why prescribed antidepressants	Reasons given for starting antidepressants
		Awareness
	Managing anxiety/depression	Coping mechanisms for management of depression or anxiety
		Other forms of treatment attempted
		Changed antidepressant
Lived experience of antidepressants	Explanations given for staying on antidepressants	Enables me to cope with life
		Stabilises emotions
		Safety net
		Preference for treatment type
		Helps with sleep
		Side effects of antidepressants (when taking)
		Addiction or dependency
		Autonomy
Factors that impact on decision to withdraw	Previous withdrawal attempts	No withdrawal effects during previous withdrawal attempts
		Reasons for previous withdrawal
		Emotional response to previous withdrawal attempt
		Support system during previous withdrawal attempt
		Withdrawal effects or return of symptoms (previous withdrawal attempt)
		Medical advice
	Beliefs about antidepressants	Impact of other people's beliefs about antidepressants
		Long-term consequences
	Barriers to withdrawal/reasons not to reduce antidepressants	Perception of self or identity
		Fear or impact on themselves
		Impact on others (fear)
		Professional support
	The 'right' time	Length of time on antidepressants
		The right time
	Facilitators to withdrawal	Prompt or opportunity to consider stopping
		Motivation to stop
		Wanting to experience full range of emotions.
		Tapering regimen

continued

TABLE 6 Themes and subthemes identified from WS4 qualitative interviews with patients (*continued*)

Contextual/background	Why prescribed antidepressants	Reasons given for starting antidepressants
		Problems with repeat prescriptions
		Extra support = incentive
	Medication	Had planned or started to reduce.
		Unnatural or chemical
		Want to reduce amount of medication taken
		Concerns about dependence or reliance
		A lot of people on them – cost to NHS
		Supporting or moving care away from busy healthcare system
		Altruistic – wanting to help others.
Reducing antidepressants – participant experiences	Emotional response	Emotional range improved
		Ability to cope while reducing/once stopped
		Identifying illness
		Stopping led to thoughts of self-harm or suicidal ideation
		Improved clarity of thought
		Return of symptoms
		Improved quality of life
	GP appointments	Initial GP appointment
		Written information
		Perception of a 'good' GP
		Medication reviews
		Follow-up
		Continuity
	Tapering regimen	Regimen provided by GP
		No tapering plans provided
		Contingencies if experience difficulties
	Patient empowerment	Did not follow tapering plan provided by GP
		Regimen negotiated with GP
	Future aspirations	Worried that side effects will get worse as reduce more
		Fear (future aspirations)
		I won't go back on medication
	Support	HCP support
		Did it alone
		Support from family and or friends
		Coping mechanisms to support discontinuation
		Impact on others (as a result of reducing antidepressants)

TABLE 6 Themes and subthemes identified from WS4 qualitative interviews with patients (*continued*)

Contextual/background	Why prescribed antidepressants	Reasons given for starting antidepressants
	Withdrawal effects	Physical symptoms (withdrawal)
		Emotional symptoms (withdrawal)
		No withdrawal effects reported
		Emotions following failed attempt to withdraw
		Improving as a result of restarting
		Plan to try again
		Need them to stay well
Experiences of participating in study	Positive aspects of study	Positive feedback about study
		Difficult to express in a questionnaire
		Normalising experience
		Improved self-awareness
		Confirmation needed to remain on antidepressants
		Improvements suggested for the study
	Negative aspects of study	Lack of support (as part of study)
		Negative feedback about study
		Arm of study
		Need to give more training for GPs
		Neutral response to study
	Questionnaires	Positive feedback (questionnaires)
		Negative feedback (questionnaires)
		Neutral response to questionnaires
		Improvements suggested (Questionnaires)
	PWP phone calls	Positive feedback (PWP phone calls)
		Negative feedback (PWP phone calls)
		Perceived role (of PWP phone calls)
		Timing of phone calls
		Neutral response to PP phone calls
	Intervention/*ADvisor*	Perceived role of *ADvisor*
		Positive feedback (*ADvisor*)
		Negative feedback (*ADvisor*)
		Use
		Neutral response to *ADvisor*
		Improvements suggested (*ADvisor*)

Note
Samantha Williams led on this analysis.

TABLE 7 Summary of changes to procedures and interventions following WS4

Comment	Change
Patient web intervention	
Difficulty remembering login details	Provide card at baseline visit with space to write down log-in details
Difficulty finding URL	E-mail URL to patients after baseline visit
Patients did not look at *ADvisor* until prompted much later	At baseline visit encourage patients to look at *ADvisor* before GP appointment
Some confusion around what *ADvisor* is/can be used for	Give more detailed introduction at baseline visit
HCPs had poor understanding of patient tool and did not encourage patients to use it	Encourage HCPs at SIV to look at patient information and invite patients to use the tool
Patient wanted to edit text after they had saved it in *ADvisor*	Add to *ADvisor* page that text cannot be edited once it has been saved
Practitioner web intervention	
Information is already known to HCPs or HCPs believe they do not need to look at *ADvisorHP*	SIV slides and *ADvisorHP* registration e-mail to highlight there is information in *ADvisorHP* that may differ from usual practice
Difficulty remembering login details, and logging in is a barrier	Encourage health professional (HP) to write down/save login details and explain at registration this is necessary for the trial
Discussing with colleagues encouraged use	At SIV, encourage discussion with colleagues
One HP wouldn't feel comfortable with antidepressant switching to avoid withdrawal symptoms	*ADvisorHP* registration e-mail: highlight an expert pharmacist has helped develop these regimens
Time constraints prevent use of *ADvisor*	Highlight at SIV that excess treatment costs cover time to look at *ADvisorHP*
Sometimes there is a gap between looking at *ADvisorHP* and seeing the first patient	Encourage HCPs to look at *ADvisorHP* before seeing a patient if possible, or keeping it saved as a favourite for easy access during consultations
Patient telephone support calls	
Patients unclear on purpose of calls and role of PWP	Give more introduction to telephone support at baseline visit
Patients felt like phone calls were tick boxes/data collection	Improve induction/training for PWPs
Patient calls were delayed/missed – in one case a patient had already finished tapering before the first call	New system for booking phone calls and alerting PWPs to expected demand in advance of booking appointments, through provider's internet platform
Missed/rearranged calls were not always communicated clearly with the patient	New system to improve rescheduling of calls when this is necessary
Relapse prevention plans not covered in great detail and some calls were shorter than others	Revise documentation and induction information for PWPs
Patients did not have as much choice in the timings of calls due to PWP availability	New system to improve booking/scheduling
GP consultations	
One GP allowed the patient to taper their medication as they felt, and one other GP only gave tapering instructions verbally	Highlight the need to give patients a written tapering regimen, at the SIV
One patient was restarted on antidepressants when it appeared to be withdrawal rather than relapse	At SIV, highlight there is information on distinguishing relapse and withdrawal in the *ADvisorHP* intervention
Two patients were not given follow-up appointments with the GP and had to book them themselves	At SIV, remind HCPs that all patients will need to be actively followed up, and should ideally be given scheduled appointments
One GP told a patient they were 'likely to relapse'	Add information to *ADvisorHP* about setting fair patient expectations; the risk of relapse is likely to be < 25% during the year of the study
One patient reported the GP had 'not done his homework' at the first appointment	At SIV and in registration e-mail, encourage HCPs to look at *ADvisorHP* before seeing patients, ideally rechecking its content just before seeing a patient

Appendix 5 Workstream 5

REDUCE randomised controlled trial to test effectiveness of the interventions

Objectives

Workstream 5 addressed the fourth objective of the programme, which was to determine the effectiveness of the intervention in helping patients reduce treatment (while avoiding worsening depression) through a randomised controlled trial, and to estimate its cost-effectiveness.

Methods

Design

Workstream 5 was a two-arm, 1 : 1 parallel-group, randomised controlled equivalence (non-inferiority) trial, with randomisation clustered by participating group general practices, using minimisation to balance practice size (large/small), location (urban/rural) and social deprivation (dichotomised around the median IMD score).

Following the successful completion of WS4, the protocol for the definitive effectiveness and cost-effectiveness trial in WS5 was published by Kendrick *et al.*[54] and the main results of the WS5 trial were published by Kendrick *et al.*[55]

Inclusion criteria

We included all adult patients taking long-term antidepressants for depression who did not have indications according to the 2009 NICE depression guideline (for more than 1 year for a first episode of depression or more than 2 years for recurrent depression), who did not currently have depression or were judged to not be at significant risk of relapse by their GP, and who wished to discontinue treatment.

Exclusion criteria

Patients were excluded for risk factors for relapse, including depression (PHQ-9 score of ≥ 12 at screening; anxiety GAD-7 score of ≥ 10); and suicidal ideas (positive score on the PHQ-9 self-harm question, or suicidal thoughts expressed at screening or baseline). Additional exclusions were current psychiatric treatment, bipolar disorder, psychosis, substance use, dementia, English language inadequate to complete questionnaires, no internet access, or another indication for antidepressants besides depression.

Practices were asked to search their computerised records for patients on long-term antidepressant treatment, and screen a random selection of 50 patients for eligibility against the inclusion and exclusion criteria. For every ineligible patient, we asked practices to select another patient from the list at random to be screened. This was repeated until approximately 50 eligible patients per practice had been identified.

To explore what proportion of patients on long-term antidepressants were ineligible for inclusion in the trial, we had asked one practice in WS4 to screen their entire list of patients identified by the search (as opposed to just 50 or so). This practice (patient list size 9300) identified 183 patients using the pre-specified search criteria. All these 183 patients were then screened for eligibility by a clinician who excluded 14 patients due to severity of depression, comorbid bipolar, schizophrenia or substance use, a recent physical health problem, and three duplicate entries.

The published protocol gives details of the patient inclusion and exclusion criteria, consent procedure, description of interventions, original sample size calculation, recruitment procedures, participant timeline, data management, statistical methods and trial oversight.[54]

Sample size recalculation

The original sample size calculation was that, to have 90% power, with a one-sided alpha of 2.5%, to establish non-inferiority in terms of depressive symptoms within 2 points (estimated to be the minimal clinically important difference) on the PHQ-9 at 6 months (SD 5.4), we needed to randomise 402 patients from 134 practices.

Following discussion with the study steering and data monitoring committees, and with the NIHR Programme Grants Board, the target sample size was reduced part-way through recruitment, in May 2021. This was to allow for a correlation factor we observed between baseline and 6-month follow-up scores on the PHQ-9 (blind to allocation to intervention or control arm), of $p = 0.47$. This allowed us to consider a deflation of the proposed sample size by a factor of $1 - p^2$. At the time of review, we were unsure whether the value of $p = 0.47$ would persist to the end of follow-up for all participants. If we assumed a more conservative estimate of correlation of $p = 0.26$ (the bottom end of the 95% CI for the factor found), the target sample size to achieve 90% power would be 375. We assumed the final figure would be somewhere in between 0.26 and 0.47, and that a sample of around 360 would therefore provide us with the necessary 90% power to test reliably for non-inferiority of the intervention in terms of depressive symptoms. The target sample size was therefore revised down to 360 patients and we aimed to recruit 180 patients in each arm (including the 52 already recruited for the internal pilot conducted in WS4).

Outcome measures

The primary outcome was depressive symptoms on the PHQ-9[52] at 6 months. Secondary outcomes were antidepressant discontinuation (for at least 2 months before the 6 month follow-up) and quality of life (on both the EQ-5D-5L[57] and SF-12[58]) measures at 6 and 12 months; and depression (PHQ-9), anxiety (GAD-7[73]), withdrawal symptoms [Discontinuation Emergent Signs and Symptoms Scale (DESS)],[74] mental well-being (WEMWBS),[75] patient enablement (PEI),[76] satisfaction with care (MISS)[77] and service use to determine costs over 12 months, gathered with a modified version of the validated Client Service Receipt Questionnaire (CSRI).[78] We simplified the CSRI during the feasibility trial to improve its usability in our study population, ensuring a balance between collecting the essential information and minimising participant burden.

We also administered bespoke questionnaires on sociodemographics, and past history of depression, to assess the similarity of patients in the two arms at baseline, and adjust for these in the analyses. Side effects of antidepressants (if still being taken) were measured at baseline, 6 and 12 months [on the Antidepressant Side Effects Checklist (ASEC)[79] and Changes in Sexual Functioning Questionnaire (CSFQ-C)].[80]

A bespoke questionnaire asking for patients' beliefs about antidepressants, and their cessation, developed by Southampton PhD student Rachel Dewar-Haggart,[66] was administered at baseline, 6 and 12 months, to enable a mediator analysis of possible effects of changes in patients' beliefs on changes in antidepressant use. At the 3-month assessment point, we also administered the Collective Efficacy Questionnaire which is a measure of the strength of support for discontinuing antidepressants which a participant perceives among their important friends and family,[81] to assess the importance of this support as a possible intervention moderator.

Predictors of outcome

We carried out an analysis of predictors of antidepressant discontinuation including past history of depression, baseline symptoms, sociodemographic factors, beliefs about antidepressants and collective efficacy.

Process evaluation

The objective of the process evaluation in WS5 was to identify, characterise and explain factors likely to inform practitioner and patient behaviour change, to inform a robust implementation plan for the appropriate discontinuation of antidepressants in clinical practice.

Quantitative

Quantitative process evaluation included:

1. An assessment of relationships between patients' use of the *ADvisor* intervention (automatically recorded by the Southampton *LifeGuide* software), and their outcomes including depressive symptoms and antidepressant discontinuation.
2. An analysis of the fidelity of the provision of telephone support provided by the PWPs compared to the guidance given by them, through recording and analysing a sample of calls.

Qualitative

The qualitative process study used the same procedures as in the feasibility trial, aiming to interview 15–20 purposively sampled patients in each arm (or more if needed for saturation), and 15–20 practitioners in each arm, remotely or face to face, for up to 60 minutes. Patients were eligible to be interviewed if they had completed their 6-month follow-up, so the interview could not influence the primary outcome, and within a month of the end of their participation to enhance accurate recall. Purposive sampling was used to recruit people of different ages, genders, recruitment sites, trial arm and intervention (*ADvisor*) usage.

Healthcare professionals were eligible to be interviewed once all patients at their practice had passed their 6-month assessment. The PWPs were interviewed after they had completed all their patient support calls.

Interviews were semistructured, focused on patient and practitioner experiences, to explore in-depth user experiences of engaging with the intervention for a prolonged period, including:

- What worked well and what could have worked better.
- Perspectives on mode of delivery and content, to gauge usability and understanding.
- Burden of treatment from the patient's perspective.

Individual practitioner interviews explored their views on:

- Negotiating the decision to taper off treatment with their patients.
- Their role as a GP/NP/PWP in terms of supporting/negotiating appropriateness of cessation.
- Support needs in practice.
- Ways to optimise implementation of cessation in routine practice.
- Follow-up monitoring of patients undergoing treatment tapering and cessation.

The interviews were audio-recorded and transcribed, and the data subjected to reflexive thematic analysis,[82] through the constant comparison method to identify themes, using NVivo software (Release 1.6.1) (QSR International, Warrington, UK). We also interpreted themes arising from the health professional interviews in light of the framework of NPT[42] with the intention of constructing a taxonomy of factors likely to affect the uptake and implementation of the intervention, and patient outcomes.

Results

Recruitment and follow-up

The CONSORT diagram for WS5 is shown in *Appendix 5*, *Figure 8*. A total of 6725 invitation letters were sent from 131 practices (66 intervention, 65 control) and 1495 responses were received (22%), of which 548 (8%) were positive about taking part. Of the 548, 330 patients were eligible on screening, consented to take part, and were randomised (5% of those contacted), including 178 in intervention arm practices, and 152 in control practices. They included 278 patients recruited during WS5, and 52 recruited during WS4. Although we finally recruited 30 patients fewer than our revised target of 360, we were confident that we would have sufficient power to answer our research questions as we had greater than the 80% follow-up anticipated for the analysis of the primary outcome: a total of 275 patients (83%), including 147 (82%) of intervention arm patients, and 127 (85%) controls. A total of 240 (73%) were followed up at 12 months.

Baseline characteristics

As expected, the practices randomised were well balanced at baseline, subject to slight differences due to a random element in the minimisation (see *Appendix 5*, *Table 8*). The key patient characteristics also seemed relatively well balanced by arm (see *Appendix 5*, *Table 9*). There were slightly more participants with no previous episodes of depression in the control arm, slightly more in full- or part-time work in the control arm and more retired in the intervention arm, slightly more married people in the control arm, and a higher proportion who were single or divorced in the intervention arm. We controlled for all these baseline past history and demographic factors in the analyses.

Main findings

Primary outcome

The primary outcome, mean PHQ-9 score, was slightly higher among control patients than intervention arm patients at 6 months [5.0 vs. 4.0; adjusted mean difference 1.07 points (95% CI 0.09, 2.06; $p = 0.033$; *Appendix 5*, *Table 10*)]. The intervention arm was therefore non-inferior to control, with no increase in depression score on the PHQ-9 and, in fact, the difference was in the direction of superiority. The mean difference of one point on the PHQ-9 may not be a clinically significant difference, although the upper end of the confidence interval does not exclude a clinically significant difference of two points.

In a missing cases multiple imputation analysis, the effect was slightly attenuated and while the non-inferiority conclusion remained, the intervention no longer appeared superior [mean adjusted difference based on 100 imputations −0.89 (95% CI −1.90 to 0.11; $p = 0.082$; *Appendix 5*, *Table 10*)].

A PPA and CACE analysis both gave the same inferences as the ITT approach for the primary outcome of depression scores at 6 months follow-up (see *Appendix 5*, *Table 10*). In the per-protocol population (including only those who complied), the estimate was in favour of the intervention with mean difference −1.25 (95% CI −2.33 to −0.17; $p = 0.023$). The CACE analysis also favoured the intervention with a difference between compliers and non-compliers of −1.35 (95% CI −2.63 to −0.06; $p = 0.040$).

For the purpose of assisting future trials in sample size calculations, the intracluster correlation coefficient was 0.

An exploratory post hoc analysis of rates of patient 'relapse' to scores of 10+ and 12+ on the PHQ-9 showed somewhat higher rates in the control arm (17.1% vs. 11.0%, and 10.1% vs. 6.9%, respectively), but these differences were not statistically significant (see *Appendix 5*, *Table 10*).

Secondary outcomes

Antidepressant discontinuation rates at 6 months were slightly higher in the intervention arm, but not significantly so: (45.5% vs. 41.9% in the control arm); at 12 months, the rates were 43.8% and 38.0%, respectively (not significantly different; *Appendix 5*, *Table 11*). Adding in those patients who managed to reduce the dose of their antidepressant but did not stop them altogether gave combined discontinuation/dose reduction rates at 6 months of 74.5% in the intervention arm versus 67.4% in the control arm (a non-significant difference).

Over 6 months, antidepressant withdrawal symptoms on the DESS scale were fewer in the intervention arm, although the difference, while statistically significant, was small [adjusted mean difference −1.56 points (95% CI −2.85 to −0.26); $p = 0.018$; (see *Appendix 5*, *Table 13*)]. It is interesting to note that the difference at 3 months was actually due to a drop in symptoms in the intervention group rather than an increase in the control. This may have been because the intervention group patients were made more aware of what symptoms might be due to withdrawal through the educational content of *ADvisor* and, therefore, did not report symptoms they thought were not due to withdrawal.

Similarly, over 12 months, mental well-being scores on the WEMWBS were slightly better in the intervention arm [mean difference 2.17 points (95% CI 0.21 to 4.14); $p = 0.030$; *Appendix 5*, *Table 13*]. The difference was due to scores worsening slightly in the control arm rather than improving in the intervention arm.

There were no significant differences in QoL on the EQ-5D-5L or SF-12 (see *Appendix 5*, *Table 13*). The QoL scores are discussed further in the section on the *Health economics evaluation*. There were also no significant differences in anxiety on the GAD-7, patient enablement on the PEI, satisfaction with services on any of the MISS satisfaction subscale scores, or antidepressant side effects (see *Appendix 5*, *Table 13*).

Adverse events

A total of 69 adverse events were experienced by 28 participants in the intervention arm (15.2%) and 22 in the control arm (15.0%), which were not significantly different rates. The main types of adverse events in each arm are listed in *Appendix 5*, *Table 14*. A total of 11 serious adverse events were recorded for two intervention arm and five control arm patients. Again, the difference was not significant, and nine of the events were hospital admissions which were unrelated to the trial.

There were two serious adverse reactions to coming off antidepressants. One intervention arm patient was admitted to a psychiatric unit for relapse of an anxiety disorder, and withdrew from the study. One control arm patient was referred urgently to psychiatric outpatients due to expressed suicidal ideas deemed by the GP to be of high risk, but was not admitted, and remained in the study.

Predictors of antidepressant discontinuation

In the absence of a significant difference between intervention and control arms in antidepressant discontinuation, we did not carry out the planned mediation analysis of possible effects of changes in patients' beliefs on subsequent changes in antidepressant use.

An analysis of possible predictors of discontinuation was carried out, including all patients across the intervention and control arms, using a mixed logistic/linear regression model, controlling for randomisation to intervention or control arm, and with a random effect for practice. We looked at whether discontinuation was predicted by baseline depressive or anxiety symptoms, number of previous episodes of depression, gender, age, marital status, dependents, ethnic group, urban/rural location, beliefs about depression and collective efficacy. The results are shown in *Appendix 5*, *Table 12*. Only a higher score for perceived necessity for antidepressants on the beliefs about depression questionnaire was associated with lower odds of discontinuation across the two groups [odds ratio OR 0.72 (95% CI 0.62 to 0.84; $p \leq 0.001$)]. None of the other variables was predictive of discontinuation, but it is possible that the sample lacked sufficient power to detect predictors accurately.

To examine whether having mental symptoms of withdrawal, which overlap with those of relapse, meant it was less likely that patients would discontinue their antidepressants, we also carried out an exploratory, post hoc analysis of the relationship between the type of withdrawal symptoms reported and discontinuation. The withdrawal symptoms measured by the DESS[68] were split into two groups: mental symptoms (items 1–14) and physical symptoms (items 15–43), and we explored whether the numbers of symptoms in these two groups reported by patients at 3 months follow-up were associated with the odds of discontinuation of antidepressants at 6 months. There were slightly fewer symptoms of both types in those who discontinued compared to those who did not, but there was no statistically significant difference in the odds of discontinuation based on the number of symptoms experienced. The adjusted ORs were 0.94 (95% CI 0.86 to 1.03; $p = 0.185$) for the mental subscale and 0.98 (95% CI 0.92 to 1.05; $p = 0.596$) for the physical subscale.

Quantitative process evaluation

Analysis of patient outcomes in relation to their recorded use of the online intervention

The initial analysis of patient outcomes in relation to their recorded use of the online *Advisor* intervention, automatically recorded by the Southampton LifeGuide software used to develop the internet guidance, is shown in *Appendix 5*, *Table 15*.

In relation to the primary outcome of depressive symptoms at 6 months, the mean PHQ-9 score tended to be slightly higher in those who used the modules at least once compared to those who did not, apart from the module on '*Dealing with withdrawal symptoms*'. However, these differences were not statistically significant.

Discontinuation of antidepressants tended to be more likely in those who completed modules on '*Keeping well*', '*Values and goals*' and '*Moving forward*'. Discontinuation was lower in those who completed modules on '*Thinking about antidepressants*', '*Dealing with withdrawal*' and '*Worry about stopping*'. Of these, the difference in the odds of discontinuing was significantly lower in those who completed the section on '*I'm worried about stopping*' (OR 0.13, 95% CI 0.04 to 0.41).

Very little technical support was needed for participants to be able to use the interventions.

Analysis of the fidelity of the psychological well-being practitioner support calls

The telephone support calls provided by four PWPs in WS5 were checked for fidelity against the guidance provided (see *Report Supplementary Material 1*). Catherine Woods measured fidelity for 35 calls that took place between 2020 and 2021. The team decided that three sets of calls (calls 1, 2 and 3) for each of the PWPs would be sufficient to explore initial fidelity (two sets of calls each) and any drift from the guide towards the end of the trial (one set of calls each). These calls were audio-recorded, transcribed verbatim and analysed for fidelity against the guidance provided.

In call 1 (n = 12), the PWPs always asked whether the patient had discussed tapering with their GP or NP, how it was going, whether they understood the tapering regimen, and whether they had any concerns or questions about the tapering process so far. They always administered the PHQ-9 questionnaire for depressive symptoms. They always asked if the patient had looked at the *Advisor* online intervention, although this was usually done briefly and not explored in any detail in most calls. All patients agreed to a second call and a date was confirmed. The PWPs scored lower on revisiting consent for the call to be recorded at the end of the call (58% of the time), and on checking with the patient whether they understood who to contact in case of difficulties (50%).

In call 2 (n = 12), the PWPs always asked the patient how tapering was going, and whether they had discussed it again with their GP following the initial consultation. They always asked about withdrawal symptoms, and discussed ways of coping with them. They always administered the PHQ-9 a second time. All agreed a date for a third call. They scored lower on asking about, and responding to other patient fears and concerns (83%), and revisiting consent to record on closing the call (25%).

In call 3 (n = 11), all patients were again asked about tapering and withdrawal symptoms, and were administered the PHQ-9. They were always asked if they knew who to contact if they had difficulties. They again scored lower on asking about other concerns or fears (82%), and lowest for revisiting consent for the recording at the end of the call (27%).

Qualitative process evaluation

Patient interviews

Semistructured telephone interviews were carried out between August 2021 and November 2022, by five members of the research team experienced in qualitative methods. Catherine Woods led on analysis of the intervention arm patient interviews, and Ellen van Leeuwen led on the control arm patient interviews.

A total of 39 participants were interviewed: 25 intervention arm and 14 control arm patients. They included 26 women and 13 men, and ranged in age from mid-20s to over 75 years. Their characteristics are shown in *Appendix 5*, *Table 16*.

Four themes were derived from the interviews:

1. Intentions, stability and willingness to try discontinuation.
2. Tapering experience.
   2a. Gradual tapering and the role of the GP.
   2b. 'Withdrawal' versus 'relapse', perseverance and tipping points.
3. Engagement with the intervention components.
   3a. '*ADvisor* for patients'
   3b. Telephone support calls
4. Reflections and realisations from tapering.

More details on the issues identified under each of the themes is presented in *Appendix 5*, *Table 17*, together with illustrative quotes from the interviews, and the outcome for each person (discontinued antidepressant, reduced the dose, or remained on the original dose).

Practitioner interviews

Twenty-seven health professionals were interviewed, including 23 GPs, 1 pharmacist, 1 MHN and 2 of the PWPs who provided support calls. Unfortunately, seven GP interview recordings proved to be inaudible and five kindly agreed to be re-interviewed. One GP provided written responses following the loss of data. Interviews with the two PWPs are reported separately as the interview schedules, data and coding were dissimilar to the other HCPs. The characteristics of the sample in terms of age, gender, experience and type of practice are described in *Appendix 5*, *Table 18*.

Hannah Bowers coded intervention arm practitioner transcripts and Riya Tiwari coded controls. Hannah integrated the coding across arms and developed a thematic structure (with a focus on the context, mechanisms and implementation of the intervention).[56]

Themes were also mapped onto constructs from NPT[42] by Hannah Bowers and Carl May, to identify the process evaluation outcomes related to the different implementation mechanisms within the NPT framework. This was the first step towards achieving Objective 5 of the REDUCE programme, which was to build a translational framework describing the intervention and addressing how it should be delivered, including overcoming practitioner and patient related barriers, to facilitate implementation of treatment cessation.

Five themes were derived from the interviews:

1. Creating the opportunity to discuss discontinuation (which had been identified in the WS1 qualitative synthesis and WS2 focus groups).
2. Slow tapering.
3. Distribution of the workload.
4. Confidence and reassurance.
5. Variable engagement with intervention components.

More details on the issues identified under each of the themes are presented in *Appendix 5*, *Table 19*, together with illustrative quotes from the interviews.

Appendix 5, *Table 20* shows the mapping of themes to NPT constructs, identifying the trial process evaluation outcomes related to NPT implementation mechanisms and patient outcomes, to provide a translational framework to overcome barriers to implementing antidepressant discontinuation in clinical practice beyond the trial situation.

Practices withdrew, or failed to conduce a mail-out, because they were too busy, particularly during the COVID-19 pandemic.

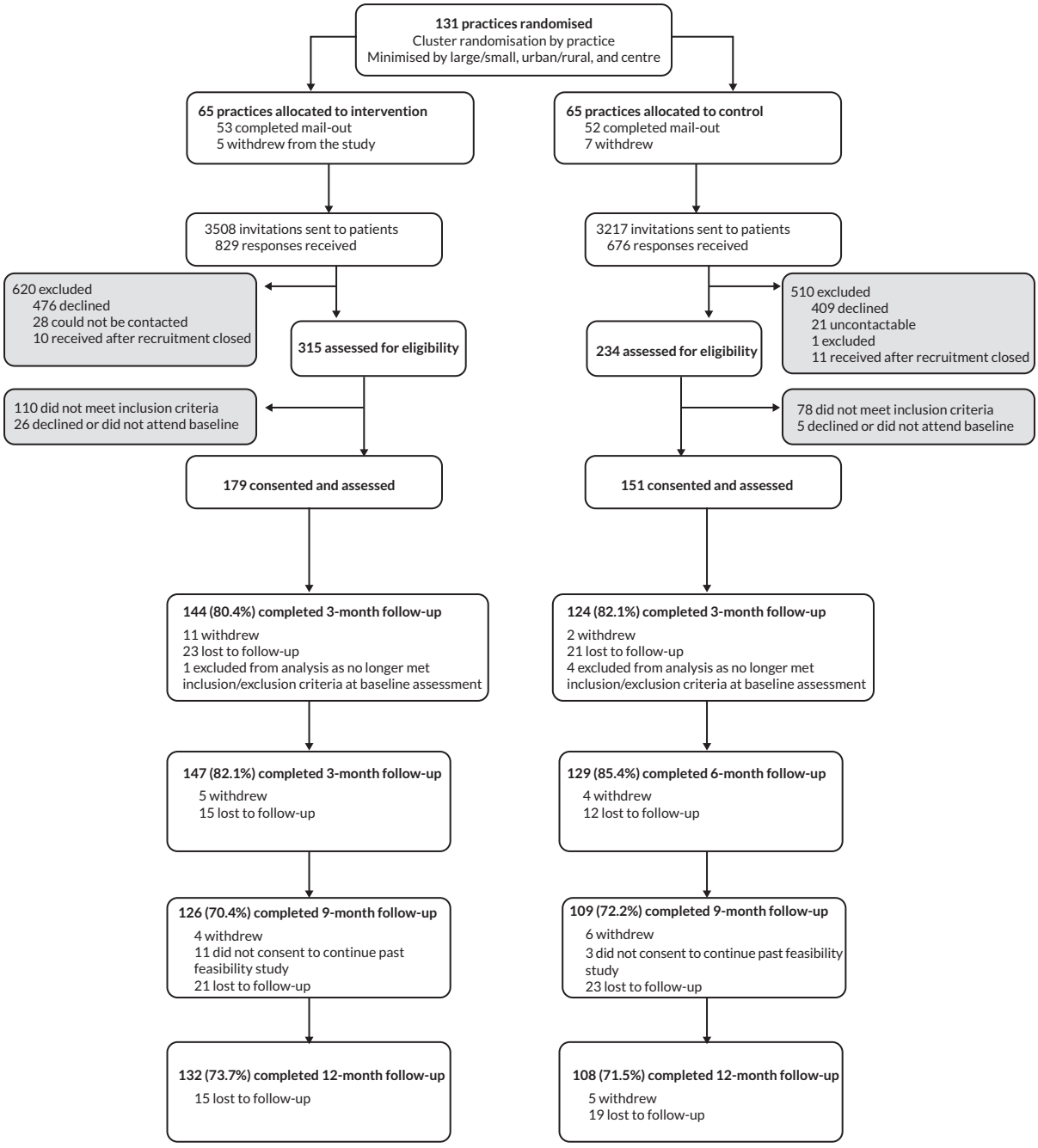

FIGURE 8 REDUCE WS5 definitive RCT CONSORT diagram.

TABLE 8 Characteristics of practices randomised to intervention and control arms in the WS5 definitive RCT

Practice characteristics	Intervention arm (*N* = 66) *N* (%)	Control arm (*N* = 65) *N* (%)	Total (*N* = 131) *N* (%)
Deprivation IMD score			
1–5 (more deprived)	24 (36.4%)	22 (33.8%)	46 (35.1%)
6–10 (less deprived)	42 (63.6%)	43 (66.2%)	85 (64.9%)

TABLE 8 Characteristics of practices randomised to intervention and control arms in the WS5 definitive RCT (*continued*)

Practice characteristics	Intervention arm (*N* = 66) *N* (%)	Control arm (*N* = 65) *N* (%)	Total (*N* = 131) *N* (%)
Patient list size[a]			
Small	19 (28.8%)	22 (33.8%)	41 (31.3%)
Large	47 (71.2%)	43 (66.2%)	90 (68.7%)
Location[b]			
Urban	48 (72.7%)	48 (73.8%)	96 (73.3%)
Rural	18 (27.3%)	17 (26.2%)	35 (26.7%)

a Practice size was dichotomised around the median list size of 8000 patients.
b Urban or rural location was determined according to the Local Authority Districts 2011 Rural Urban Classification.

TABLE 9 Baseline characteristics of patients in intervention and control arms of the WS5 definitive RCT

Patient characteristics	Intervention arm (*N* = 178)[a] *N* (%)	Control arm (*N* = 147)[a] *N* (%)	Total (*N* = 325)[a] *N* (%)
Declared gender N (%)			
Woman	126 (70.8%)	97 (66.0%)	223 (68.6%)
Man	52 (19.2%)	50 (34.0%)	102 (31.4%)
Other/prefer not to say	0	0	0
Age (years) at baseline			
Mean (SD)	54.4 (15.01)	53.5 (14.70)	54.0 (14.86)
Ethnicity			
White	176 (98.9%)	142 (97.3%)	318 (98.1%)
Other ethnic group[b]	2 (1.1%)	4 (2.7%)	6 (1.8%)
Missing	0	1	1
Previous depression episodes			
None	69 (38.8%)	66 (44.9%)	135 (41.5%)
One	42 (23.6%)	23 (15.6%)	65 (20.0%)
Two or more	67 (37.6%)	58 (39.5%)	125 (38.5%)
Marital status			
Married	101 (56.7%)	97 (66.0%)	198 (60.9%)
Cohabiting	19 (10.7%)	15 (10.2%)	34 (10.5%)

continued

TABLE 9 Baseline characteristics of patients in intervention and control arms of the WS5 definitive RCT (*continued*)

Patient characteristics	Intervention arm (*N* = 178)[a] *N* (%)	Control arm (*N* = 147)[a] *N* (%)	Total (*N* = 325)[a] *N* (%)
Widowed	12 (6.7%)	7 (4.8%)	19 (5.8%)
Separated	5 (2.8%)	3 (2.0%)	8 (2.5%)
Divorced	15 (8.4%)	8 (5.4%)	23 (7.1%)
Single	26 (14.6%)	15 (10.3%)	41 (12.6%)
Missing	0	2	2
Number of dependents in household			
None	143 (80.3%)	123 (83.7%)	266 (81.8%)
1	7 (3.9%)	2 (1.4%)	9 (2.8%)
2	10 (5.6%)	7 (4.8%)	17 (5.2%)
3	3 (1.7%)	1 (0.7%)	4 (1.2%)
4	9 (5.1%)	11 (7.5%)	20 (6.2%)
5	2 (1.1%)	0 (0.0%)	2 (0.6%)
6	4 (2.2%)	3 (2.0%)	7 (2.2%)
Highest educational qualification[c]			
None	8 (4.5%)	4 (2.7%)	12 (3.7%)
CSE/NVQ Level 1	8 (4.5%)	12 (8.2%)	20 (6.2%)
GCSE/O Level	32 (18.0%)	27 (18.4%)	59 (18.2%)
A Level/BTEC	16 (9.0%)	19 (12.9%)	35 (10.8%)
HNC/HND/City and Guilds	22 (12.4%)	15 (10.2%)	37 (11.4%)
Degree/Higher degree	67 (37.6%)	54 (36.7%)	121 (37.2%)
Vocational qualification	14 (7.9%)	6 (4.1%)	20 (6.2%)
Other	9 (5.1%)	7 (4.8%)	16 (4.9%)
Missing	2	3	5
Employment			
Full-time work	72 (40.5%)	55 (37.4%)	127 (39.1%)
Part-time work	27 (15.2%)	39 (26.5%)	66 (20.3%)
Permanently sick/disabled	4 (2.3%)	1 (0.7%)	5 (1.5%)
Unemployed	3 (1.7%)	1 (0.7%)	4 (1.2%)
Retired	59 (33.2%)	42 (28.8%)	101 (31.1%)
Student	1 (0.6%)	2 (1.4%)	3 (0.9%)
Homemaker	4 (2.3%)	2 (1.4%)	6 (1.8%)
Voluntary work	2 (1.1%)	1 (0.7%)	3 (0.9%)
Other	6 (3.4%)	3 (2.0%)	9 (2.8%)
Missing	0	1	1

TABLE 9 Baseline characteristics of patients in intervention and control arms of the WS5 definitive RCT (*continued*)

Patient characteristics	Intervention arm (*N* = 178)[a] *N* (%)	Control arm (*N* = 147)[a] *N* (%)	Total (*N* = 325)[a] *N* (%)
Accommodation			
Owner-occupied	141 (79.2%)	115 (78.2%)	256 (78.8%)
Council/housing association	9 (5.0%)	9 (6.1%)	18 (5.5%)
Private rental	19 (10.7%)	15 (10.2%)	34 (10.5%)
Job related	1 (0.6%)	0 (0.0%)	1 (0.3%)
Lives with parents	4 (2.2%)	5 (3.4%)	9 (2.8%)
Other	3 (1.7%)	2 (1.4%)	5 (1.5%)
Missing	1	1	2

a One intervention and four control patients consented at screening were subsequently excluded as they no longer met inclusion/exclusion criteria by baseline assessment.
b The self-declared ethnicities within 'Other' are not specified as some were very uncommon, and could potentially identify participants.
c CSE is the Certificate of Secondary Education, a qualification in a specific subject formerly taken by school students aged 14–16, at a level below O (Ordinary) level. Both the CSE and O level were replaced in 1988 by the GCSE, or General Certificate of Secondary Education. NVQ Level 1 is the first level National Vocational Qualification, a work-based job-specific qualification. A Level is the Advanced secondary education qualification in a specific subject taken by school students aged 17–19. BTEC is the Business and Technology Education Council certificate work-based vocational qualification taken after secondary school above the age of 16. HNC (Higher National Certificate), HND (Higher National Diploma), and City and Guilds are more advanced vocational qualifications.

TABLE 10 Differences in depressive symptoms between control and intervention arms in the WS5 definitive RCT

Outcome	Intervention *N* = 145[b] Mean (SD)	Control *N* = 129 Mean (SD)	Mean adjusted difference (95% CI) and *p*-value[a]								Adjusted odds ratio (95% CI) and *p*-value	*p*-value
			Complete case analysis	*p*-value	PPA analysis	*p*-value	CACE analysis	*p*-value	ITT analysis with 100 imputations[c]	*p*-value		
PHQ-9 score at baseline	4.2 (3.57)	4.3 (3.18)	N/A		N/A		N/A		N/A			
PHQ-9 score at 6 months	4.0 (4.33)	5.0 (4.68)	−1.08 (−2.06 to −0.09)	0.03	−1.25 (−2.33 to −0.17)	0.02	−1.35 (−2.63 to −0.06)	0.04	−0.89 (−1.90 to 0.11)	0.08		
PHQ-9 score ≥ 10 at 6 months (post hoc analysis)	16/145 (11.0%)	22/129 (17.1%)	N/A		N/A		N/A		N/A		0.58 (0.24 to 1.41)	0.23
PHQ-9 score ≥ 12 at 6 months (post hoc analysis)	10/145 (6.9%)	13/129 (10.1%)	N/A		N/A		N/A		N/A		0.62 (0.22 to 1.72)	0.36

N/A, not applicable.
a Models controlled for baseline PHQ-9 score, baseline GAD-7 anxiety score, declared gender, age, employment status, housing type, education level, marital status, number of dependents and previous history of depression, and included a random effect for practice to allow for the clustered nature of the design.
b Two of the 147 intervention arm patients followed up at 6 months did not complete all the PHQ-9 questions and could not be assigned a total score.
c An unstructured covariance matrix was used, and the imputations were combined using Rubin's rules.

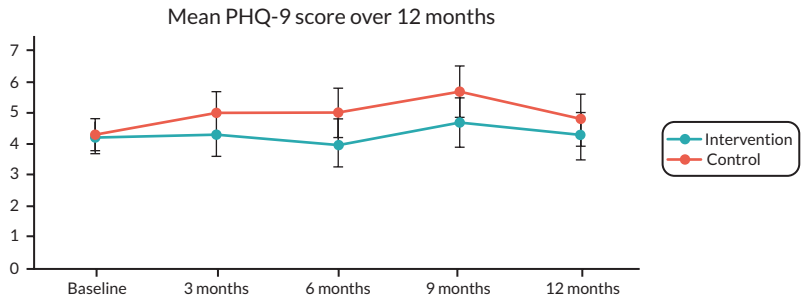

FIGURE 9 Patient Health Questionnaire-9 items depression scores over 12 months follow-up.

TABLE 11 Main secondary outcome: self-reported antidepressant discontinuation at 6 and 12 months

	Intervention arm *N* = 145[a] *N/N* with data at each time point (%)[a]	Control arm *N* = 129 *N/N* with data at each time point (%)	Adjusted odds ratio (95% CI)[b]	*p*-value	Adjusted odds ratio based on 100 imputations (95% CI)[c]	*p*-value
Number who had discontinued antidepressants (for > 2 months) at 6 months	66/145 (45.5%)	54/129 (41.9%)	1.02 (0.52 to 1.99)	0.96	1.03 (0.55 to 1.90)	0.93
Number who had discontinued (for > 2 months) at 12 months	46/105 (43.8%)	30/79 (38.0%)	1.24 (0.62 to 2.47)	0.54	1.45 (0.76 to 2.74)	0.26
Number at 12 months who had restarted antidepressants after 6 months	10/42 (23.8%)	11/33 (33.3%)	N/A		N/A	
Number who discontinued antidepressants between 6 and 12 months	13/58 (22.4%)	6/43 (14.0%)	N/A		N/A	
Number who either discontinued or reduced the dose of their antidepressant by 6 months (post hoc analysis)	108/145 (74.5%)	87/129 (67.4%)	0.97 (0.39 to 2.39)	0.95	N/A	

N/A, not applicable.
a Two of the 147 intervention arm patients followed up at 6 months did not answer the question on discontinuation of antidepressants.
b Models controlled for baseline PHQ-9 score, baseline GAD-7 questionnaire anxiety score, declared gender, age, employment status, housing type, education level, marital status, number of dependents and previous history of depression, and included a random effect for practice to allow for clustering.
c An unstructured covariance matrix was used, and the imputations were combined using Rubin's rules.

TABLE 12 Predictors of antidepressant discontinuation across both arms of the trial

Variable	Odds ratio (95% CI)
Arm	
Usual care	Ref.
Intervention	1.17 (0.67 to 2.39)
Perceived behavioural control	0.91 (0.65 to 1.26)
Beliefs about medication necessity	0.72 (0.62 to 0.84)
Beliefs about medication concerns	1.05 (0.95 to 1.15)
Collective efficacy responsiveness	0.76 (0.44 to 1.32)

TABLE 12 Predictors of antidepressant discontinuation across both arms of the trial (*continued*)

Variable	Odds ratio (95% CI)
Collective efficacy access	0.74 (0.49 to 1.12)
Baseline PHQ-9	1.00 (0.88 to 1.13)
Baseline GAD-7	1.10 (0.94 to 1.30)
Previous attempts at stopping	
None	Ref.
One successful attempt	0.71 (0.26 to 1.94)
One or more unsuccessful attempts	0.66 (0.28 to 1.57)
Previous episodes of depression	
None	Ref.
One	1.06 (0.34 to 3.33)
Two or more	1.02 (0.39 to 2.64)
Gender	
Male	Ref.
Female	0.61 (0.29 to 1.27)
Marital status	
Married	Ref.
Cohabiting	1.24 (0.35 to 4.43)
Widowed	0.70 (0.16 to 3.11)
Separated	5.23 (0.47 to 58.82)
Divorced	0.49 (0.13 to 1.96)
Single	2.34 (0.64 to 8.54)
Ethnic group	
White	Ref.
Other	0.30 (0.02 to 3.63)
Age	1.02 (0.98 to 1.05)

TABLE 13 Secondary outcomes in intervention and control arms

Outcomes	Intervention arm Mean (SD)					Control arm Mean (SD)								
Follow-up point Number followed up	Baseline *N* = 178[b]	3 months *N* = 144	6 months *N* = 147	9 months *N* = 126	12 months *N* = 132	Baseline *N* = 147[b]	3 months *N* = 124	6 months *N* = 129	9 months *N* = 109	12 months *N* = 108	Adjusted mean difference over 6 months (95% CI)[a]	*p*-value	Adjusted mean difference over 12 months (95% CI)[a]	*p*-value
PHQ-9 depression symptom score	4.2 (3.57)	4.3 (4.21)	4.0 (4.33)	4.7 (4.76)	4.2 (4.21)	4.3 (3.18)	5.0 (4.06)	5.0 (4.68)	5.7 (4.54)	4.8 (4.68)	N/A		−0.72 (−1.41 to −0.01)	0.05
GAD-7 anxiety symptom score	3.2 (2.80)	3.7 (4.0)	3.2 (3.83)	3.7 (4.37)	3.4 (3.85)	3.4 (3.38)	3.8 (3.30)	3.8 (3.94)	4.1 (4.12)	3.9 (3.79)	N/A		−0.20 (−0.82 to 0.42)	0.53
DESS withdrawal symptoms scale	12.6 (7.28)	10.8 (7.33)	11.8 (8.46)	N/A	N/A	12.6 (7.83)	12.6 (7.60)	12.8 (8.55)	N/A	N/A	−1.56 (−2.85 to −0.26)	0.02	N/A	
WEMWBS mental well-being score	50.3 (9.44)	N/A	49.8 (11.21)	N/A	48.6 (12.36)	51.0 (9.26)	N/A	48.3 (10.32)	N/A	47.3 (13.41)	N/A		2.17 (0.21 to 4.14)	0.03
EQ-5D-5L quality of life score	0.74 (0.11)	N/A	0.75 (0.13)	N/A	0.74 (0.13)	0.74 (0.11)	N/A	0.72 (0.12)	N/A	0.71 (0.13)	0.049 (−0.002 to 0.099)	0.06	0.022 (−0.030 to 0.075)	0.36
Medical Outcomes Study SF-12 score	0.84 (0.14)	N/A	0.83 (0.16)	N/A	0.83 (0.15)	0.81 (0.16)	N/A	0.78 (0.17)	N/A	0.80 (0.16)	0.041 (−0.012 to 0.093)	0.12	0.010 (−0.060 to 0.080)	0.74
PEI score	N/A	N/A	1.1 (0.97)	N/A	1.3 (1.01)	N/A	N/A	1.3 (0.97)	N/A	1.5 (1.10)	N/A		−0.21 (−0.43 to 0.01)	0.06
MISS distress relief score	N/A	N/A	42.5 (14.05)	N/A	40.4 (12.75)	N/A	N/A	41.3 (13.25)	N/A	38.4 (12.96)	N/A		−0.02 (−3.03 to 3.00)	0.99
MISS communication comfort score	N/A	N/A	17.0 (4.99)	N/A	16.2 (4.77)	N/A	N/A	17.3 (4.81)	N/A	15.5 (4.60)	N/A		−0.13 (−0.94 to 1.20)	0.81

TABLE 13 Secondary outcomes in intervention and control arms (*continued*)

Outcomes	Intervention arm Mean (SD)					Control arm Mean (SD)					Adjusted mean difference over 6 months (95% CI)[a]	*p*-value	Adjusted mean difference over 12 months (95% CI)[a]	*p*-value
Follow-up point Number followed up	Baseline *N* = 178[b]	3 months *N* = 144	6 months *N* = 147	9 months *N* = 126	12 months *N* = 132	Baseline *N* = 147[b]	3 months *N* = 124	6 months *N* = 129	9 months *N* = 109	12 months *N* = 108				
MISS rapport score	N/A	N/A	46.8 (13.29)	N/A	44.6 (13.23)	N/A	N/A	46.8 (12.41)	N/A	41.1 (14.67)	N/A		−0.25 (−2.71 to 3.21)	0.87
MISS compliance intent score	N/A	N/A	17.1 (4.71)	N/A	16.8 (4.61)	N/A	N/A	17.1 (4.45)	N/A	15.3 (4.51)	N/A		0.36 (−0.64 to 1.37)	0.48
ASEC total score	7.5 (5.00)	N/A	6.2 (6.15)	N/A	5.9 (5.52)	7.5 (5.28)	N/A	7.1 (5.51)	N/A	6.1 (5.11)	−0.63 (−1.46 to 0.20)	0.14	−0.89 (−2.03 to 0.25)	0.12
CSFQ total score	33.6 (11.23)	N/A	33.9 (12.19)	N/A	31.6 (14.68)	35.2 (11.39)	N/A	33.8 (12.94)	N/A	31.7 (14.43)	N/A		0.56 (−2.21 to 3.33)	0.69
Contacts with primary care health services Mean (95% CIs)	N/A	N/A	N/A	N/A	6.1 (5.6 to 7.7)	N/A	N/A	N/A	N/A	6.7 (5.9 to 7.7)	N/A		−0.6 (−1.8 to 0.5)	0.80
Contacts with secondary care health services Mean (95% CIs)	N/A	N/A	N/A	N/A	1.7 (1.3 to 2.1)	N/A	N/A	N/A	N/A	1.9 (1.5 to 2.4)	N/A		−0.2 (−0.8 to 0.4)	0.87
Total costs of health service contacts	N/A	N/A	N/A	N/A	GB£596 (1663) US$757 (2112)	N/A	N/A	N/A	N/A	GB£669 (922) US$850 (117)	N/A		GB−£69 (−77 to 207)[c] −US$88 (−98 to 263)	0.82

GB£, Great British pounds; N/A, not applicable (not all outcomes were analysed at each time point, as specified in the protocol); US$, US dollars (Bank of England exchange rate GB£1 = US$1.27 on 23 January 2024).

a Models controlled for baseline score of the variable being analysed, employment, housing type, education, marital status, dependents, gender, age, past history of depression, baseline PHQ-9 depression score, baseline GAD-7 anxiety score and practice as a random effect to allow for the clustered design.

b One intervention and four control participants withdrew immediately after randomisation, so baseline measures were collected for 325/330 participants.

c The difference in costs between the arms was estimated using bootstrapping, with 1000 resamples with replacement.

TABLE 14 Types of adverse events in the intervention and control arms

	Intervention (*n* = 178)	Control (*n* = 147)	Total (*n* = 325)
Total number of adverse events	**41**	**28**	**69**
Suicidal ideation on PHQ-9 or at assessment	30	17	47
Withdrawal symptoms	6	5	11
Other	5	6	11
Total number of serious adverse events	**6**	**5**	**11**
Total number of serious adverse reactions	**1**	**1**	**2**

TABLE 15 Participants' use of the *ADvisor* online intervention

Modules of the *ADvisor* online intervention	Number who completed the module (%)	Mean PHQ-9 at 6 months for those who completed the module (SD)	Mean PHQ-9 at 6 months for those who did not complete module (SD)	Proportion who discontinued antidepressants among those who completed the module (%)	Proportion who discontinued antidepressants among those who did not complete module (%)
Introduction to *ADvisor*	118/179 (65.9%)	4.0 (4.21)	4.1 (4.71)	49/106 (46.2%)	17/39 (43.6%)
Thinking about antidepressants	40/169 (23.7%)	4.1 (3.95)	4.0 (4.28)	12/34 (35.3%)	52/106 (49.1%)
Dealing with withdrawal symptoms	72/169 (42.6%)	3.4 (3.58)	4.5 (4.60)	28/63 (44.4%)	36/77 (46.8%)
I'm worried about stopping	41/169 (24.3%)	4.4 (4.52)	3.9 (4.09)	7/35 (20.0%)	57/105 (54.3%)
Keeping well	56/169 (33.1%)	4.3 (4.51)	3.8 (4.02)	26/52 (50.0%)	38/88 (43.2%)
Values and goals	34/169 (20.1%)	4.8 (4.52)	3.8 (4.09)	15/31 (48.4%)	49/109 (45.0%)
Moving forward	60/169 (35.5%)	4.4 (4.87)	3.7 (3.71)	27/55 (49.1%)	37/85 (43.5%)

Workstream 5: Qualitative process evaluation interviews with patients

TABLE 16 Participant demographics: process evaluation qualitative interviews with patients

Characteristic	Control	Intervention	Total
Study arm	14	25	39
Gender			
Female	7	19	26
Male	7	6	13
Age (years) reported at the time of interview			
18–24	0	0	0
25–34	1	4	5
35–44	2	2	4
45–54	3	6	9
55–64	5	7	12
65–74	2	6	8
75+	1	0	1

continued

TABLE 16 Participant demographics: process evaluation qualitative interviews with patients (*continued*)

Characteristic	Control	Intervention	Total
Follow-up completed at the time of the interview			
6 months	3	3	6
9 months	9	13	22
12 months	2	9	11
Stage of tapering at the time of the interview			
Stopped	7	10	17
Reduced	4	10	14
Taking original dose of antidepressant	3	5	8

Theme 1: Intentions, stability and willingness to try discontinuation

All participants were willing to try discontinuation when they consented to take part in the trial. Some participants expressed existing intentions to discontinue, which were either recent thoughts or formed when they were first put on antidepressants. Additionally, some reported being in a better (i.e. more stable) place compared to when they were first put on their medication, not feeling as depressed or anxious, related to better life circumstances (e.g. leaving a difficult relationship). For these participants, the invitation to take part in the research 'came at the right time'. For others, an intention to discontinue was provoked by the invitation to review their antidepressants.

Theme 2: Tapering experience

2a. Gradual tapering and the role of the general practitioner

Several participants, across both arms, reported that their tapering regimen involved a gradual reduction in antidepressants, often over several months. Descriptions included the words 'gradual', 'steady' and 'slow'. They valued this non-pressured approach to discontinuation, that emphasised they could give tapering a 'try', they could return if they were struggling, and their prescription would not be stopped immediately. Others across both arms, however, thought that their GP did not provide clear guidance about how discontinuation would work.

A number of participants valued getting an appointment to review their medication and clear information about tapering, but did not expect much additional support from their GP via follow-up appointments (and many of those interviewed did not receive any). These expectations could have been related to the COVID-19 pandemic (i.e. the nationwide difficulty of getting an appointment), and/or not knowing what to expect from taking part in the trial medication review process.

2b. 'Withdrawal' versus 'relapse', perseverance and tipping points

Most participants reported minimal to no withdrawal symptoms when reducing their antidepressants, which may have been related to the gradual tapering regimens described. Symptoms included headaches, slight mood disturbances and some difficulty sleeping, but often dissipated within a few days or weeks. The main reasons for choosing not to continue to discontinue antidepressants were perceptions of 'relapse', specifically that symptoms developed which reminded them how they felt when first diagnosed with depression; and not feeling able to cope without antidepressants. Several reported that they encountered most difficulties in the latter stages of tapering, when reducing to a low dose or fully discontinuing, which is consistent with the literature on the effects of tapering (REF). Willingness to persevere through this last part of tapering varied, and it was at least partly related to intentions to discontinue and how strongly these were felt.

Theme 3: Engagement with the intervention components

3a. '*ADvisor* for patients'

Participants were generally positive about having an information-based resource like *ADvisor* to support the tapering process. Positive evaluations focused on its usability, being 'straightforward' and 'simple' to use, with information that was 'clear', 'logical' and 'useful'. Several reported they felt 'reassured' by *ADvisor*, either from knowing they had access to a form of support or by specific information provided, in relation to what to expect from tapering, normalising withdrawal symptoms, and how to differentiate them from relapse. One participant noted it 'reinforced' the message to come off antidepressants, which was valued and important for progressing through the programme.

While the majority of participants evaluated *ADvisor* positively, it seemed that most did not feel the need to engage with the intervention much after initial familiarisation with the content. This was related to several factors, including many participants feeling they had a good baseline knowledge about their diagnosis and their own coping strategies, developed over time and/or from previous therapy, to manage their mental health. The content therefore was not 'new' to them, and did not need to be consulted frequently, but they felt it could be useful for people newly diagnosed with depression, who might not have come across information or techniques described. Some participants tended to avoid computers and the internet, not identifying as a 'computer-person', particularly 'technical', or with a preference for 'talking things through'. Some participants reported that they did not feel the need for support or information because they did not experience many (or any) withdrawal symptoms when tapering.

3b. Telephone support calls

Many participants reported that they valued the telephone support calls, perhaps more than having access to an internet-based resource. Positive evaluations centred on how the calls were useful to monitor progression when tapering, as they made the person 'aware' and 'mindful' of how they were feeling (based on the symptom measures administered within the call), and provided opportunities to 'reflect'. The interactive nature of the calls, particularly being able to ask questions, was key to why they were seen as more valuable than *ADvisor*. Relatedly, participants discussed feeling a sense of 'reassurance' from the calls, either just knowing that somebody was going to 'check-in' in the near future or in that any risks associated with the participant continuing in the trial would have been flagged from completing the questionnaire.

While some participants were relatively content with repeating a PHQ-9 during the telephone support calls, others felt that the calls were too centred around the questionnaire, leading some to conclude that the calls were a 'box-ticking exercise' (to serve the study more than the person). Participants reported that they would have appreciated more opportunities to discuss how they were feeling, in their own words, rather than being restricted by a limited number of questions that did not resonate with their personal circumstances. While the use of open questions was encouraged in the guidance created by the study team for the PWPs, there appeared to be variation in what providing support meant to the practitioners (see section below on *Qualitative process evaluation interviews with health professionals*).

Some participants identified logistical problems around timing and arranging the calls which impacted their experience of the intervention. Some felt that the timing of the calls was problematic in relation to their tapering regimen, as they did not experience withdrawal symptoms or feelings of possible relapse until after the calls had taken place. Three participants reported difficulties in securing a time that would suit them, and two could not remember receiving telephone calls at all, which could be related to the timing of the interviews (which were delayed until after the 6-month follow-up), but could have related to the difficulties found in arranging calls.

Theme 4: Reflections and realisations from the tapering process

All participants, regardless of their outcome (discontinued antidepressants, reduced the dose, or returned to the original dose), reported that taking part was worthwhile, primarily because it made them reflect on their relationship with antidepressants. For some, tapering showed that they did not need antidepressants, that they could discontinue (with relative ease for many), and that they generally felt better in themselves without medication (e.g. more resilient; or healthier without physical side effects). Others reflected that they now know they can reduce their medication and might attempt to discontinue in the future, but realised they need to address certain things in their life in order to feel in a more stable place to try again (e.g. by having more talking therapy). Some pointed to the instability that can arise from

discontinuing antidepressants (i.e. feelings of relapse), which they would be reluctant to experience again in the near future. One participant from each arms reflected that their unsuccessful attempt to discontinue this time within the trial highlighted a continuing need for antidepressants, with medication as something they need in order to 'function', although this was not reported as negative by either participant.

Finally, some participants pointed to the need for more information about the harms of taking antidepressants long term, which could help people in general make more of an informed choice about whether to take them when first diagnosed with depression, or, for the participants, help inform their decision about whether to try discontinuation again in the future.

TABLE 17 Themes and illustrative quotes from patient trial participants

Number	Theme/subtheme	*Quotes*	Arm	Outcome
1	**Intentions, stability and willingness to try discontinuation**	*So I think it was a combination of REDUCE, the boys leaving home, my life getting a little bit simpler and having the opportunity. I probably [wouldn't have] thought about it if REDUCE hadn't come along. I might have reduced it but I wouldn't have thought of coming off because it has, for so long, it wasn't in my head to do that.* [0110402011]	INT	Discontinued
2		*Yes, positive. I thought, you know, I've been on these a long time now; I ideally don't really want to be on them forever, one, mainly because I don't want to be taking medication and, two, because of the cost of it as well. It's an extra £9, more like 10 every month now. So I thought, you know, if I'm going to do it, this is the way to do it, really, with that extra bit of – people checking in and making sure that I'm doing it right. So, yes, I thought it was a good chance for me to try and see if I could – could do it.* [0201101180]	CON	Reduced
3		*I think just receiving a letter from yourselves, I wouldn't have even thought of it without receiving the letter.* [0202601121]	INT	Discontinued
4		*Um okay, yes, I felt alright, I didn't mind. I didn't have any strong feelings actually; I just thought well if I have the time, I retired now so, you know, if you want, if it would help you and I might find interesting, I'd give it a go.* [0131401010]	CON	Reduced
5	**2a. Gradual tapering and the role of the GP**	*I would say not really, to be fair. I mean when I tried, or when I have withdrawn from them before, I think probably I've done it too quickly in the past. I mean when I was first on them due to suffering bereavement, after about 6–12 months I didn't really feel comfortable with taking the medication, so I did reduce them, but I reduced it too quickly and then I felt that I was still quite depressed, so it wasn't the right time. But this time, because it's been over a longer period of time of reducing it, then I haven't felt any side effects or issues, if that's the right words to use.* [0120801049]	CON	Discontinued
6		*[A]t the time I think I must have been on 20 because he tapered it very slowly; he did it over three months and initially I dropped to 10 and then I think we went for a month. Then he called me back and I was, it seemed to be fine, so we dropped again, I think we did alternate days. And then I think because I was feeling okay that was August last year and we went through to October, November, by which time it was every three or four days and at that point he said, if you're feeling okay just stop it. I think I got to the end of my prescription and stopped.*	INT	Original dose
7		*He sounded like he didn't really have a full understanding of what it was that was going on, so maybe that might have been good. But – yes – we discussed it and he was like, okay, you can – try if you want, see how you go; that was it really.* [0110402005]	INT	Original dose

TABLE 17 Themes and illustrative quotes from patient trial participants (*continued*)

Number	Theme/subtheme	*Quotes*	Arm	Outcome
8		*INT: And what was your experience like with your GP during the study? P: I think I've only seen her or spoken to her actually a couple of times but, yes, she was lovely. She was quite keen to see me about coming off the Lorazepam, like she didn't put me under any pressure or anything. She just said come and see me as and when and because of Covid I haven't really been down to the doctor's. I just think they've got more to worry about at the minute … But I will, when things get back to more normality, I probably will pop down and see her.*	INT	Reduced
9	**2b. 'Withdrawal' vs. 'relapse', perseverance and tipping points**	*Not that I'm aware of, really. I've come off caffeine in the past and I was much more aware of withdrawal there, so I think I'd know if I was experiencing withdrawal symptoms that I could attribute specifically to that. So no, I don't think so.* [102101032]	CON	Discontinued
10		*I think, I'm trying to remember, I think I just felt like quite down and just quite not like myself. I could definitely feel and see a difference, which is why I was like, no, I didn't want to do it, which is why I didn't want to carry on and I was a bit disappointed because I wanted it to work and I wanted it to go down … And there was no other reason for it, there wasn't anything else happening that would have made me feel like that. I knew it was literally down to the decreasing tablets.* [0301801008]	CON	Original dose
11		*Um. I think it was the side-effects actually of – it and then once I'd sort of got over some of the side effects, then going back to how I was before taking the tablets, which isn't how I wanted to be and isn't how I wanted to feel, so – I then knew that sort of increasing it, then maybe it made me feel better.* [0120401022]	INT	Reduced
12		*Oh sorry, no, the withdrawal was fine … The withdrawal initially, when I was going 5, 5, 5, was perfect; it was when I come off them altogether and then it got to about week 3 and I was doing – like you could tell because – I could feel it coming back in a bit of a way, that's how I'd describe that, and I was starting to – I wanted to go away from people, I wanted to get away from everybody. And I just didn't like them feelings and I realised myself that it had gone too far, so I thought I'd better do something about it.* [0301101017]	INT	Reduced
13	**3a. '*ADvisor* for patients'**	*[I]t helped me understand why I was probably feeling like I was feeling and there was one occasion when I felt, I'm not good for this, it's not working. And I went in and it's like, no, this is how you could feel and I was like, okay, that's normal, that's fine,* ***I'll carry on****. So, yes, I could relate to what it was saying because it was how I was feeling at that point. So, yes, that did help.* [0301101017]	INT	Reduced
14		*I suppose it is quite handy to have something there, because I suppose for some people, they'd rather read than talk. To me, it made no difference if it was there or not, to be fair because like I said, I was in an okay place and I didn't really need it, but I would have probably [preferred] the phone rather than gone and looked on the website.* [0301001030]	INT	Reduced
15		*It was reassuring to know it was there if I needed it, but I didn't need it … If I'd have felt that I was slipping again or if I'd have felt that I was experiencing negative side effects coming off the tablets, or if I'd have felt that my – you know – my condition was getting worse.* [201201016]	INT	Discontinued
16		*Yes, I think I did read through it. But then when I went downhill again, I didn't look at the information on it; I just thought, I don't know how long I can go on like this, that's what I thought to myself. Then the doctor rang and I stopped it, which was good, really. I would have rung up the surgery myself, I think; it got so bad.*	INT	Original dose

continued

TABLE 17 Themes and illustrative quotes from patient trial participants (*continued*)

Number	Theme/subtheme	*Quotes*	Arm	Outcome
17	**3b. Telephone support calls**	*I used those calls as sort of a refresher block because while I was speaking to whoever it was, they were asking questions, it gave me the time to reflect on how I'm feeling, because I'm a great one for going, oh yes, I'm fine and then under the surface I'm not, but being asked questions, it focused my attention on actually – am I fine? Am I okay? Am I struggling? they were helpful that way for me.* [201201016]	INT	Discontinued
18		*They were quite useful. It was like another push towards helping me do what I was doing, so it was quite useful.* [0302701056]	INT	Reduced
19		*The benefits are they help keep you on the programme because you're much less likely, well for me anyway, I was much less likely to give up and go back on the higher dose again because I knew that there was a call there. I felt a responsibility to the programme … obviously I knew I had that support and that call and that questionnaire where it will be assessing how I was and I found that reassuring that I had that in place.* [0110402011]	INT	Discontinued
20		*The only criticism I would make is life isn't really a box ticking experience, it isn't multiple-choice.* [131601011]	INT	Discontinued
21		*Me personally, I needed it after I'd come off it and I started to experience the withdrawal symptoms of not feeling well … where I had to then get in touch, there was nobody to talk to as such.* [201301017]	INT	Reduced
22		*I think I had a psychologist ring me one day but I can't remember much about the conversation, to be honest with you.* [0102302005]	INT	Original dose
23	**4. Reflections and realisations from the tapering process**	*Well at the beginning it was a little bit up and down, but I had – you know – I still had some bad days and some bad times, but now I very rarely have bad days. I have, well I have all good days really, there's just an odd occasion when, you know, you just get an off day, but I have more good days than bad now, and I feel a lot more positive.*	CON	Discontinued
24		*So it's pushed me to be outside my comfort zone, which is what I try to do every day now. So it's absolutely helped; it's been invaluable, yes, it's pushed me on to the next stage of dealing with life and its ups and downs and coping without anything exterior to prop me up.* [131601011]	INT	Discontinued
25		*But I think it was useful because it shows that I can come off it. I got to the point of coming off and then again, I went on simply because of circumstantial things, which aren't going to be there hopefully in a year or two's time, we shall see, but – yes. So it's been positive, it has been a positive experience, even though I've had a sort of step back.* [0102302005]	INT	Original dose

Workstream 5: Qualitative process evaluation interviews with health professionals

Theme 1: Creating the opportunity to discuss discontinuation

In both arms, HCPs talked about medication reviews as a good opportunity to broach discontinuation, but many admitted these were not conducted frequently or in enough detail. If patients arranged an appointment themselves with a view to stopping their antidepressant, this was a facilitator to discontinuation, saving time spent arranging appointments for the GPs and showing patient readiness to stop, which increased the GPs' confidence. The responsibility to initiate these discussions was often reported as shared, including the HP's responsibility to offer reviews, but patient responsibility to be proactive about raising the topic too. The REDUCE trial was seen as an opportunity to have discussions with patients about stopping that otherwise would not happen. The control arm was therefore considered by one GP to represent '*best practice*' as opposed to '*usual care*'.

TABLE 18 Participant demographics: process evaluation qualitative interviews with practitioners

Role	
GP	23
Pharmacist	1
MHN	1
PWP	2
Age: mean (range)	44.25 (31–70)
Female (*n*)	12
Years of experience [mean (range)]	14.22 (2.5–40)
High deprivation practices (*n*)	9
Urban practices (*n*)	18
Large practices (*n*)	12

Healthcare professionals talked about prompting patients to consider stopping antidepressants. This was done through text messaging or a note on the prescription. They frequently reported the importance of ensuring the patient's mood and life situation were stable at the point of stopping. The trial helped them identify patients who may be able to discontinue, but the processes (searching records for eligible patients and inviting them by letter) were seen as challenging and time-consuming. Some discussed a need for prompting or 'flagging' patients who may be able to discontinue, within existing systems.

When the decision was made to begin tapering, HCPs in both arms discussed the importance of informing the patient of possible withdrawal symptoms, with some highlighting how these may feel like anxiety and depression, including one who reported they now did it because of *ADvisorHP*.

Theme 2: Slow tapering

Two control arm and eight intervention arm GPs talked about slowly tapering medication. HCPs who used *ADvisorHP* often discussed the tapering regimens and how these were useful: 10 specifically mentioned having looked at or used them, 2 saying they shared this with patients. One found them most useful for less familiar medications. The MHN stated they tapered slowly due to guidance from outside the trial, as did two GPs, one of whom now placed more emphasis on slow tapering with the patient due to *ADvisorHP*. Three felt it caused them to reduce more slowly and one that *ADvisorHP* meant they were more likely to persevere with a slower taper when patients stopped and re-started tapering. One said they would usually go slower than the regimens in *ADvisorHP*, but having read it felt confident in tapering more quickly.

Theme 3: Distribution of the workload

Healthcare professionals thought the work involved in discontinuation could be managed differently to address their time constraints. GPs felt advanced nurse practitioners, MHNs and pharmacists were well-placed to broach the idea of stopping antidepressants, conduct medication reviews and monitor patients who were tapering, but some highlighted not all practices have these practitioners. Others who could follow up patients after they have had an initial consultation with another practitioner included social prescribers and PWPs. The MHN and pharmacist both felt well-placed to manage medication reviews and discontinuation, having more time than a GP. The pharmacist said patients do not seem to mind the reviews being conducted by them instead of a GP. HCPs discussed using practice level meetings, training events, and WhatsApp groups to share information and discuss practice.

Healthcare professionals frequently discussed the role of technology in managing workload, including telephone consultations and text messaging which had increased during the COVID-19 pandemic. Text messaging was used to invite patients to medication reviews and send links to resources, tapering regimens and questionnaires (in one case

asking about intentions to stop antidepressants). HCPs in the intervention arm also would have liked to text patients a link to *ADvisor*. While the initial consultation was often conducted face-to-face, HCPs reported using telephone consultations for the majority of follow-ups, managing workload and viewed positively by patients. Face-to-face consultations were considered superior in terms of building rapport and providing non-verbal cues, particularly important for mental health consultations. It was important for new resources to be integrated in existing systems to streamline processes and reduce work. Screen pop-ups could prompt them to have conversations about stopping, to conduct a medication review, and to link them to *ADvisorHP* or other guidance.

Theme 4: Confidence-building and reassurance

Healthcare professionals who had used *ADvisorHP* most frequently discussed the utility of the tapering regimens but also felt they had learnt how to distinguish relapse and withdrawal and understand patient perspectives. *ADvisorHP* built confidence in their ability to support patients, and one felt reassured by the information on risk of relapse. For some, the *ADvisorHP* information was not new, but a good reminder.

Theme 5: Variable engagement with intervention components

Most HCPs found it useful to read *ADvisorHP* in one sitting at the start of the trial. Some referred back to it when consulting patients, others only looked at it once, and two not at all. The MHN stated they did not need to because everything was going well with their patients and they had not recruited many anyway. If there had been more patients, and more difficult situations, they may have used it. One GP who did not look at *ADvisorHP* appeared to conflate the patient and HP interventions and seemed unaware there was an online resource for HCPs.

Materials were sometimes shared with the patient, through printing materials or sharing the screen, but not all HCPs did this. In the intervention arm *ADvisorHP* advised HCPs to conduct regular follow-up appointments with the patient during the tapering process. While some arranged these appointments, many asked patients to request them as needed, across both arms. Whether the follow-up appointment was pre-arranged or left to the patient was sometimes dependent on the needs of the patient. One GP discussed how a more pro-active approach to following up patients might be preferable but was not always feasible.

Relation to the logic models for the interventions

In our logic model for the HP intervention (see *Appendix 6*), we proposed mechanisms of action involving changes in the beliefs and behaviours of the GPs. Of these, there was evidence from the interviews to support effects of the intervention on *'improved knowledge of reduction schedules'*, *'improved self-efficacy*, improved *'confidence to discontinue'* and on an *'increase in GPs raising the topic of discontinuation with the patient'*.

There was limited evidence supporting effects of the intervention on *'increased motivation to withdraw patients'*, *'better understanding of the patient's perspective'*, *'detachment from the serotonin hypothesis'*, *'discussion of withdrawal during the initial prescription of antidepressants'*, or *'being less likely to restart ADs in the face of mild and moderate withdrawal symptoms'*. There was no evidence to support *'not restarting antidepressants when faced with initial warning signs of relapse'*. HCPs did however report discussing withdrawal symptoms with the patient at the point of tapering as a way of managing expectations about the process, which was not proposed within the logic model.

'GP raises the topic of discontinuation with the patient' was an inherent requirement of the trial, in both arms, through checking the records searches and selecting patients who were well enough to stop antidepressants. The fact that patients and practitioners in both arms highlighted its importance suggests it may be a key mechanism for enabling discontinuation, as it was not a process specific to the intervention arm, and antidepressant discontinuation rates were unexpectedly high, and similar across the two arms of the trial.

In our patient interviews, there did not appear to be a difference in recall of patient follow-up appointments between trial arms, so this is not likely to have influenced the outcome, despite originally expecting the intervention arm GPs would provide better follow-up as a result of the guidance in *ADvisorHP*. This was also supported in the HP data. HCPs did not differ between arms in how they talked about the amount of follow-up either – there was a mix in both arms in terms of pre-arranged follow-up and leaving it up to the patient.

The importance of slow tapering was discussed in both arms but was more frequently highlighted in the intervention arm. Given that HCPs reported using the tapering regimens in *ADvisorHP*, it is possible that slower tapering in the intervention arm might explain the fewer reported withdrawal symptoms by intervention arm patients. However, this is uncertain as we did not have data on the tapering regimens recommended by the GPs for patients in each arm.

TABLE 19 Themes and illustrative quotes from practitioner trial participants

Theme	Supporting quotes
Creating the opportunity to discuss discontinuation	*[I]f I hadn't been doing the control arm of the study, maybe I would have had a review with those patients where we didn't go into the depth of discussing whether they wanted to reduce them and maybe – maybe that's something [they received], inviting them to the study, even though.* (GP Control arm 02011GP001) *[S]earching for patients who have been on long-term antidepressants and – and – looking through those – those sort of patients and highlighting patients who might benefit from weaning has been a useful, worthwhile process.* (GP intervention 0132GP001) *it literally probably took me six hours to do all the searches for these and that's – that's a lot of patients not being seen.* (GP Control arm 02028GP001) *We could – we could do a search on everybody who's on long-term antidepressants and arrange a phone call with everybody but that's such a workload issue for us.* (GP Intervention arm 03026GP001) *the similarity between anxiety symptoms and withdrawal symptoms and that's something I do tend to talk to patients about now, which I probably didn't do before.* (GP Intervention arm 03026GP001)
Slow tapering	*Basically when I'm talking with patients about reviewing, reducing or stopping medication, I've become much more – much more cautious about sort of just encouraging people to really, really take their time, just tail off over much longer periods than I used to. I probably used to be quite gung ho and say – just sort of halve it and then halve it and, you know, two or three weeks and you'll be fine. I don't tend to say that now. I say – just take them, just take your time and – and it's – yes and I think. patients seem to appreciate that.* (GP Control arm 03014GP001) *I think, for me, when I'm doing the patients, you know, in the future, I can talk to them, we can do a very slow tapering process, to see how they feel and there's no hurry to stop on a certain date and time. So that's the things I think – when I'm looking at your scheme – I'm thinking, oh, that's good, we can do it slowly.* (GP Intervention arm 02029GP001) *I think it made me go a bit slower than I was accustomed to doing, not – marginally, but a little bit, a little bit more cautious perhaps but – I don't remember anything else, other than that.* (GP Intervention arm 01028GP001)
Distribution of the workload	*[A]s a mental health nurse in the surgery, our role can be to offer a patient a lot more contact when doing that* (Mental Health Nurse Intervention arm 01344NP002) *Firstly I think it's sharing the load, so we are completely overloaded in general practice and that could be great to have somebody else.* (GP Control arm 01208GP001) *It's really well here. It doesn't need to be a GP; it's almost a bit of a – a waste of GP time. I think – I think you could – you could have any sort of healthcare professional doing it, I'm just trying to think of other – I don't think – well no – I'm just thinking, no, I suppose most of the prescribers in this business – in our PCN – are either ACPs, pharmacists or GPs: there aren't many nurse prescribers, only ACPs. But any of us can do it and I don't think it really matters – and the patients don't – they often call you doctor.* (Practice Pharmacist Control Arm 02028GP001) *[D]oesn't it make a bit more sense that potentially they can sort of like discuss through a plan or with the prescriber, the doctor or the ANP, but actually some of those follow-ups be with a known PWP to them or like a practice PWP; that would almost make a bit more sense.* (GP Intervention arm 02026GP001) *[S]o it's looking at digital ways of working and flagging up patients so that it doesn't become a never-ending prescription.* (GP Intervention arm 02017GP001) *I think – interesting at the start of REDUCE – clearly I didn't have all the digital technology and the AccuRx messaging. I think if I were doing it again now I would build those in., but that was because it was all pre-COVID.* (GP Intervention arm 02017GP001) *We printed off the sort of algorithm page and shared it with other clinicians to say – what do you think of this plan; should it be adopted or do we do it? So we had a bit of a discussion around that, so that was quite useful.* (GP Intervention arm 02025GP02) *It was – do you know what – I actually think it came up in one of our GP WhatsApp groups; somebody sent it over.* (Mental Health Nurse Intervention arm 01344NP002)
Confidence and reassurance	*Adviser side of things, but there was sort of – I suppose none of it was necessarily surprising to me, but it did remind me of – of the issues and things.* (GP Intervention arm 01320GP001) *And I think some of the background in terms of the – the information about, you know, success and risk of relapse and things, was also very reassuring as well.* (GP Intervention arm 01320GP001) *[I]t's like another tool that I've got there that, if I need it, I can call upon it if I'm not sure what to do or something is a bit outside of my experience or something like that, then I might – I know it's there and that gives me confidence to know that I can – I can manage this.* (GP Intervention arm 01028GP001)

continued

TABLE 19 Themes and illustrative quotes from practitioner trial participants (*continued*)

Theme	Supporting quotes
Variable engagement with intervention components	*I didn't make formal follow-up appointments. I probably did it on a very patient initiated follow-up basis and – our numbers were small in the study but I don't think there were any that actually did end up coming off their antidepressants and I wondered, in hindsight, whether, if I had – arranged a formal, regular review, whether we may have had more success.* (GP Control arm 03012GP001) *Certainly I would ask people whether they used it, whether they looked at it and I would encourage them to, you know, refer back to it if they had questions.* (GP Intervention arm 01320GP001) *Yes, as I said, I don't really know what they had, but I'm expecting it's something similar to what I have; so something explained to them, you know, if they have any symptoms, what they are.* (GP Intervention arm 02029GP001) *I said come back for a follow-up and have a chat and I got a message saying – I've got a really good thing going on with this Adviser so far, so can I postpone and stick with the plan. I'm still tapering, I'll come and see you a bit later.* (GP Intervention arm 02025GP02)

Qualitative interviews with psychological well-being practitioners

Two PWPs were interviewed about their experiences of delivering telephone support to patients. They differed in their qualification level and level of experience; one being qualified to deliver more complex talking therapies. The more experienced PWP reported using their clinical skills to guide the conversations with patients while the less experienced PWP talked about following the telephone support guide closely, feeling that their role and the purpose of the telephone calls was unclear.

The data from these interviews highlighted training and support needs if the support calls were to be implemented by PWPs:

- Administrative support for booking and rearranging calls.
- Education around antidepressants and discontinuation.
- Ways to link the patient directly to *ADvisor*.
- Better management of patient expectations of the phone calls.
- Increased support for reporting patient risk (e.g. suicidal ideation) out of hours.

TABLE 20 Implementation mechanisms and process outcomes

		Implementation process putcomes			
		Intervention performance: How do REDUCE components perform in practice?	**Relational restructuring: How do REDUCE components change interactions between doctor and patient?**	**Normative restructuring: How did REDUCE components change the rules of practice?**	**Sustainability/normalisation: What needs to be done to ensure that tapering and discontinuation are sustainable?**
Implementation mechanisms	**Coherence-building**: How do Doctors and patients make sense of implementing tapering and discontinuation	(+) REDUCE created opportunities for discussing discontinuation.	(−) Sharing of materials by GPs with patients was variable.	(+) *ADvisorHP* can increase GP/health practitioner confidence about speed of tapering and discontinuation.	(+) Importance of making patients aware of 'symptoms' experienced during tapering (*ADvisorHP* supports this).
	Cognitive participation: How do doctors and patients initiate and legitimise implementing tapering and discontinuation?	(+) GPs prompting discontinuation and linking to *ADvisorHP* through text messaging.	(+) Patient-initiated discontinuation demonstrates commitment. (−) Patient-initiated discontinuation overcomes lack of GP time for initiation.	(−) Processes for prospectively identifying suitable patients challenging and time consuming.	(+) Need to flag suitable patients in EPRs.
	Collective action: How do doctors and patients perform implementing tapering and discontinuation?	(+) Tapering needs to be done slowly, (*ADvisorHP* supports this even if patient stops and restarts tapering).	(−) Currently medication reviews are infrequent and lack detail. (+) Medication reviews and tapering support can be delegated to other health professionals.	(−) Follow-up consults can be delivered by phone, even though face-to-face consults are superior.	(+) Ensuring patient mood and circumstances were stable before commencing discontinuation.
	Reflexive monitoring: How do participants evaluate implementing tapering and discontinuation?	(+) Medication reviews: opportunity to consider discontinuation.	(−) Follow up appointments were sometimes left to patients to arrange.	(−) Proactive approaches to follow up preferable but not always feasible.	(+) Need to embed treatment resources in EPRs.
GP work with patients		Medication review work		Electronically mediated work	

EPRs, electronic patient records.

Appendix 6 Health economics evaluation

Aim

The health economics evaluation was a key component of the REDUCE programme, undertaken from an NHS and PSS perspective. The aim was to assess the costs and cost-effectiveness of the online and telephone support interventions, compared with usual care in the definitive trial.

Methods

The analyses were conducted using individual patient-level data extracted by general practice staff from patients' computerised medical records after the 12 months follow-up. Patient questionnaires were also used to collect data on use of antidepressants, other medication and NHS services at baseline, 6 and 12 months follow-up, together with out-of-pocket spending and sickness absence to allow a comparison of costs from a societal perspective. Service use measured by the patient questionnaires will be compared later with the data collected from the medical records to look at differences between them, but this was not a prime objective.

National Health Service services recorded included those provided in the primary care setting (face-to-face GP and nurse consultations, GP and nurse telephone contacts, and GP and nurse e-mail or e-consult contacts); community health services (e.g. health visitors, district nurses, counselling or psychological therapists); and secondary care mental and physical health services (inpatient, outpatient, day patient and accident and emergency attendances). The questionnaire and medical records data extraction form were identical in structure and recorded whether patients had used specific services, how many contacts they had received, and where relevant the average duration of service contact (i.e. across all contacts the individual made with each service). The names of medications were recorded along with doses, frequency and duration of use.

The economic analyses followed the ITT principle. Unit costs for health service use were derived from the PSSRU schedules for primary and community care contacts;[83] *British National Formulary* (https://bnf.nice.org.uk/; accessed 27 November 2024) for costs of antidepressant drug treatments; and national NHS reference cost schedules (www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/; accessed 27 November 2024) for secondary care costs. All costs were based on the year 2023–4, adjusting for inflation from PSSRU 2022 unit costs.

The cost of the online interventions was calculated on the principle of including only the real cost that would occur when an intervention is being rolled out, for hosting and maintenance of the website. The research and development costs were therefore excluded. A quote was obtained in April 2023 of £1512 plus £420 for yearly website maintenance and hosting respectively from a relevant technology company, giving an average cost per patient in the trial intervention arm of £1932/178 = £11 over the 12 months. In addition to the online intervention costs, the cost per patient in the trial included 1 hour of PWP time for the telephone support, estimated at £14 (NHS Reference Costs), giving a total cost of £25 per patient. Future development of wider access to the online interventions would diminish the cost per person rapidly. However, we conducted an additional analysis for a cost of £50 for the intervention, to determine the sensitivity of the cost-effectiveness to a greater cost for PWP time spent providing telephone support.

Quality of life was measured using both the EQ-5D-5L[57] and Medical Outcomes Study SF-12 questionnaires[58] at baseline, 3, 6, 9 and 12 months. We chose the EQ-5D-5L instrument due to a potential ceiling effect with the original EQ-5D-3L questionnaire. We included the SF-12 in addition, as there were suggestions in the literature that it is more sensitive to changes in mental health than the EQ-5D-5L.[84–86] Crosswalk methods were applied to derive the utility scores, using the algorithm from the EuroQol-5 Dimensions (EQ-5D) website at: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/ (accessed 27 November 2024) as recommended by NICE.[87] The SF-12 scores were translated into Short Form questionnaire-6 Dimensions scores to derive patient utilities using the UK

tariff.[58] QALYs were calculated using the area under the curve approach. As the trial period was limited to 12 months, no discounting rates were applied.

Generalised linear mixed modelling, using log link and gamma distributions, was employed to estimate the difference in mean costs, adjusting for baseline characteristics including baseline QoL scores, employment status, housing type, education, marital status, dependents, gender, age, past history of depression, baseline GAD-7 anxiety score and practice as a random effect to allow for the clustered design.

The primary outcome was cost–utility expressed as incremental cost per QALY gained. Generalised linear mixed models with identify link function were employed to estimate the difference in utility scores and QALYs between intervention and control groups, adjusting for baseline patient characteristics as above, as well as baseline utility scores.

The bootstrapping method with 1000 resamples with replacement was used to estimate the ICERs between the two arms. Main differences in costs and QALYs along with their associated standard errors were estimated from each bootstrapping sample. Incremental costs and incremental QALYS and their rates were calculated through dividing the estimated mean difference in cost by the mean difference in QALYs from each sample data. The distributions of those estimates were used to estimate mean ICERs and 95% percentiles, and to produce a CEAC for a range of thresholds for societal willingness to pay per QALYs gained. The base analyses were based on completed case analysis and used utility scores generated by the EQ-5D instrument. Utility scores derived from the SF-12 were also analysed in a sensitivity analysis to compare the cost–utility when changing the data collection instrument.

Multiple imputation by chained equation was used in sensitivity analyses to impute missing values, given the loss to follow-up over 12 months which significantly reduced the number of patients with complete QoL data for computing QALYs gained.

Differences in personal costs were also analysed include patient and carer time off work, and personal expenses for use of the internet, and travel.

The economic evaluation followed published good practice guidelines,[88] and the report was written following the recommendation of the Consolidated Health Economic Evaluation Reporting Standards statement (www.ispor.org/CHEERS; accessed 27 November 2024). All the health economic analyses were conducted using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA).

TABLE 21 Number and costs of items of NHS services used by patients in the intervention and control groups (from practices' computerised medical records data)

	Intervention group (*N* = 178)			Control group (*N* = 147)		
Item of service	Recorded number	Mean no. per patient (SD)	Mean costs (£) (SD)	Recorded number	Mean no. per patient (SD)	Mean costs (£) (SD)
Medications	125	4.3 (3.3)	23.7 (30.8)	107	3.9 (3.2)	20.6 (40.9)
GP face-to-face contact	115	2.1 (2.1)	91.2 (90.1)	105	2.5 (2.4)	107.4 (105)
GP telephone contact	125	4.1 (2.5)	66.7 (41.6)	101	3.6 (2.7)	58.6 (44.4)
GP online contact	36	2.1 (2.1)	90.4 (88.5)	13	2.5 (2.6)	108.6 (111.4)
GP out of hour contact	8	1.1 (0.4)	96.4 (30.3)	8	1 (0)	85.7 (0)
Practice nurse face-to-face contact	84	2.8 (2.5)	30.5 (26.9)	65	2.2 (1.5)	23.5 (15.8)
Practice nurse out-of-hours contact	4	1.8 (1.5)	36.9 (31.7)	2	1 (0)	21.1 (0)

continued

TABLE 21 Number and costs of items of NHS services used by patients in the intervention and control groups (from practices' computerised medical records data) (*continued*)

Item of service	Intervention group (*N* = 178)			Control group (*N* = 147)		
	Recorded number	Mean no. per patient (SD)	Mean costs (£) (SD)	Recorded number	Mean no. per patient (SD)	Mean costs (£) (SD)
Community MHN	1	3	55.1	1	1	18.4
Other nurse contacts	35	2.2 (2.0)	39.8 (36)	10	1.6 (1)	29.4 (17.7)
Community doctor contacts	5	1.8 (1.3)	61.8 (44.8)	9	1.8 (1)	61 (33.4)
Counsellor contacts	4	2.3 (2.5)	77.3 (85.9)	4	2.3 (2.5)	77.3 (85.9)
Psychiatrist contacts	2	2.5 (2.1)	171.7 (145.7)	1	1	68.7
Psychologist contacts	2	1 (0)	42.9 (0)	0		
Other therapist contacts	15	2.3 (1.7)	97.3 (71.6)	16	2.1 (1.9)	91.2 (79.7)
Walk-in service contacts	6	1	57.5 (0)	5	1 (0)	57.5 (0)
NHS 111 contacts	5	1 (0)	12.3 (0)	9	1.2 (0.4)	15.1 (5.4)
Outpatient appointments	64	2 (1.1)	421.5 (237.5)	54	1.9 (1.1)	402 (221.5)
Day case attendances	10	1 (0)	1077.7 (0)	15	1.3 (0.5)	1365 (493.3)
Accident and emergency attendance	16	1.2 (0.4)	298.4 (101.3)	20	1.2 (0.5)	301.5 (131.4)
Inpatient stay	6	2 (0)	4355.60 (7802.70)	6	2 (0)	1756.3 (1012.2)
Intervention	178	1 (0)	25 (0)			
Total	**178**		**595.50 (1662.50)**	**147**		**668.9 (921.50)**

Cost-effectiveness and cost–utility of the interventions compared to usual care

TABLE 22 Costs, PHQ-9 scores and incremental cost per point on the PHQ-9 gained (ICER) using bootstrap methods for completed depression data at 6 months

Group	Cost (£) mean (95% CI)	Incremental cost (£) mean (95% CI)	PHQ-9 score mean (95% CI)	Reduction in PHQ-9 mean (95% CI)	ICER (£/PHQ-9) mean (95% CI)
Control	666 (662 to 808)		5.0 (4.3 to 5.7)		
Intervention	597 (582 to 828)	−69 (−77 to 207)	4.0 (3.5 to 4.6)	−1 (−1.8 to 0)	−88 (−653 to 382)

(*continued*)

TABLE 23 Costs, QALYs and incremental cost per QALY gained (ICER) based on EQ-5D-5L and SF-12 values, using bootstrap methods for completed QoL data

Group	Cost (£) mean (95% CI)	Incremental cost (£) mean (95% CI)	QALYs mean (95% CI)	Incremental QALY mean (95% CI)	ICER (£/QALY) mean (95% CI)
EQ-5D-5L					
Control	666 (662 to 808)		0.805 (0.806 to 0.832)		
Intervention	597 (582 to 828)	−69 (−77 to 207)	0.829 (0.83 to 0.851)	0.024 (0.023 to 0.059)	−2839 (−30,024 to 22,227)
SF-12					
Control	666 (662 to 808)		0.717 (0.698 to 0.736)		
Intervention	597 (582 to 828)	−69 (−77 to 207)	0.733 (0.716 to 0.751)	0.016 (0.008 to 0.042)	−3312 (−42,043 to 38,998)

TABLE 24 Costs, QALYs and incremental cost per QALY gained (ICER) based on EQ-5D-5L and SF-12 values, using bootstrap methods for imputed QoL data

Group	Cost (£) mean (95% CI)	Incremental cost (£) mean (95% CI)	QALYs mean (95% CI)	Incremental QALY mean (95% CI)	ICER (£/QALY) mean (95% CI)
EQ-5D-5L					
Control	666 (662 to 808)		0.792 (0.772 to 0.81)		
Intervention	597 (582 to 828)	−69 (−77 to 207)	0.827 (0.814 to 0.84)	0.035 (0.013 to 0.059)	−4678 (−11,265 to 8268)
SF-12					
Control	666 (662 to 808)		0.718 (0.706 to 0.731)		
Intervention	597 (582 to 828)	−69 (−77 to 207)	0.738 (0.726 to 0.75)	0.02 (0.003 to 0.038)	−4100 (−26,851 to 14,610)

TABLE 25 Sensitivity analysis of change of intervention cost from £25 to £50 per patient (with QALYs based on the EQ-5D-5L)

Group	Cost (£) mean (95% CI)	Incremental cost (£) mean (95% CI)	QALYs mean (95% CI)	Incremental QALY mean (95% CI)	ICER (£/QALY) mean (95% CI)
Control	666 (662 to 808)		0.805 (0.806 to 0.832)		
Intervention	622 (457 to 853)	−44 (−272 to 232)	0.829 (0.830 to 0.851)	0.024 (0.023 to 0.059)	−1418 (−28,295 to 23,974)

FIGURE 10 Scatter plot of intervention compared with control based on QALYs from completed EQ-5D-5L values over 1 year.

TABLE 26 Summary of patient/carer sickness absence and out-of-pocket expenses in control and intervention groups

Group	Items	Number of patients (%)	Mean number of days off sick (SD)	Mean costs (£) (SD)
Control (*N* = 147)	Patient/carer sickness absence	13 (8.8)	1.4 (0.8)	170.3 (94.5)
	Out-of-pocket expenses	21 (14.3)		22.8 (40.2)
Intervention (*N* = 178)	Patient/carer sickness absence	17 (9.6)	2.1 (1.4)	253.2 (171.0)
	Out-of-pocket expenses	19 (12.9)		2.1 (6.9)

TABLE 27 Sensitivity analysis of costs, PHQ-9 scores and incremental cost per point on the PHQ-9 gained (ICER) using bootstrap methods for completed depression data at 6 months, including personal costs

Group	Cost (£) mean (95% CI)	Incremental cost (£) mean (95% CI)	PHQ-9 score mean (95% CI)	Reduction in PHQ-9 mean (95% CI)	ICER (£/PHQ-9) mean (95% CI)
Control	667 (538 to 807)		5 (4.3 to 5.7)		
Intervention	622 (457 to 850)	−45 (−273 to 222)	4 (3.5 to 4.6)	−1 (−1.8 to 0)	−49 (−225 to 156)

TABLE 28 Sensitivity analysis of costs, QALYs and incremental cost per QALY gained (ICER) based on EQ-5D-5L and SF-12 values, using bootstrap methods for completed QoL data, including personal cost

Group	Cost (£) mean (95% CI)	Incremental cost (£) mean (95% CI)	QALYs mean (95% CI)	Incremental QALY mean (95% CI)	ICER (£/QALY) mean (95% CI)
EQ-5D-5L					
Control	667 (538 to 807)		0.805 (0.806 to 0.832)		
Intervention	622 (457 to 850)	−45 (−273 to 222)	0.829 (0.83 to 0.851)	0.024 (0.023 to 0.059)	−1977 (−33,379 to 17,634)
SF-12					
Control	667 (538 to 807)		0.717 (0.698 to 0.736)		
Intervention	622 (457 to 850)	−45 (−273 to 222)	0.733 (0.716 to 0.751)	0.016 (0.016 to 0.042)	−2388 (−45,409 to 32,269)

TABLE 29 Sensitivity analysis of costs, QALYs and incremental cost per QALY gained (ICER) based on EQ-5D-5L and SF-12 values, using bootstrap methods for imputed QoL data, including personal costs

Group	Cost (£) mean (95% CI)	Incremental cost (£) mean (95% CI)	QALYs mean (95% CI)	Incremental QALY mean (95% CI)	ICER (£/QALY) mean (95% CI)
EQ-5D-5L					
Control	667 (538 to 807)		0.792 (0.772 to 0.81)		
Intervention	622 (457 to 850)	−45 (−273 to 222)	0.827 (0.814 to 0.84)	0.035 (0013 to 0.059)	−1634 (−10,458 to 9714)
SF-12					
Control	667 (538 to 807)		0.718 (0.706 to 0.731)		
Intervention	622 (457 to 850)	−45 (−273 to 222)	0.738 (0.726 to 0.75)	0.02 (0.003 to 0.038)	−2796 (−31,727 to 21,317)

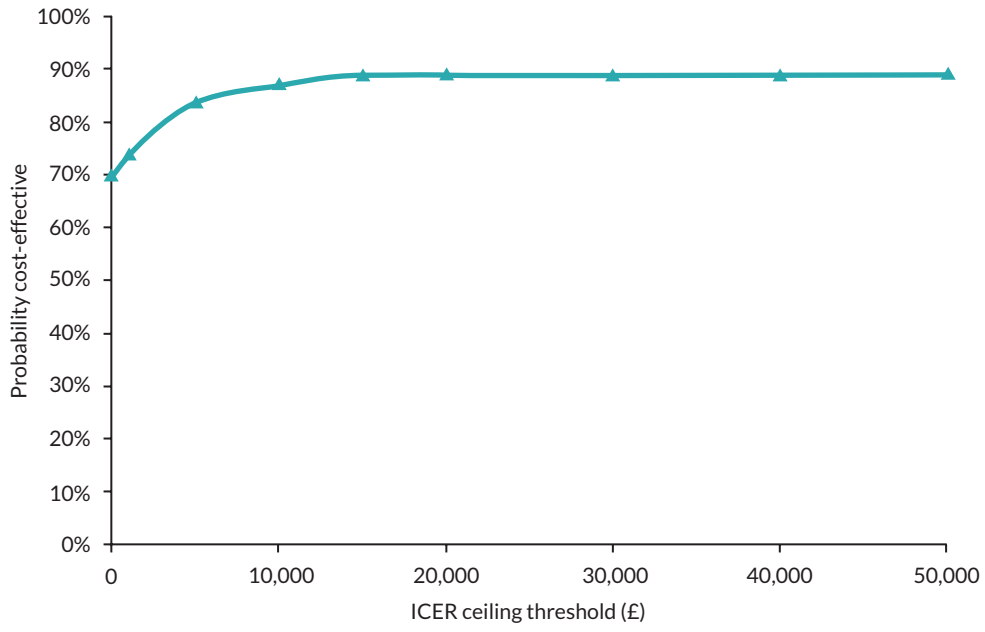

FIGURE 11 Cost-effectiveness acceptability curve of the intervention based on QALYs from completed EQ-5D-5L values over 1 year.

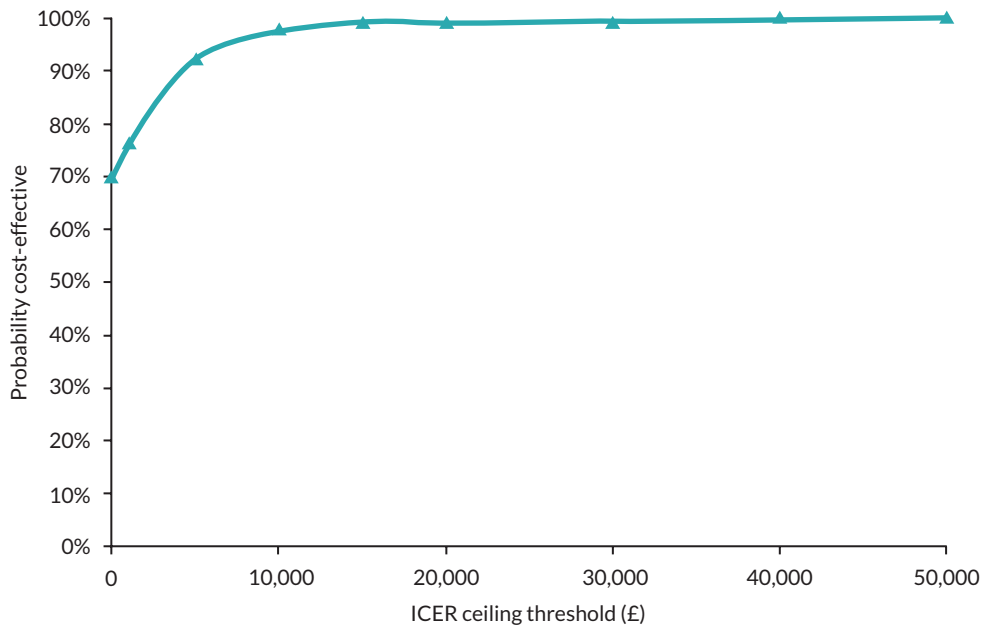

FIGURE 12 Cost-effectiveness acceptability curve of the intervention based on QALYs from imputed EQ-5D-5L values over 1 year.

Appendix 7 Additional workstream: the REDUCE-Urdu study

Background

It is crucial that psychosocial interventions are made more accessible to people from ethnic minority communities.[59,60] The NIHR Programme Grants Board therefore requested that we add a workstream in the programme on developing an intervention for a minority ethnic group for whom English was not their first language, because being a non-English speaker was an exclusion criterion for the main study.

We had relevant expertise in the team, as co-applicant Chris Dowrick had researched this issue, through the NIHR PGfAR-funded AMP (Access to Mental Health in Primary Care) programme.[89] The critical issue is that the central mechanism of internet interventions is language.[90] It is feasible to extend interventions like this to members of ethnic minority communities, but it does need careful additional work, as experience with the AMP programme had indicated.[91] We chose to focus on the South Asian community who comprise a sizable proportion of the UK ethnic minority community and are relatively well clustered in the North West, near to the University of Liverpool REDUCE recruiting centre.

The overall prevalence of common mental disorders is not higher in the British South Asian community, though there are certain at-risk groups: women of reproductive age are more susceptible to perinatal depression,[92] and elderly women are at higher risk of suicide compared to their White British counterparts.[93] In addition, South Asians are considered 'harder to engage' due to language and cultural barriers. They also tend to lack social support and are more likely to experience marked marital or relationship difficulties.[94]

Studies show South Asians' perceptions of mental illness and its treatment are different. Spiritual aspects seem to be important, and the perceived aetiology may be seen as a punishment or a will of God.[92] Cultural adaptations of therapies to a South Asian community have important elements to consider, including language used (with regards to respect) and how to assess healing beliefs and identifying and coping with culturally accepted dysfunctional beliefs.[95,96] Furthermore, the ROSHNI-2 and other studies on South Asian populations have shown that other important factors are important to include in interventions for South Asian women such as addressing ways of engaging the whole family, self-esteem, social support, independent coping strategies, child care and transport provision and the use of storytelling.[97] There is also some qualitative evidence that South Asians may find pharmacological interventions unhelpful, follow-up and support inaccessible or unacceptable to them, and would not be concordant with their beliefs.[98,99] These multiple factors including South Asian community beliefs, practices and support, and poor adaptation of the health system would therefore likely impact on South Asians' help-seeking with regards to coming off antidepressants, and no previous study had addressed this issue.

In the UK, several programmes have looked at how to better engage South Asians. In the AMP programme, to ensure their proposed intervention was acceptable and culturally sensitive, Dowrick *et al.*[91] undertook a series of focus groups with service users, members of the community, and service providers. These were conducted either through interpreters or by researchers speaking the relevant languages. Focus groups were recorded, transcribed and analysed for key findings. This enabled them to produce modified interventions which were demonstrably feasible and acceptable, and which showed promise for effectiveness.[100]

Aim and objectives

The REDUCE-Urdu study aimed to develop a version of the patient internet support intervention for South Asian Urdu-speaking patients and test it using 'think-aloud' interviews. This was led by the team at the University of Liverpool.

The study had three principal objectives:

- Phase 1 – REDUCE Urdu formative work
- Phase 2 – Developing the Urdu *ADvisor*
- Phase 3 – Piloting the Urdu *ADvisor*

The following REDUCE Study team members developed a protocol for the study: Nadja van Ginneken, Tasneem Patel, Chris Dowrick, Tony Kendrick and Adam Geraghty. Research Fellow Yumna Masood was recruited to carry out focus groups and qualitative interviews with patients and community leaders to elicit perceived barriers and facilitators to discontinuation of antidepressants, and their views on a possible online intervention for Urdu speakers.

Phase 1: REDUCE Urdu formative work

The first phase was an opportunity to explore the Urdu-speaking South Asian population's views on mental health, on using and stopping antidepressants, and on a possible online intervention to help Urdu-speaking people come off antidepressants when appropriate.

Step 1: Focus group of healthcare professionals

A focus group of HCPs was organised. The focus group included GPs, both English and Urdu, working with Urdu-speaking South Asian communities in the North-West of England. Recruitment of HCPs was from Shifa Surgery, Pendle View Medical Practice and Moorgate Primary Care. The main issues explored were HCPs' perspectives on potential barriers affecting the Urdu-speaking South Asian group when coming off antidepressants, which could be addressed in the intervention. We also included questions on the possible content and presentation of an online intervention for Urdu speakers without showing them the *ADvisor* intervention.

Step 2: Focus group of community leaders

A focus group was carried out with community leaders (CLs), that is people within the community who were representative of a community organisation. Local community groups in Manchester and Rochdale were contacted to recruit CLs who were supporting men and women in the community. We included one mixed group of men and women. The focus group was used to explore CLs' perceptions of mental health, antidepressants and long-term antidepressant use. We also included questions on the possible content and presentation of an online intervention for Urdu speakers, again without showing them the *ADvisor* intervention.

Step 3: Focus groups with the Urdu-speaking South Asian community

Two focus groups from the Urdu-speaking South Asian community were organised, including 14 men and women who had prior or current experience of treatment with antidepressants. Community groups around the Rochdale area were contacted for recruitment. We included one women-only group and one mixed gender group, and found that women in the first group were more comfortable in expressing their views. We explored barriers and facilitators to stopping antidepressants which were specific to the Urdu-speaking South Asian community. We also included questions on the possible content and presentation of an online intervention for Urdu speakers, again without showing them the *ADvisor* intervention.

Phase 2: Developing the Urdu ADvisor

The Urdu intervention was developed on the basis of the work above, and most significantly on the basis of the main result found in the focus groups, which was that most of the Urdu speakers did not want an interactive online digital intervention. We found that most Urdu speakers did not read and write Urdu, and so written material and exercises would not work in the same way as the *ADvisor* intervention we had developed for the main study. The intervention developed was therefore based on online videos and a paper booklet, in both Urdu and English, which could be read or viewed together with family and friends, rather than being based on an interactive website for an individual.

In addition to the PBA,[46] we used the framework for cultural adaptation and development of psychosocial treatments for ethnic minority groups originally developed with Hispanic people by Bernal *et al*.[101] This includes eight dimensions: language, persons, metaphors, content, concepts, goals, methods and context, and serves as a guide for developing culturally sensitive treatments and adapting existing psychosocial treatments to specific ethnic minority groups.

After a careful review of the first phase interviews, PBA analysis and *ADvisor* online intervention, it was found that the core structure, techniques, and elements of the intervention and materials were culturally compatible and did not require significant changes. However, subtle but critical adaptations were needed in all of the domains. Key areas of adaptation were considered language, persons, metaphor, content, concepts, methods and context.[101]

The *ADvisor* online intervention module content was first developed into a paper booklet in English. We then translated the content into Urdu in line with Bernal's framework. The translation process considered the conceptual equivalent of a phrase, rather than a word-for-word translation, while considering the target audience.[101] The language was kept simple, clear and concise by avoiding long and complex sentences. Specialised terms and jargon were avoided. Later, links to online versions of the booklet in English and Urdu were created by Yumna Masood.

The final versions of the Urdu *ADvisor* English and Urdu booklets and online links were critically reviewed by the rest of the study research team. In addition, an expert group was established, which included the lead bilingual researcher Yumna, and three patient and public involvement and engagement members. The group discussed issues that occurred during the translation process. Frequent discussions resulted in translated content comparable on a technical level (i.e. grammar, tense, acceptable level of abstraction) and on a conceptual level (obtaining an identical meaning of concepts which may have different cultural expressions, e.g. idioms or metaphors). The expert group finalised the cultural adaptation of the intervention. The final step was external evaluation of the booklets and video links by Urdu- and English-speaking Urdu community members. After evaluation by the external reviewers, it was found that some literal translations of the content were incorrect, and some images were considered too general and did not reflect the South Asian community. Specific recommendations were followed to revise parts of the booklet and online videos.

Phase 3: Piloting the Urdu ADvisor

Think-aloud interviews were conducted with 10 Urdu-speaking people on long-term antidepressant treatment who fitted the study inclusion and exclusion criteria for WS4 and WS5. Participants were recruited from the local community in Rochdale. The interviews were conducted in English or Urdu, depending on which language the participant felt comfortable with. Interviews were conducted in batches, and after the first six interviews and analysis were conducted, the research team agreed on changes to be implemented before the next wave of four interviews. This allowed for iterative improvements to be assessed and commented on by patients. Interviews with patients continued until data saturation was reached, and no further changes were necessary according to the PBA.

Participating individuals had experienced feelings of depression, particularly when isolated during the COVID-19 lockdown. They reported they felt medication could not fully alleviate depression and emphasised the importance of actively working on one's mental health in other ways, while not stopping antidepressants suddenly. Some shared various side effects and symptoms experienced during medication use, including dizziness, sleep problems, fatigue, dry mouth, anxiety and feelings of inferiority, while expressing concerns about the negative impact and long-term use of medications on their well-being. The participants expressed dissatisfaction with a perceived lack of support and guidance from doctors in managing medication-related issues.

Generally, participants provided positive feedback on the Urdu booklet and video links. It was seen as a useful self-management tool for people who wanted to come off antidepressants and a way to increase awareness of possible discontinuation strategies in the community. They expressed appreciation of the effort put into its creation, highlighting the likely effectiveness of self-management techniques, alternative approaches to medication and the importance of family support. Some suggested wider distribution of the intervention in GP surgeries, and the use of telephone support in addition to the intervention.

In the light of the feedback, some further adaptations to the Urdu *ADvisor* booklets were made. However, due to logistical and time constraints, further changes to the video links were not possible, but the comments on the video links were documented, and could be implemented in future research on these interventions.

Conclusion

Overall, the Urdu *ADvisor* development and refinement process was undertaken successfully. Feedback on the final version of the Urdu version of *ADvisor* was positive, and it is now available for further feasibility and evaluation work.

Links to English and Urdu versions of online slideshows on modules within the Urdu version of *ADvisor*

English version

ADvisor: Helping South Asians to reduce intake of antidepressants

The video slides links are on the *ADvisor* programme. The links contain slides with a lot of information, support and advice on reducing intake of antidepressants

ADvisor video slides links are for you to use as you want to. You can come back and use it when you feel it's best.

Slide 1: Welcome

https://drive.google.com/file/d/1jqUSJUvRFCT7LKBkbFICNikrD3P0nYMp/view?usp=sharing

Slide 2: Reducing and stopping antidepressants

https://drive.google.com/file/d/1a4A_axpZNzfXNS7xdnkoyUlDiL5QNBW9/view?usp=sharing

Slide 3: Thinking about antidepressants

https://drive.google.com/file/d/1BgKZS3gK7U7v__Sen_SSKAowTc_DHmbZ/view?usp=sharing

Slide 4: I'm worried about stopping

https://drive.google.com/file/d/1FHNRlHcTmXwGnH2mb5ZkTw3N1V61lA7f/view?usp=sharing

Slide 5: Dealing with symptoms of coming off antidepressants

https://drive.google.com/file/d/1s4HoLHv7xIr-JsN8ayDCNvQu0KXtSdpd/view?usp=sharing

Slide 6: Thinking about what you value in life

https://drive.google.com/file/d/1XJOGqRd_rra6HbBEJaC5dewGnxnKYqcu/view?usp=sharing

Slide 7: Keeping well

https://drive.google.com/file/d/18MjXJbIma7Se8jzU6LulkmMeRIUouXVx/view?usp=sharing

Slide 8: Moving forward

https://drive.google.com/file/d/1kIpgom-dQq4hg2XYGHSG_KIFIexwEGfh/view?usp=sharing

Slide 9: Resources

https://drive.google.com/file/d/1WFfGMOgzs7FWcS2p5r4INwTxA67QqQFy/view?usp=sharing

Thank you very much

REDUCE Team

Urdu version

ایڈوائزر: ذہنی دباؤ کی ادویات کا استعمال کم کرنے میں جنوبی ایشیائی لوگوں کی مدد کرنا

ویڈیو سلائیڈ کے لنکس ایڈوائزر پروگرام میں شامل ہیں۔ لنکس میں بہت ساری معلومات، معاونت، اور ذہنی دباؤ کی ادویات کے استعمال کو کم کرنے کے بارے میں مشورے والی سلائیڈز شامل ہیں۔

جیسا کہ آپ جانتے ہیں ایڈوائزر ویڈیو سلائیڈ کے لنکس آپ کے لیے ہیں۔ آپ جب چاہیں انہیں استعمال کر سکتے ہیں یا جب آپ محسوس کریں کہ یہ سب سے بہتر ہیں آپ انہیں استعمال کر سکتے ہیں۔

خوش آمدید: Slide 1

https://drive.google.com/file/d/1YfKdbqwA5fk9IEK1b4evy0F4l80dUuAn/view?usp=sharing

ذہنی دباؤ کی ادویات کے استعمال کو کم کرنا اور روکنا: Slide 2

https://drive.google.com/file/d/1P5Ron64RYk88F6Mxc9J2nb5O17lk02qN/view?usp=sharing

ذہنی دباؤ کی ادویات کے بارے میں سوچنا: Slide 3

https://drive.google.com/file/d/1x0yMnwbQcRtglDugRE3zXwiwNSLwqcYe/view?usp=sharing

میں ادویات کے رکنے سے پریشان ہوں: Slide 4

https://drive.google.com/file/d/13Y2D1i4-sC3x3bqZ0A5mX6dAPF4sQfJx/view?usp=sharing

ذہنی دباؤ کی واپسی کی علامات سے نمٹنا: Slide 5

https://drive.google.com/file/d/1vPvFz0F1ztFAbWVt2wX49auLqiYwOiSL/view?usp=sharing

زندگی میں آپ کی کیا تر جیحات ہیں اس کے بارے میں سوچنا: Slide 6

https://drive.google.com/file/d/1FqN9Z1HFkp010uT0igHjb6ercbyXI_RC/view?usp=sharing

اپنی صحت کو بہتر رکھنا: Slide 7

https://drive.google.com/file/d/1Y2V14sTdnq2gRNW_4KSkuIRaymT4kvzh/view?usp=sharing

زندگی میں آگے بڑھتے رہنا: Slide 8

https://drive.google.com/file/d/10SaMSr73V7V4Y62_zDbfLIEg3M3ssi_V/view?usp=sharing

حوالہ جات: Slide 9

https://drive.google.com/file/d/1e24kuge77DQlVejnrs1cdHTyr_XO8X36/view?usp=sharing

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