# Manuscript Details

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**Abstract**

Background: Relapse is common in depression and relapse prevention strategies are not well researched in primary care settings. Collaborative care is effective for depression in the acute phase and its effect is sustained into the longer term. Little is known about the use of relapse prevention strategies in collaborative care. We undertook a systematic review to identify and characterise relapse prevention strategies in the context of collaborative care. Methods: We searched for Randomised Controlled Trials (RCTs) of collaborative care for depression. In addition to published material, we obtained provider and patient manuals from authors to provide more detail on intervention content. We reported the extent to which collaborative care interventions addressed four relapse prevention components. Results: 93 RCTs were identified. 31 included a formal relapse prevention plan; 42 had proactive monitoring and follow-up after the acute phase; 39 reported strategies for optimising sustained medication adherence; and 20 of the trials reported psychological or psych-educational treatments persisting beyond the acute phase or focussing on long-term health/relapse prevention. 30 (32.3%) did not report relapse prevention approaches. Limitations: We did not receive trial materials for approximately half of the trials, which limited our ability to identify relevant features of intervention content. Conclusion: Relapse is a significant risk among people treated for depression and interventions are needed that specifically address and minimise this risk. Given the advantages of collaborative care as a delivery system for depression care, there is scope for more consistency and increased effort to implement and evaluate relapse prevention strategies.



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| **Keywords** | Collaborative care; depression; relapse prevention. |



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Dear Editor,

Thank you for considering this paper for publication as a research article. We report the results of a systematic review investigating the relapse prevention content in trials of collaborative care for depression. Relapse is a major problem for people with depression and collaborative care is a successful mode of intervention delivery. We now have a significant number of trials of collaborative care interventions and its effectiveness is well established.

This is the first systematic review aiming to map the relapse prevention components of collaborative care. It builds on previous work by our group looking at the participant and study level factors driving the effectiveness in the acute phase. This review describes the relapse prevention approaches taken by trials and also the way in which the key features of collaborative care have facilitated the delivery of relapse prevention. In addition to published materials, we contacted all of the authors of trials and acquired trial materials, including training manuals and patient workbooks where possible.

We suggest future directions for research, such as evaluating the effectiveness of relapse prevention during implementation of collaborative care, discuss the implications for clinical practice and make recommendations about the reporting of intervention content in future trials.

We look forward to hearing from you.

Best wishes,

**Dr Andrew Moriarty**
**On behalf of The Authors**

**Highlights**

- This is the first systematic review to map the relapse prevention content of trials of collaborative care for depression and to provide a description of the different strategies employed.

- Of 93 RCTs identified, 31 included a formal relapse prevention plan; 42 had proactive monitoring and follow-up after the acute phase; 39 reported strategies for optimising sustained medication adherence; and 20 of the trials reported psychological or psych-educational treatments persisting beyond the acute phase or focussing on long-term health/relapse prevention. 30 (32.3%) did not report relapse prevention approaches.

- Given the advantages of collaborative care as a delivery system for depression care, there is scope for more consistency and increased effort to implement and evaluate relapse prevention strategies. There most likely is not mileage in further effectiveness trials of collaborative care. However, relapse is an important issue and we need innovative research methods to explore the impact of relapse prevention content. This might involve embedding studies of relapse prevention in ongoing implementation of collaborative care or using cohort multiple RCT.

- We recommend that researchers use the TIDieR checklist when reporting intervention content.

**Abstract**

**Background:** Relapse is common in depression and relapse prevention strategies are not well researched in primary care settings. Collaborative care is effective for depression in the acute phase and its effect is sustained into the longer term, but little is known about the use of relapse prevention strategies in collaborative care. We undertook a systematic review to identify and characterise relapse prevention strategies in the context of collaborative care.

**Methods**: We searched for Randomised Controlled Trials (RCTs) of collaborative care for depression. In addition to published material, we obtained provider and patient manuals from authors to provide more detail on intervention content. We reported the extent to which collaborative care interventions addressed four relapse prevention components.

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**Limitations:** We did not receive trial materials for approximately half of the trials, which limited our ability to identify relevant features of intervention content.

**Conclusion:** Relapse is a significant risk among people treated for depression and interventions are needed that specifically address and minimise this risk. Given the advantages of collaborative care as a delivery system for depression care, there is scope for more consistency and increased effort to implement and evaluate relapse prevention strategies.

**Key words:** Collaborative care; depression; relapse prevention.

**Relapse prevention in collaborative care for depression: A systematic review**

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## Introduction

Approximately half of patients will relapse after their first episode of depression and this risk increases to 70% and 90% after a second and third episode respectively (Tylee et al., 2007). There is evidence that the severity of depression and resistance to treatment increases with each successive episode of relapse (Kendler et al., 2000), highlighting the potential benefits of intervening early to prevent relapse and improve the overall trajectory of depression.

Relapse has been defined as the re-emergence of depressive symptoms following some level of remission but preceding recovery and is distinguished in the literature from recurrence (the onset of a new episode of depression following an extended period of remission) (Frank et al., 1991). This can provide a useful theoretical distinction, although evidence for its clinical utility is lacking. The definitions can however be useful when considering the trajectory of depression and its treatment phases: those implemented before any symptomatic improvement with a view to achieving remission (acute phase), those employed after symptomatic improvement but before recovery (continuation phase) and those that extend past the point of recovery (maintenance phase) (Bockting et al., 2015).

Relapse prevention interventions are those aimed at people with depression who have had symptomatic improvement and have entered the continuation or maintenance phases or can be applied during the acute phase with the intention of exerting a protective effect against relapse in the future (Bockting et al., 2015). Most commonly they constitute a combination of continuation antidepressant medication and psychological therapies. There have been only a small number of studies exploring which relapse prevention interventions are most effective, particularly in a primary care context (Gili et al., 2015; Rodgers et al., 2012).

Collaborative care is a framework, drawing on principles of chronic disease management, developed to optimise the provision and delivery of depression care. As such, it is best thought of as a system level intervention rather than as a therapeutic intervention in and of itself. Collaborative care incorporates the following four constituent parts to support the delivery of depression interventions: i) multidisciplinary working with input from two or more health care professionals, ii) structured evidenced-based case management, iii) proactive and scheduled patient follow-up, and iv) enhanced inter-professional communication systems (Gunn et al., 2006).

A Cochrane review of 79 RCTs showed that, compared with usual care or active control groups, collaborative care is more effective for treating depression and anxiety in the short-term (6 months or less) and that these effects persist into the longer term (13-24 months) (Archer et al,, 2012). Improvements in social functioning outcomes have also been demonstrated in patients treated using a collaborative care approach compared with those receiving usual care (Hudson et al., 2016). Further work has explored study-level factors (Coventry et al., 2014) and participant-level factors (Panagioti et al., 2016) moderating treatment outcomes in the short term and, as such, we have a good understanding of the components driving acute phase response.

It is important to be mindful of the significant associated risk of relapse when developing and implementing interventions for people with depression. While the long-term beneficial effects of collaborative care are well evidenced (Camacho et al., 2018), it is unclear whether a focus on relapse prevention might account for this. We are now well positioned, with a large number of trials of collaborative care, to identify and characterise relapse prevention strategies to gain a better understanding of how these approaches might be used in the context of implementing collaborative care.

In this review, we aim to better understand whether relapse prevention is a common and key component of collaborative care. We describe the means by which relapse prevention has been addressed in trials of collaborative care and how the principles of collaborative care have been utilised to optimise the delivery of relapse prevention strategies.

## Methods

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) and was produced according the Centre for Reviews and Dissemination guidance on systematic reviews for healthcare (Centre for Reviews and Dissemination, 2009).

### Literature search

The literature search was originally conducted for a Cochrane review (Archer et al., 2012) and has been subsequently updated in December 2013, October 2016 and May 2017. This last update added 1 study to the review.

The original review (Archer et al., 2012) searched the Cochrane Collaboration Depression, Anxiety and Neurosis (CCDAN) group (now Common Mental Disorders group) trial register on 9th February 2012. The CCDAN trial register comprehensively indexed trials registered to MEDLINE, EMBASE, PsychINFO, CENTRAL, World Health Organisation's trials portal, Clinicaltrials.gov, and CINAHL. The search was updated using the CENTRAL database in December 2013 and to inform a subsequent meta-regression (Coventry et al., 2014). For the current review, we updated the search using the CENTRAL database in October 2016 and in

May 2017. This method is considered a sufficient and cost-effective approach for the systematic detection of RCTs of health care interventions (Royle and Waugh, 2005).

## Inclusion criteria

We kept to the same inclusion criteria used in previous systematic reviews and meta-regression analyses of collaborative care (Archer et al., 2012; Coventry et al., 2014). RCTs were included if they met the following criteria:

*Participants:* Adults (aged 18 years or over) who met criteria (self-report or diagnostic interview) for a diagnosis of depression or who had mixed anxiety and depression.

*Intervention:* Collaborative care including these four components (Gunn et al., 2006):

a. A multidisciplinary approach to care delivery, defined as two or more health care professionals, of which one must include a primary care provider.
b. A structured treatment plan delivered by a health care professional/case manager who is not the patient's primary care provider. Treatment plans could include pharmacotherapy and/or psychotherapy.
c. Scheduled and proactive patient follow-up consisting of one or more planned sessions.
d. Enhanced inter-professional communication/support, for example: team meetings, supervision from a senior health care professional/mental health specialist.

*Comparator:* Usual care or enhanced usual care.

*Outcome:* Measured change in depression end of treatment outcomes using self-report measures or diagnostic clinical interviews. Binary self-report depression outcomes may have included either remission or reduction in depression symptoms according to a priori defined threshold (e.g. ≥50%).

*Study Design:* Individual or cluster RCT, in primary or community setting. The original trial report paper was in the English language.

**Study Selection**

For this review, eligible studies were identified for inclusion from a previous meta-regression of 84 collaborative care RCTs for depression (Coventry et al., 2014). In addition, 3 authors (JH, PC, RC) screened potentially eligible studies identified from CENTRAL search updates against the above inclusion criteria, as described above.

**Other sources**

In addition to using the RCT report papers for details of intervention content, we contacted the authors to request that they share any additional trial materials, particularly manuals used to train the professionals implementing the intervention (provider manuals) and materials given to patients to guide their self-management (patient workbooks). The aim was to optimise the amount of information available for deriving a description of relapse prevention strategies. Corresponding or other appropriate authors were contacted up to a maximum of 3 times. In the absence of materials or where authors did not reply, we accessed publically

112 available protocols and companion papers that provided more information on intervention
113 content.

114

115 **Data extraction and synthesis**

116 We extracted data about intervention content (i.e. the commonly used relapse prevention
117 strategies and approaches reported by trialists) and intervention delivery (i.e. the ways in
118 which collaborative care facilitated the delivery of intervention content).

119 In terms of intervention content, we defined relapse prevention components as any that are
120 introduced after acute treatment has been successfully completed (continuation phase), or that
121 were applied during the acute phase with the intention of exerting a protective effect against
122 relapse in the future (Bockting et al., 2015). We identified four common relapse prevention
123 components *a priori*, on pragmatic grounds:

124 1. Formal relapse prevention planning: taking place either during the acute or
125 continuation phase;
126 2. Proactive symptom monitoring and follow-up beyond the acute phase;
127 3. Strategies to promote continuation medication adherence: occurring during the acute
128 or continuation phase, as long as focus was on long-term medication adherence and
129 relapse prevention rather than initial symptom improvement;
130 4. Psychological or psycho-educational treatments: again, these could be implemented
131 during the acute phase with a focus on strategies for relapse prevention or could be
132 implemented during the continuation phase (e.g. "booster" sessions).

Each trial was reviewed for information about the intervention content. We reviewed the materials for each RCT and identified the components used in the intervention. Where relapse prevention components were present, a descriptive paragraph was written on the approach taken for each trial.

The intervention content was mapped to the four key components of collaborative care, as described by Gunn et al. (2006), to better understand how collaborative care facilitates the delivery of intervention content aimed at relapse prevention. By definition, all four components were present in each trial and so we have recorded specifically where these components have been used to facilitate relapse prevention. Results were validated and coded by two independent reviewers per paper (AM, NC and OJF) and any disagreements were referred to a third reviewer (DM).

### Risk of bias

Risk of bias assessment has been undertaken and reported elsewhere for all included trials using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials.

## Results

### Study selection

In total, 93 RCTs of collaborative care for depression were identified for inclusion in this review (see Figure 1 for PRISMA flow diagram outlining search). See Appendix 1 for relevant study characteristics. 79 of these were identified for the original Cochrane review

(Archer et al., 2012), 5 were added in updated search in 2014 (Coventry et al., 2014), 8 were added in the CENTRAL search update in October 2016 and 1 study was added during the updated search in May 2017.

**[Figure 1: PRISMA Flow chart of included studies]**

After collating responses from authors and accessing materials online where they were available, we identified additional trial materials for 44 (47.3%) of the 93 trials identified. Of these 13 had a provider manual, 2 had a patient workbook and the remainder (n=29) had both. For the trials where there were no materials available, we were able to gain further information regarding intervention content from email correspondence with the authors of 7 of the trials and from reference to the original programme grant application for 1.

For the remaining trials (n=49), we consulted the main trial papers and any associated publications.

## Data synthesis

The relapse prevention components identified were: presence of a formal relapse prevention plan (31 out of 93, 33.3%), active monitoring and follow up after the acute phase (42 out of 93, 45.2%), focus on medication adherence beyond the acute phase (39 out of 93, 41.9%) and psychological therapies beyond the acute phase (20 out of 93, 21.5%).

RCTs of collaborative care for depression have addressed relapse prevention to varying degrees. Table 1 maps the relapse prevention components used across trials. Table 2 provides a description of the relapse prevention approach taken and how the collaborative care framework has facilitated the delivery of these.

8 studies (Bogner and de Vries, 2008, 2010; Bogner et al., 2012; Dwight-Johnson et al., 2010; Lerner et al., 2015; McCusker et al., 2008; McMahon et al., 2007; Menchetti et al., 2013) focussed on acute-phase treatment and recovery, with very short-term follow-up and no emphasis on relapse prevention. 2 studies (Adler et al., 2004; Finley et al., 2003) focussed entirely on pharmacological interventions with medication maintenance primarily aimed at short-term improvement and only indirectly targeted at relapse prevention.

Only 1 of the 93 trials (Katon et al., 2001) tested a collaborative care relapse prevention intervention. In this trial, patients who had recovered after 8 weeks of antidepressant treatment were randomised to usual care or a relapse prevention intervention, which consisted of two primary care visits with a depression specialist and three telephone calls over a one-year period. The intervention aimed to monitor symptoms, increase medication adherence and involved the writing of a personalised relapse prevention plan. The usual care and intervention groups had similar rates of relapse, although medication adherence was significantly improved in the intervention group.

Others reported a significant focus on relapse prevention while primarily focussing on acute treatment outcomes. Notably, the inclusion of relapse prevention in CADET (Clinical effectiveness of collaborative care for treatment of depression in UK primary care), the largest UK-based collaborative care trial, came directly from qualitative and public involvement findings in the original development and feasibility trial. The original pilot trial

did not address relapse prevention until analysis of the acceptability data and subsequent change to the protocol to account for the findings (Richards et al., 2009; 2013).

30 trials had no reported approach to relapse prevention, 21 had one approach only, 25 reported using two approaches, 5 reported three and 12 reported using all 4 relapse prevention components. 9 studies (9.6%) reported outcomes beyond 12 months and only one study (Katon et al., 2001) reported relapse data (Table 2).

**[Table 1: Summary of relapse prevention components used in each RCT]**

**[Table 2: Description of relapse prevention approaches used in RCTs of collaborative care]**

***Intervention content: Relapse prevention components***

*Relapse prevention plan*

One third of the studies (n=31) reported that the professional administering the intervention was trained to develop a formal relapse prevention plan with patients. All of the studies reporting a relapse prevention plan went on to provide further details of what this entailed (Bartels et al., 2004; Buszewicz et al., 2010, 2016; Ciechanowski et al., 2004, 2010; Coventry et al., 2015; Datto et al., 2003; Davidson et al., 2013; Ell et al., 2008; Gilbody et al., 2017; Grote et al., 2015; Huijbregts et al., 2013; Johnson et al., 2014; Katon et al., 1996, 2001, 2004, 2010; Ludman et al., 2007, 2016; Mavandadi et al., 2015; Oslin et al., 2003, Piette et al., 2011; Richards 2008, 2012; Rollman et al., 2009; Ross et al., 2008; Salisbury et al., 2015; Simon et al., 2004; Smit et al., 2005; Unutzer et al., 2002; Vlasveld et al., 2011). 5 of the included studies used the Foundations for Integrated Care manuals (US Department of

Veterans Affairs, 2017) to guide the delivery of their intervention (Bartels et al., 2004; Datto et al., 2003; Mavandadi et al., 2015; Oslin et al., 2003; Ross et al., 2008). The manuals advise that patients are educated about risk of relapse and to make a plan for "relapse prevention treatment", including "reinforcing self-monitoring skills for signs of recurrence". Patients are encouraged to identify "personal" early warning signs of recurrence and individual triggers. Self-care skills in the event of recurrence may include "calling friends or relatives, preparing for stressful events by writing down a coping plan, pursuing interests, and continuing to take medication as prescribed". Patients are also given written instructions on when they should consult a doctor (worsening PHQ-9 or GAD-7 scores, especially if scoring 14 or above, unable to perform daily activities or thoughts of suicide).

The Collaborative Interventions for Circulation and Depression (COINCIDE) trial instructed professionals and patients on following a "staying well" (Coventry et al., 2015) plan that encouraged patients to identify protective factors and behaviours to implement these on a long-term basis. Buszewicz et al. (2012, 2016) similarly advised professionals on the importance of discussing relapse prevention with patients and identifying triggers, which would put patients in "a better position to avoid relapse in the future or to seek help at an early stage". Ciechanowski et al. (2004, 2010) and Richards et al. (2009, 2013) gave patients a written relapse prevention plan template with headings including "personal warning signs" and "things that make me feel better".

*Proactive monitoring and follow-up*

A number of the trials used proactive symptom monitoring and proactive follow-up, ranging from informal follow-up to regular use of psychometric tools for tracking deterioration. The

Foundations for Integrated Care manuals (US Department of Veterans Affairs, 2017) strategy was to follow up with the patient once a month, until they had gone for 3 months without depressive symptoms, to obtain a PHQ-9 or GAD-7 score. There are specific instructions within the healthcare professional manual that if a patient becomes symptomatic (defined as a score above 10), they should then be reassessed in one week to determine if relapsing. If the score remains elevated at that point, the treatment plan will be reassessed, including discussion regarding adding pharmacological treatment if the patient is not already on this. Ciechanowski et al., (2004, 2010) also had provision for monthly phone calls after the acute phase with administration of the PHQ-9.

Coventry et al. (2015) made use of a RAG (Red, Amber, Green) system wherein patients were encouraged to self-administer psychometric tools (in this case, the PHQ-9 or GAD-7) and the score would correspond to traffic lights system. This would prompt the patient to take no action, use the "action plan" and monitor their mood more closely or consider contacting a health worker if above a specified threshold ("red"). The action plan recapped signs and triggers of depression and reminded patients of details of their support network. Pyne et al. (2011) used regular telephone monitoring once remission had been reached, although the details of these were not reported. Others such as Ell et al. (2008) provided a robust monitoring system with proactive telephone follow-up to monitor symptoms and in-person visits if needed.

In the True Blue trial, conducted in Australian general practices, patients were monitored and completed a PHQ-9 at 13-week intervals for 12 months. The authors of this trial explained that the intervention was designed to be feasible in the Australian Medicare system and so the follow-up periods were not "unrealistically regular" (Morgan et al., 2009).

*Medication maintenance*

Notable methods of ensuring medication maintenance were asking patients and reassuring about side effects (Landis et al., 2007), ensuring longer term medication in those at higher risk of relapse (Davidson et al., 2013) and offering an alternative antidepressant in the case of relapse or where the medication is poorly tolerated (Kroenke et al., 2010). Capoccia et al. (2014) and Finley et al. (2003) both trialled pharmacist-led collaborative care-based interventions to promote medication adherence and address medication-related issues arising throughout the maintenance and continuation phases.

Again, the Foundations for Integrated Care manuals (US Department of Veterans Affairs, 2017) had detailed information about the specific medication maintenance strategies used in their trial. The manuals advise that if patients are assessed to be at low risk of relapse (fewer than two prior episodes of depression and no history of dysthymia), they should complete 6 to 9 months and if at high risk (more than 2 episodes or history of dysthymia), they should complete at least two years of antidepressant therapy. Katon et al. (1995, 1999) used active monitoring of automated pharmacy data to monitor medication adherence during the continuation phase (3-7 months) without monitoring for depressive symptoms.

*Psychological or psycho-educational treatments*

The final intervention component noted was the provision of psychotherapeutic or psycho-educational approaches. Araya et al. (2003) provided a psycho-educational group as part of a multi-component programme of treatment and these included “booster” sessions occurring

during the continuation phase at weeks 9 and 12 with a focus on relapse prevention techniques. It was unclear from the trial paper what these techniques were. Oladeji et al. (2015) similarly provided a programme consisting of psycho-education, problem-solving therapy and activity scheduling and patients who improved (as measured by PHQ-9 scores) were offered four fortnightly "top up talking therapies" for a period of 8 weeks.

Simon et al. (2004) offered an 8-session manualized cognitive behavioural therapy (CBT)-based programme followed by three to four telephone relapse prevention sessions. Ludman et al. (2007) similarly offered acute and "booster" psychotherapy sessions, focussing on behavioural activation and identification and interruption of automatic negative thoughts. Piette et al. (2011) offered counselling sessions monthly for nine months following the acute phase to "minimize relapse". Ell et al. (2008) provided on-going psychotherapeutic approaches (behavioural activation and problem solving therapy) extending beyond the acute phase.

***Intervention delivery: Collaborative care components***

Gunn et al. (2006) outlined the four key characteristics of a collaborative care intervention: a multidisciplinary approach to care delivery; structured treatment plan delivered by a health care professional/case manager who is not the patient's primary care provider; scheduled and proactive patient follow-up consisting of one or more planned sessions; and enhanced inter-professional communication/support.

Where collaborative care appears to be particularly well placed to address relapse prevention is through its use of structured management plans, including an organised approached to providing evidence-based treatments. Whether these are pharmacological or psychological or

311 a combination of both, they can be tailored to address relapse prevention in a standardised
312 and consistent manner and implemented either during the continuation phase or during the
313 acute phase with a view to maintaining longer-term health. The other key and recurring area
314 in which collaborative care seems to confer a particular benefit is its focus on scheduled
315 patient follow-up, particularly in the form of symptom monitoring and facilitating treatment
316 adherence.

317 Multi-professional approach and enhanced inter-professional communication have been less
318 explicitly employed as a means of facilitating the delivery of relapse prevention intervention
319 content. A multi-professional approach is key feature of collaborative care interventions, but
320 the way in which this has been used to optimise relapse prevention is not well documented.
321 Enhanced inter-professional communication includes strategies such as team meetings and
322 shared medical notes. The only trial to report using it in a way that facilitated relapse
323 prevention was Katon et al. (1999) which used the collaborative care framework to
324 implement a system wherein the psychiatrist reviewed monthly automated pharmacy data on
325 antidepressant refills to monitor the patient's adherence to the acute and continuation phases
326 of treatment and was able to alert the primary care physician if premature discontinuation of
327 medication occurred. It is possible and perhaps likely, however, that systems to facilitate
328 multi-professional working and enhanced communication have been a feature of relapse
329 prevention provision in collaborative care trials but have not been reported.

330

331 **Discussion**

332 This is the first systematic review to map the relapse prevention content of trials of
333 collaborative care for depression and to provide a description of the different strategies

334 employed. Overall, researchers have been inconsistent in their approaches and in the way that
335 interventions are reported and described in the literatures. We identified 4 recurring relapse
336 prevention strategies or components across two thirds of the trials identified. The established
337 key features of collaborative care, particularly structured management plans and scheduled
338 patient follow-up, facilitated the delivery of these relapse prevention strategies.

339

340 *Implications for research and policy*

341 With its focus on multi-professional approach, proactive and structured follow-up and
342 enhanced inter-professional communication, collaborative care has potential advantages over
343 other methods for providing relapse prevention in depression. There are now a significant
344 number of collaborative care trials and the evidence base is such that new trials may not be an
345 efficient use of resources. The effectiveness of collaborative care on depression outcomes is
346 well established. However, relapse is an important issue and we need innovative research to
347 explore the impact of relapse prevention content. This might involve embedding studies of
348 relapse prevention in ongoing implementation of collaborative care.

349 Novel trial methods offer opportunities to trial the effectiveness of relapse prevention
350 components without the need for a conventional RCT. The Cohort Multiple Randomised
351 Controlled Trial (cmRCT) allows pragmatic trials of interventions on large numbers of
352 patients at a lower cost with more detail on longer-term outcomes derived from patients
353 within routine practice. The relapse prevention components of the interventions reported here
354 are of low intensity and are likely to be desirable to patients and well accepted, overcoming
355 the risk of patient non-compliance or refusal to accept interventions, which is one of the key
356 limitations of cmRCTs (Relton et al., 2010). The cmRCT model itself has been shown to be

357 acceptable to patients with depression (Richards et al., 2014). We recommend that this
358 approach be considered to enable to researchers to better assess the effectiveness of the
359 components described here in practice.

360 There is a growing role for digital health interventions in the treatment of depression. Mobile
361 apps exist which allow patients to record and monitor their scores on validated tools such as
362 the PHQ-9 and then share the results with clinicians. However, there is as yet little evidence
363 for the effectiveness of these approaches (Hollis et al., 2017) and, while one can envisage
364 versions of these apps that would flag patients and allow them to re-enter the acute phase
365 treatment early, they would require formal assessment of clinical and cost-effectiveness in
366 practice and would need to be standardised and integrated into existing systems in order to be
367 successfully implemented.

368 Cross-sectorial working is also likely to be key, given that patients will leave therapy services
369 to be monitored in primary care and one of the challenges will be setting up lines of
370 communication between providers to track patient recovery (Winters et al., 2016).
371 Collaborative care is well placed to support enhanced modes of communication across
372 disciplines and sectors to facilitate more coordinated follow-up and it is important that we
373 evaluate how best to maintain such communication models after the acute phase of treatment.
374 We recommend that work be done around understanding how monitoring and recall can be
375 built into collaborative care protocols to ensure that interventions are more responsive to
376 patients at risk of relapse.

377 We have described the difficulty in extracting a description of the intervention content
378 pertaining to relapse prevention from the trial publications alone. The Template for
379 Intervention Description and Replication (TIDieR) checklist provides a framework for

reliably reporting intervention content (Hoffman et al., 2014). We recommend that researchers use the TIDieR checklist when reporting intervention content, which would better enable researchers to understand what was done. In the case of this review, more consistent reporting and describing of interventions would enable researchers to adopt and incorporate common intervention components when developing novel relapse prevention interventions for implementation in practice.

*Limitations*

A limitation of this work is that we did not receive manuals for the majority of trials and, as such, were limited to describing the intervention components as published and supplemented by accessory materials which were freely available online. Furthermore, of the trials reviewed, most had at best medium term (12 month) follow-up and only a small number reported longer-term (n=9; 9.6%) or relapse data (n=1). We have therefore been unable to perform a quantitative analysis to explore the effectiveness of the relapse prevention intervention components described in this review.

## Declaration of interest

None

401 **References**


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**Figure 1: PRISMA flow chart of included studies**

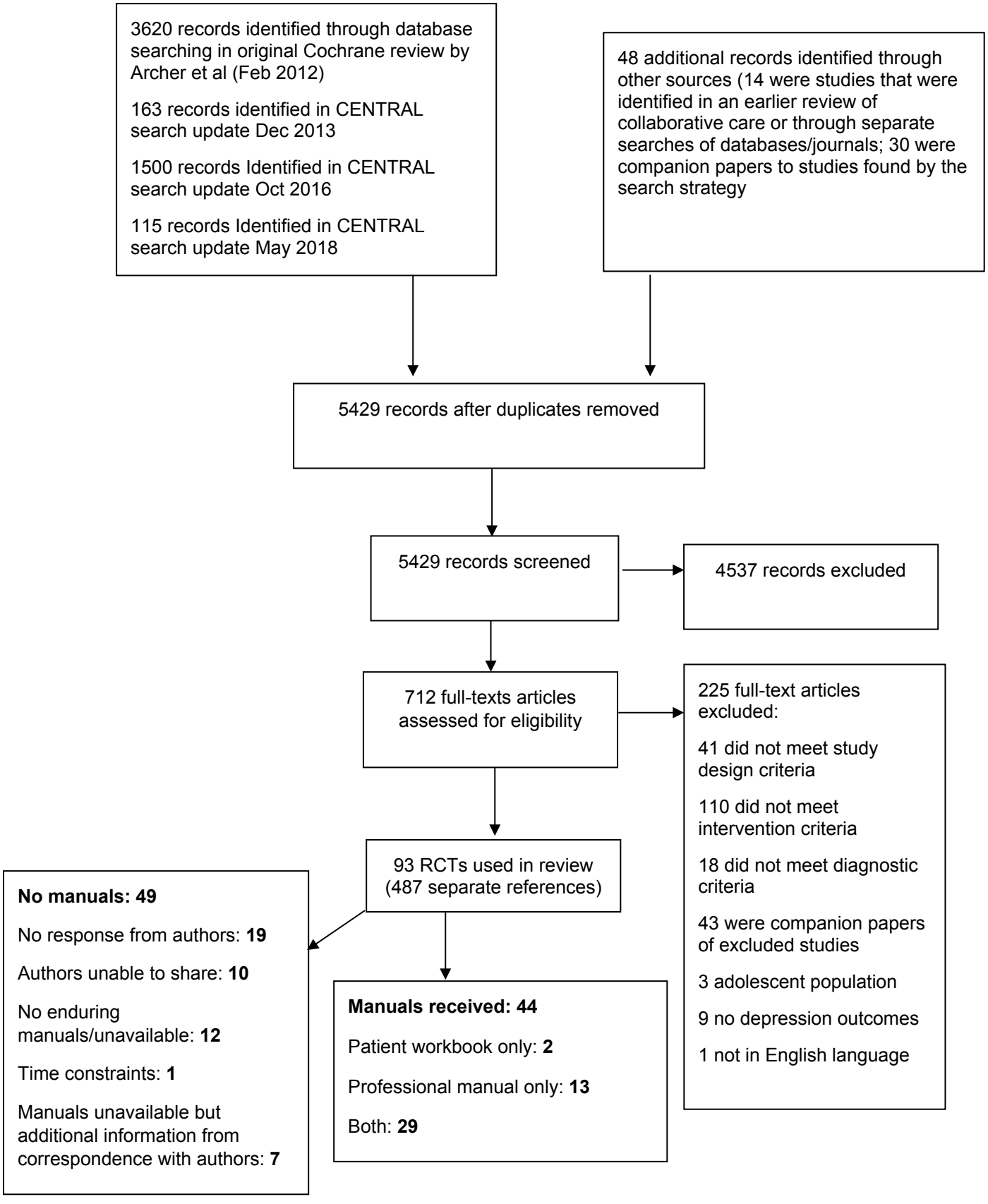

**Table 1:** Summary of trials and the included relapse prevention components

| | Intervention content: relapse prevention approaches use | | | | | Collaborative care components facilitating delivery of relapse prevention | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Study** | **Relapse prevention plan** | **Symptom monitoring and follow up beyond the acute phase** | **Medication adherence** | **Psycho-education or psychological treatment** | **No relapse prevention components** | **Multi-professional approach** | **Structured management plan** | **Scheduled follow-up** | **Enhanced inter-professional communication** |
| **Adler 2004** | | X | X | | | X | X | X | |
| **Aragones 2012** | | X | X | | | | X | X | |
| **Araya 2003** | | | | X | | | X | | |
| **Bartels 2004** | X | X | X | | | | X | X | |
| **Blanchard 1995** | | | | | X | | | | |
| **Bogner 2008** | | | | | X | | | | |
| **Bogner 2010** | | | | | X | | | | |
| **Bogner 2012** | | | | | X | | | | |
| **Bruce 2004** | | X | X | | | | X | X | |
| **Bruce 2015** | | X | X | | | | X | X | |
| **Buszewicz 2011** | X | | | | | | X | | |
| **Buszewicz 2016** | X | | | | | | X | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Capoccia 2014** | | X | X | | | | X | X | |
| **Carney 2016** | | X | | | | | X | | |
| **Chaney 2011** | | | | | X | | | | |
| **Chen 2015** | | | X | | | | X | | |
| **Chew-Graham 2007** | | | | | X | | | | |
| **Ciechanowski 2004** | X | X | X | X | | | X | X | |
| **Ciechanowski 2010** | X | X | X | X | | | X | X | |
| **Cole 2006** | | | | | X | | | | |
| **Coventry 2014** | X | X | | | | | X | X | |
| **Datto 2003** | X | X | | | | | X | X | |
| **Davidson 2013** | X | | X | | | | X | X | |
| **Dietrich 2004** | | | | | X | | | | |
| **Dwight-Johnson 2005** | | | | | X | | | | |
| **Dwight-Johnson 2010** | | | | | X | | | | |
| **Dwight-Johnson 2011** | | | | | X | | | | |
| **Ell 2007** | | | | | X | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Ell 2008** | X | X | X | X | | | X | X | |
| **Ell 2010** | | X | | | | | X | X | |
| **Engel 2016** | | | | | X | | | | |
| **Finley 2003** | | | X | | | | X | | |
| **Fortney 2007** | | X | X | | | | X | X | |
| **Gensichen 2009** | | X | X | X | | | X | X | |
| **Gilbody 2017** | X | | | | | | X | | |
| **Gjerdingen 2009** | | | | | X | | | | |
| **Grote 2015** | X | X | X | X | | | X | X | |
| **Hedrick 2003** | | | | | X | | | | |
| **Huffman 2011** | | | | | X | | | | |
| **Huffman 2014** | | | | | X | | | | |
| **Huijbregts 2013** | X | | X | | | | X | | |
| **Hunkeler 2000** | | X | X | | | | X | X | |
| **Johnson 2014** | X | X | X | X | | | X | X | |
| **Katon 1995** | | | X | | | | X | X | |
| **Katon 1996** | X | | | | | | X | X | |
| **Katon 1999** | | | X | | | X | X | X | X |

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|---|---|---|---|---|---|---|---|---|---|
| **Katon 2001** | X | X | X | X | | | X | X | |
| **Katon 2004** | X | X | X | | | | X | X | |
| **Katon 2010** | X | X | X | X | | | X | X | |
| **Katzelnick 2000** | | | X | | | | X | X | |
| **Kroenke 2010** | | X | X | | | | X | X | |
| **Landis 2007** | | X | X | | | | X | X | |
| **Lerner 2015** | | | | | X | | | | |
| **Lobello 2010** | | | | | X | | | | |
| **Ludman 2007** | X | X | X | X | | | X | X | |
| **Ludman 2016** | X | X | X | X | | | X | X | |
| **Mann 1998** | | | | | X | | | | |
| **Mavandadi 2015** | X | X | | | | | X | X | |
| **McCusker 2008** | | | | | X | | | | |
| **McMahon 2007** | | | | | X | | | | |
| **Melville 2014** | | X | | | | | | X | |
| **Menchetti 2013** | | | | | X | | | | |
| **Morgan 2013** | | X | | | | X | X | X | |
| **Oladeji 2015** | | | | X | | | X | X | |

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| **Oslin 2003** | X | | X | | | | X | | |
| **Patel 2010** | | X | X | | | | | | |
| **Piette 2011** | X | X | X | X | | X | X | X | |
| **Pyne 2011** | | X | | | | | X | X | |
| **Richards 2008** | X | | | X | | X | X | X | |
| **Richards 2012** | X | | | X | | X | X | X | |
| **Rojas 2007** | | | | | X | | | | |
| **Rollman 2009** | X | X | X | | | | X | X | |
| **Ross 2008** | X | X | | | | | X | X | |
| **Rost 2002** | | | X | | | | X | | |
| **Rubenstein 2006** | | | | | X | | | | |
| **Salisbury 2015** | X | X | X | X | | | X | X | |
| **Sharpe 2014** | | X | | | | | X | X | |
| **Simon 2000** | | X | | X | | | X | | |
| **Simon 2004** | X | | | X | | | X | X | |
| **Simon 2011** | | | | | X | | | | |
| **Smit 2005** | X | | X | | | | X | | |
| **Strong 2008** | | X | | | | | X | X | |
| **Swindle 2003** | | X | X | | | | X | X | |

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| **Uebelacker 2011** | | | X | | | | X | | |
| **Unutzer 2002** | X | X | | | | | X | X | |
| **Vera 2010** | | X | X | | | | X | X | |
| **Vlasveld 2011** | X | X | X | X | | | X | X | |
| **Walker 2014** | | X | | | | | X | X | |
| **Wells 2000** | | | | | X | | | | |
| **Wilkinson 1993** | | | | | X | | | | |
| **Williams 2007** | | | | | X | | | | |
| **Yeung 2010** | | X | X | X | | | X | X | |
| **Zimmerman 2016** | | | | | X | | | | |
| **Total (out of 93)** | **31** | **42** | **39** | **20** | **30** | **6** | **61** | **49** | **1** |

**Table 2:** Summary of trial characteristics and description of approach to relapse prevention

| Study | Participants | Baseline reported N (% Female) | Mean age | Intervention (comparator) | Study setting | Maximum follow-up/outcomes reported | Relapse data reported? | Details of additional materials (other than main trial publication) referenced | Description of approach to relapse prevention | Collaborative care components facilitating relapse prevention approach |
|---|---|---|---|---|---|---|---|---|---|---|
| **Adler 2004** | Major depression and/or dysthymia | 507 (72) | 42.3 | Pharmacist-led CC intervention (usual care) | US, Primary care | 18 months | No | Companion paper describing intervention (Bungay, 2004) | • Proactive follow-up<br>• Focus on medication maintenance | • Multi-professional approach<br>• Structured management plan<br>• Scheduled patient follow-up |
| **Aragones 2012** | Major depression | 268 (79) | 48 | INDI Project: Nurse-led programme based on chronic care model (usual clinical management) | Spain, Primary care | 12 months | No | Patient workbook and professional training manuals | • Patients advised to complete all 6 months of pharmacotherapy to prevent relapses.<br>• Patients at high risk of relapse/recurrence advised to extend treatment for 2 years or more.<br>• Systematic clinical monitoring using PHQ-9. | • Structured management plan<br>• Scheduled patient follow-up |
| **Araya 2003** | Female patients with major depression | 240 (100) | 42.6 | Stepped-care improvement programme (usual care) | Chile, Primary care | 6 months | No | None | • "Relapse prevention techniques" discussed as part of psycho-educational sessions.<br>• Patients given a | • Structured management plan |

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| | | | | | | | | | manual with detailed information. Unclear from paper what this included. | |
| **Bartels 2004** | Older people with depression, anxiety or at-risk alcohol consumption | 1531 (31) | 73.9 | Integrated care (enhanced referral) | US, Primary care and speciality mental health/substance abuse clinics | 6 months | No | Patient workbook and professional training manuals | • If patient more symptomatic (PHQ-9 >10) reassess to determine if relapsing.<br>• Formal relapse planning.<br>• Patients educated about early warning signs.<br>• Risk stratification and medication maintenance plan according to risk. | • Structured management plan<br>• Scheduled patient follow-up |
| **Blanchard 1995** | Older people with depression | 96 (85) | 76.3 | Primary care nurse intervention (normal GP care) | UK, Primary care | 3 months | No | None | Relapse not mentioned | |
| **Bogner 2008** | Patients with depression and hypertension | 64 (77) | 58.6 | Integrated care (usual care) | US, Primary care | 6 weeks | No | None | Relapse not mentioned | |
| **Bogner 2010** | Patients with Type 2 Diabetes Mellitus and Depression | 58 (85) | 60.2 | Integrated care (usual care) | US, Primary care | 6 weeks | No | None | Relapse not mentioned | |
| **Bogner 2012** | Patients with Type 2 Diabetes Mellitus and Depression | 180 (68) | 57.5 | Integrated care (usual care) | US, Primary care | 3 months | No | None | Relapse not mentioned | |
| **Bruce 2004** | Older primary care patients with depression | 598 (72) | ≥60+ | PROSPECT Intervention (enhanced usual care) | US, Primary care | 12 months | No | Manuals unavailable; additional detail on intervention content gained from direct email correspondence with author | • "At week 12, patients who are asymptomatic or minimally symptomatic (BDI-PC ≤ 10) will be moved into continuation pharmacotherapy of six months | • Structured management plan<br>• Scheduled patient follow-up |

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| | | | | | | | | | duration. During this treatment phase, clinical status assessed every month by telephone. The primary care clinician will meet with the patient if clinical status worsens."<br>• "Patients successfully completing continuation therapy with a history of recurrent depressions will be entered into maintenance therapy of two years duration. Evaluations of such patients will occur every 2-3 months by telephone and by the Primary care physician during the patient's routine office visits." | |
| **Bruce 2015** | Medicare Home Health recipients screening positive for depression | 213 (70) | 77 | Depression CAREPATH (enhanced usual care) | US, Primary care | 12 months | No | Manuals unavailable; additional detail on intervention content gained from direct email correspondence with author | • "At week 12, patients who are asymptomatic or minimally symptomatic (BDI-PC $\leq$ 10) will be moved into continuation pharmacotherapy of six months duration. During this treatment phase, clinical status assessed | • Structured management plan<br>• Scheduled patient follow-up |

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| | | | | | | | | | every month by telephone. The primary care clinician will meet with the patient if clinical status worsens."<br>• "Patients successfully completing continuation therapy with a history of recurrent depressions will be entered into maintenance therapy of two years duration. Evaluations of such patients will occur every 2-3 months by telephone and by the Primary care physician during the patient's routine office visits." | |
| **Buszewicz 2010** | Major depression or dysthymia | 558 (75) | 48.3 | Practice-nurse led intervention (usual GP care) | UK, Primary care | 24 months | No | Patient workbook and professional manuals | From trial manual: "Once you know each other reasonably well, it is also worth discussing relapse prevention with your patients, in that if they can work out what may trigger their episodes of depression, they are in a better position to avoid this in future or to seek help at an early stage." | • Structured management plan |
| **Buszewicz 2016** | Major depression or dysthymia | 558 (75) | 48.3 | Practice-nurse led intervention (usual GP care) | UK, Primary care | 24 months | No | Patient workbook and professional manuals | From trial manual: "Once you know each other reasonably well, it is also worth discussing relapse prevention with your patients, in that if they can | • Structured management plan |

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| | | | | | | | | | work out what may trigger their episodes of depression, they are in a better position to avoid this in future or to seek help at an early stage." | |
| **Capoccia 2014** | Patients with new episode of depression and started on antidepressant | 74 (77) | 38.7 | Pharmacist intervention (usual care) | US, Primary care | 12 months | No | None | • Focus on adjustment of antidepressant doses, management of adverse reactions and monitoring adherence to prevent relapse.<br>• Proactive symptom monitoring and follow-up. | • Structured management plan<br>• Scheduled patient follow-up |
| **Carney 2016** | Patients screening positive for depression in outpatient cardiology clinic | 84 (42) | 63 | Collaborative care intervention (usual care) | US, Outpatient cardiology setting | 6 months | No | | Relapse not explicitly addressed but depression symptoms were monitored and treatment plan modified in response to symptoms that were worsening or not improving | • Structured management plan |
| **Chaney 2011** | Depression | 20 (4) | 64.2 | TIDES CC Intervention (usual care) | US, Primary care | 7 months | No | Companion paper describing intervention (Liu, 2008) | Relapse prevention not addressed. | |
| **Chen 2015** | Patients aged 60 and over with major depression | 207 (64) | 70 | Depression care management intervention (enhanced care-as-usual) | China, Primary care | 12 months | No | None. | Continuation treatment with antidepressant medication for 8 months once improved | • Structured management plan |
| **Chew-Graham 2007** | Older people aged 60 and over with depression | 105 (72) | 75.5 | Community psychiatric nurse-led intervention (usual care) | UK, Primary care | 12 weeks | No | "Shade" Patient manual | Relapse prevention not addressed. | |
| **Ciechanowski 2004** | Older people aged 60 and over with minor depression or dysthymia | 138 (79) | 73 | PEARLS Intervention (usual care) | US, Primary care | 12 months | No | Patient workbook and professional manuals | • Problem solving therapy focussing on long-term behavioural change<br>• Formal relapse | • Structured management plan<br>• Scheduled patient follow-up |

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| | | | | | | | | | prevention plan, including medication maintenance<br>• Monthly phone calls after acute phase to monitor symptoms, including administering PHQ-9 | |
| **Ciechanowski 2010** | Epilepsy and depression | 80 (53) | 43.9 | PEARLS Intervention (usual care) | US, Primary care | 12 months | No | Patient workbook and professional manuals | • Problem solving therapy focussing on long-term behavioural change<br>• Formal relapse prevention plan, including medication maintenance<br>• Monthly phone calls after acute phase to monitor symptoms, including administering PHQ-9 | • Structured management plan<br>• Scheduled patient follow-up |
| **Cole 2006** | Medical inpatients screening positive for major depression within 48 hours of admission | 157 (69) | 78 | Multidisciplinary care (usual care) | Canada, medical inpatients | 6 months | No | Manuals unavailable; additional detail on intervention content gained from direct email correspondence with author | No material on relapse. | |
| **Coventry 2014** | Patients with diabetes or heart disease, and depressive symptoms for at least two weeks | 147 (38) | 59 | Collaborative care (usual care) | UK, Primary care | 24 months | No | Patient workbook and professional manuals (COINCIDE) | • Relapse prevention (“staying well”) plan<br>• Monitoring systems chosen in collaboration with patients<br>• Use of RAG (Red, | • Structured management plan<br>• Scheduled patient follow-up |

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| | | | | | | | | | Amber, Green) system and action plan | |
| **Datto 2003** | Depression | 61 (61) | 47.6 | Telephone disease management (usual care) | US, Primary care | 4 months | No | Patient and professional manuals (Foundations for Integrated Care) | • Regular monitoring and if patient more symptomatic reassess to determine if relapsing<br>• Formal relapse prevention planning<br>• Patients educated about early warning signs<br>• Use of risk stratification | • Structured management plan<br>• Scheduled patient follow-up |
| **Davidson 2013** | Post-Acute Coronary Syndrome Depression | 150 (42) | 59.6 | Stepped, patient preference-based care (usual care) | US, ambulatory centres | 6 months | No | Professional manual (CODIACS) | • Formal relapse prevention plan for all patients after the acute phase<br>• Focus on medication maintenance<br>• Opportunity for patients to contact therapist if symptoms recur<br>• Identification of patients at increased risk of relapse and encouraged to maintain medications for at least 2 years. | • Structured management plan<br>• Scheduled patient follow-up |
| **Dietrich 2004** | Depression | 405 (80) | 42 | Care manager-led intervention (usual care | US, Primary care | 6 months | No | Reference to online supplementary materials and companion papers | Relapse prevention not reported. | |
| **Dwight-Johnson 2005** | Low-income Latina patients with breast or | 55 (100) | 47.3 | Multifaceted Oncology Depression | US, Medical centre | 8 months | No | None | Relapse prevention not reported. | |

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| | cervical cancer and depression | | | Program Intervention (usual care) | | | | | | |
| **Dwight-Johnson 2010** | Low-income Latinos with depression | 339 (84) | 49.8 | Collaborative care (enhanced usual care) | US, Primary care | 4 months | No | None | Relapse prevention not reported. | |
| **Dwight-Johnson 2011** | Latino patients with depression living in rural areas | 101 (78) | 39.8 | Telephone-based Cognitive Behaviour Therapy (enhanced usual care) | US, Primary care | 6 months | No | None | Relapse prevention not reported. | |
| **Ell 2007** | Older adults in Home Health Care | 311 (72) | ≥65 | Collaborative care intervention (enhanced usual care) | US, Primary care | 12 months | No | None | Relapse prevention not reported. | |
| **Ell 2008** | Low-income patients with cancer and depression | 472 (79) | ≥18 | Alleviating Depression Among Patients with Cancer (ADAPt-C) collaborative care intervention (enhanced usual care) | US, Primary care | 12 months | No | None | • "After acute treatment, patients received a treatment maintenance and relapse prevention program"<br>• Monthly telephone contacts up to 12 months after treatment initiation to monitor symptoms<br>• Additional in-person visits if indicated<br>• Ongoing behavioural activation<br>• Motivational support for ongoing problem solving therapy and medication adherence | • Structured management plan<br>• Scheduled patient follow-up |
| **Ell 2010** | Low-income predominantly | 387 (82) | ≥18 | Multifaceted Diabetes and | US, Primary care | 18 months | No | None | Patients with full response to treatment move to | • Structured management |

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| | Hispanic patients with Diabetes and Depression | | | Depression Program (enhanced usual care) | | | | | monthly relapse prevention telephone monitoring | • plan<br>• Scheduled patient follow-up |
| **Engel 2016** | Military personnel with PTSD and Depression | 127 (19) | 31 | Centrally Assisted Collaborative Telecare (usual care) | US, Primary care | 12 months | No | None | Relapse prevention not reported. | |
| **Finley 2003** | Depression | 125 (85) | 54.3 | Pharmacist intervention (usual care) | US, Primary care | 6 months | No | None | Focus on medication maintenance. | • Structured management plan |
| **Fortney 2007** | Depression | 395 (100) | 59.2 | Telemedicine-based CC intervention (usual care) | US, community-based outpatient clinics | 12 months | No | Manuals unavailable; additional detail on intervention content gained from direct email correspondence with author. Companion paper outlines intervention (Fortney, 2006) | Follow-up encounters to monitor symptoms and medication adherence every 4 weeks during the continuation phase. | • Structured management plan<br>• Scheduled patient follow-up |
| **Gensichen 2009** | Depression | 535 (79) | 51.1 | Health care assistant-led intervention | Germany, Primary care | 12 months | No | None | • Telephone symptom monitoring once monthly for 11 months<br>• Depression symptoms and medication adherence monitored using Depression Monitoring List<br>• Focus on self-management including behavioural activation | • Structured management plan<br>• Scheduled patient follow-up |
| **Gilbody 2017** | Older adults with sub-threshold depression | 407 (58) | 77 | Collaborative care (usual care) | UK, Primary care | 12 months | No | Patient and professional manuals: | • Formal “Keeping well” plan, made in collaboration | • Structured management plan |

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| | | | | | | | | CASPER | with the patient<br>• Identification of triggers and education about early symptoms<br>• Emphasis not on medication maintenance as sub-threshold depression | |
| **Gjerdingen 2009** | Post-partum depression | 39 (100) | 27.6 | Stepped collaborative care (usual care) | US, Primary care | 9 months | No | None | Relapse prevention not addressed | |
| **Grote 2015** | Perinatal depression in socioeconomically disadvantaged women | 168 (100) | 27 | Collaborative care (usual care) | US, Public health centres | 18 months | No | Professional manual | • Participants were followed up monthly during the maintenance phase of treatment (up to 18 months)<br>• Formal relapse plan made and patients prepared to recognise onset of relapse<br>• More frequent psychotherapy or medication maintenance available if increase in symptoms | • Structured management plan<br>• Scheduled patient follow-up |
| **Hedrick 2003** | Major depression and/or dysthymia. | 18 (5) | 57.2 | Collaborative care (usual care | US, Primary care | 9 months | No | None | Approach to relapse prevention not reported | |
| **Huffman 2011** | Depressed patients hospitalized with cardiac conditions | 175 (49) | 62.3 | Collaborative care program (usual care) | US, Inpatient and post-discharge | 6 months | No | None | Approach to relapse prevention not reported | |
| **Huffman 2014** | Patients hospitalized with cardiac conditions and found to have depression, anxiety or panic disorder | 97 (53) | 61 | Collaborative care program (usual care) | US, Inpatient and post-discharge | 6 month | No | None | Approach to relapse prevention not reported | |
| **Huijbregts** | Depression | 150 | 48.7 | Collaborative | Netherlands, | 12 months | No | Patient | • Patients educated | • Structured |

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| **2013** | | (72.7) | | care model (usual care) | Primary care | | | workbook and professional manuals | regarding alarming symptoms suggesting relapse<br>• Focus on antidepressant medication maintenance | management plan |
| **Hunkeler 2000** | Depression | 302 (70) | 55.4 | Nurse Telehealth Care (usual care) | US, Primary care | 6 months | No | None | Regular telephone monitoring and approach to medication maintenance but no follow up beyond 16 weeks | • Structured management plan<br>• Scheduled patient follow-up |
| **Johnson 2014** | Diabetes and depressive symptoms | 127 (56) | 60 | Collaborative care (usual care) | Canada, Primary care | 12 months | No | | • Case Manager (CM) worked with the patient to develop a shared care plan, offered support and problem solving techniques to optimize self-management, and closely monitored treatment adherence and outcome.<br>• The CM provided active in-person or telephone follow-up once to twice per month to reassess symptoms and assist patients in achieving goals<br>• Relapse prevention plan made once entered remission | • Structured management plan<br>• Scheduled patient follow-up |
| **Katon 1995** | Depression | 217 (77.4) | 47.8 | Collaborative care (usual care) | US, Primary care | 12 months | No | Patient workbook and professional manuals | Active monitoring of automated pharmacy data to monitor medication adherence during the continuation phase (3-7 | • Structured management plan<br>• Scheduled patient follow- |

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| | | | | | | | | | months) | up |
| **Katon 1996** | Depression | 153 (73.9) | 46.4 | Collaborative care (usual care) | US, Primary care | 4 months | No | Patient workbook and professional manuals | Relapse prevention plan made. 4 month follow up only. | • Structured management plan<br>• Scheduled patient follow-up |
| **Katon 1999** | Persistent major depression | 228 (75) | 47 | Stepped collaborative care (usual care) | US, Primary care | 6 months | No | Patient workbook and professional manuals | Psychiatrist reviewed monthly automated pharmacy data on antidepressant refills to monitor the patient's adherence to the acute and continuation phases of treatment and alerted the primary care physician and/or telephoned the patient if premature discontinuation of medication occurred. | • Multi-professional approach<br>• Structured management plan<br>• Scheduled patient follow-up<br>• Enhanced inter-professional communicatio n |
| **Katon 2001** | Recurrent major depression or dysthymia | 386 (74) | 46 | CC-based relapse prevention intervention (usual primary care) | US, Primary care | 12 months | Yes | Patient workbook and professional manuals | • Relapse prevention intervention.<br>• Aimed at increasing patient education and enhancing self-treatment of their depression.<br>• BDI and medication monitored.<br>• The other goals included increasing the daily use of depression treatment techniques, such as increasing pleasant activities, exercise, and socializing, and identifying | • Structured management plan<br>• Scheduled patient follow-up |

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| | | | | | | | | | potential high-risk situations to promote problem-solving ability, coping, and self-efficacy for managing depression.<br>• The ultimate aim of the intervention was to have each patient complete and follow a 2-page written personal relapse prevention plan. | |
| **Katon 2004** | Diabetes and depression | 329 (65) | 58.3 | Collaborative care (usual care) | US, Primary care | 12 months | No | Patient workbook and professional manuals | Detailed patient-centred relapse prevention plan, including warning signs, coping strategies, medication maintenance and use of PHQ to monitor symptoms. | • Structured management plan<br>• Scheduled patient follow-up |
| **Katon 2010** | Depression and coronary heart disease, diabetes or both | 214 (52) | 56.8 | Collaborative care (usual care) | US, Primary care | 12 months | No | Patient workbook and professional manuals | • Monitoring of symptoms during maintenance phase with PHQ-9 and regular follow-up.<br>• Medication maintenance and psychotherapy focussing on long-term mental health. | • Structured management plan<br>• Scheduled patient follow-up |
| **Katzelnick 2000** | Depressed "high-utilizers" of medical care | 407 (77) | 45.5 | Depression management program (usual care | US, Primary care | 12 months | No | None | Telephone monitoring of treatment adherence for up to 42 weeks if needed. | • Structured management plan<br>• Scheduled patient follow-up |
| **Kroenke 2010** | Depression and cancer-related pain | 405 (68) | 58.8 | Telecare management (usual care) | US, rural oncology practices | 12 months | No | Professional manual | • Use of PHQ-9 to track any deterioration<br>• Focus on medication | • Structured management plan<br>• Scheduled patient follow- |

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| | | | | | | | | | adherence<br>• Consider changing medication in event of relapse | up |
| **Landis 2007** | Depressed Medicaid patients | 45 (96) | 39.7 | Generalist care manager intervention (usual care) | US, Primary care | 6 months | No | None | • Follow up every 4 weeks during maintenance phase and monitoring with PHQ-9<br>• Focus on medication maintenance | • Structured management plan<br>• Scheduled patient follow-up |
| **Lerner 2015** | Depression and work limitations | 309 (72) | 55 | Telephone Depression Intervention (usual care) | US, Primary care | 4 months | No | Patient workbook and professional manuals | Relapse prevention approach not reported in paper and intervention as described is more focussed on acute phase | |
| **Lobello 2010** | Patients with major depressive disorder treated with extended-release venlafaxine | 520 (73) | 44.5 | Collaborative care (usual care) | US, Outpatients | 6 months | No | None | Relapse prevention is a stated goal of the intervention, however the approach is not explicitly reported. | |
| **Ludman 2007** | Chronic or recurrent depression | 104 (70.2) | 50.4 | Collaborative care (usual care) | US, Primary care | 12 months | No | Patient and professional | • Focus on identifying triggers and self-management<br>• Personalised action plan<br>• Monitoring of symptoms and medication adherence<br>• Acute and “booster” psychotherapy sessions (behavioural activation) | • Structured management plan<br>• Scheduled patient follow-up |
| **Ludman 2016** | Chronic depression | 205 (68) | 50 | Collaborative care (usual care) | US, Primary care | 18 months | No | Patient and professional | • Focus on identifying triggers and self-management<br>• Personalised | • Structured management plan<br>• Scheduled patient follow- |

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| | | | | | | | | | action plan<br>• Monitoring of symptoms and medication adherence<br>• Acute and "booster" psychotherapy sessions (behavioural activation) | up |
| **Mann 1998** | Depression | 577 (78) | 50 | Practice nurse and GP-led intervention (usual care) | UK, Primary care | 4 months | No | NIHR Programme grant used for reference | No explicit focus on relapse prevention | |
| **Mavandadi 2015** | Older adults with depression and anxiety | 847 (83) | 78 | Telephone-based collaborative care(usual care) | US, Primary care | 6 months | No | Patient and professional manuals (Foundations for Integrated Care) | • Regular monitoring and if patient more symptomatic reassess to determine if relapsing<br>• Formal relapse prevention planning<br>• Patients educated about early warning signs<br>• Use of risk stratification | • Structured management plan<br>• Scheduled patient follow-up |
| **McCusker 2008** | Older patients with depression | 68 (66) | 73.3 | Collaborative care (usual care) | Canada, Primary care | 2 months | No | Professional and patient manuals | No explicit approach to relapse prevention<br>Medication maintenance mentioned briefly in professional manual | |
| **McMahon 2007** | Depression | 62 (NR) | Range 18-65 | Case management (usual care) | UK, Primary care | 6 months | No | None | No approach to relapse reported. | |
| **Melville 2014** | Depression in obstetrics and gynaecology | 205 (100) | 39 | Collaborative depression management (usual care) | US, Outpatient clinics | 18 months | No | Patient workbook and professional manuals | • Monitoring of symptoms using PHQ-9 up to 12 months.<br>• Medication maintenance with focus more on recovery than | • Scheduled patient follow-up |

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| | | | | | | | | | relapse prevention | |
| **Menchetti 2013** | Depression | 227 (58.2) | 51.8 | Collaborative care (usual care) | Italy, Primary care | 3 months | No | None | No approach to relapse prevention reported | |
| **Morgan 2013** | Depression and diabetes or heart disease | 317 (46.7) | 67.8 | True Blue model of collaborative care (usual care) | Australia, Primary care | 12 months | No | True Blue patient and professional manuals | • Patients recalled systematically to monitor the progress of their care: patients will complete a new PHQ-9 questionnaire so that any changes to their mental health can be monitored.<br>• Additional therapies or new strategies can be considered during the consultations if the PHQ-9 score has not improved by at least 50% or dropped below 5. These strategies may include changing or adding medication or referral to a mental health professional. | • Multi-professional approach<br>• Structured management plan<br>• Scheduled patient follow-up |
| **Oladeji 2015** | Depression | 208 (80) | 43 | Stepped care intervention (usual care) | Nigeria, Primary care | 6 months | No | None | Participants who improve, indicated by a PHQ-9 score of 5 or lower or less than half of baseline score, receive four fortnightly top up talking therapy sessions over an additional 8 weeks. | • Structured management plan<br>• Scheduled patient follow-up |
| **Oslin 2003** | Older population of veterans with depression and at-risk drinking | 97 (4) | 61.6 | Telephone disease management (usual care) | US, Primary care | 4 months | No | Patient and professional manuals (Foundations for Integrated | • If there is high risk for relapse (history of dysthymia or more than two | • Structured management plan |

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| | | | | | | | | Care) | prior depressive episodes) – Patients should be encouraged to stay on current treatment (usually full dose of the pharmacotherapy that led to clinical response) for at least 2 years. This information should also be shared with the patient's primary care clinician.<br>• Formal relapse prevention planning | |
| **Patel 2010** | Depressive an anxiety disorders | 2796 (82) | 46.3 | Lay health counsellor-led intervention (enhanced usual care) | India, Primary care | 6 months | No | Patient workbook and professional manuals | "Adherence management", recognising triggers, follow up, medication maintenance | |
| **Piette 2011** | Diabetes patients with depression | 291 (52) | 56 | Telephonic counselling plus walking (enhanced usual care) | US, Primary care | 12 months | No | Patient workbook and professional manuals | • Primary Care Physicians received summary fax reports about patients' PHQ scores every three months with more frequent reports noting significant changes.<br>• Instruction to therapist: "To minimize relapse following completion of the intensive counseling phase, you will schedule monthly follow- | • Multi-professional approach<br>• Structured management plan<br>• Scheduled patient follow-up |

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| | | | | | | | | | up sessions for nine months. Both during the intensive phase and at the time of follow-up, reinforce the idea that the client (wherever possible) needs to keep practicing the skills on a regular basis."<br>• Relapse prevention planning/strategies discussed. | |
| **Pyne 2011** | Depression in HIV clinics | 249 (3) | 49.8 | Collaborative care (usual care) | US, HIV clinics | 12 months | No | | The DCM conducted telephone-based monitoring every 2 weeks during acute treatment (before achieving a sustained 50% decrease in PHQ-9 score) and every 4 weeks during watchful waiting or continuation treatment (for 2 months after maintaining re-mission [PHQ-9 score, 5] or 6 months after maintaining a 50% decrease in the PHQ-9 score). | • Structured management plan<br>• Scheduled patient follow-up |
| **Richards 2008** | Depression | 114 (77) | 42.5 | Collaborative care (usual care) | UK, Primary care | 3 months | No | Case manager guide: CADET | • The case manager should help the patient make a specific relapse prevention plan. This should include a written commitment to continue both medication and psychological interventions according to the | • Multi-professional approach<br>• Structured management plan<br>• Scheduled patient follow-up |

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| | | | | | | | | | patient's wishes and informed by sound information giving. It should also include a list of trigger symptoms and situations which act as alerts for the patient to plan re-instating either/or medical and psychological strategies.<br>• The case manager should end treatment with the patient. The patient should have a clear plan as to what to do should their symptoms return.<br>• If the patient has either not improved or only partially benefitted from the collaborative care intervention, the case manager should recommend that the patient returns to their GP and seeks referral to specialist mental health services. | |
| **Richards 2013** | Depression | 581 (72) | 44.8 | Collaborative care (usual care) | UK, Primary care | 12 months | No | Case manager guide: CADET | • The case manager should help the patient make a specific relapse prevention plan. This should include a written | • Multi-professional approach<br>• Structured management plan<br>• Scheduled |

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| | | | | | | | | | commitment to continue both medication and psychological interventions according to the patient's wishes and informed by sound information giving. It should also include a list of trigger symptoms and situations which act as alerts for the patient to plan re-instating either/or medical and psychological strategies.<br>• The case manager should end treatment with the patient. The patient should have a clear plan as to what to do should their symptoms return.<br>• If the patient has either not improved or only partially benefitted from the collaborative care intervention, the case manager should recommend that the patient returns to their GP and seeks referral to specialist mental health services. | patient follow-up |
| **Rojas 2007** | Postnatal | 230 (100) | 26.6 | Multicomponent | Chile, Primary | 6 months | No | None | Relapse prevention not | |

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| | depression in low-income mothers | | | intervention (usual care) | care | | | | addressed | |
| **Rollman 2009** | Post-CABG Depression | 302 (41) | 64 | Telephone-delivered collaborative care | US, Primary care | 8 months | No | Bypassing the Blues: Professional manual | • Self-management techniques<br>• Review stressors and how to cope with them<br>• Regular symptoms monitoring and maintenance plan<br>• Medication maintenance | • Structured management plan<br>• Scheduled patient follow-up |
| **Ross 2008** | Minor depression | 223 (7) | 59.2 | Telephone-based close monitoring programme (usual care) | US, Primary care | 6 months | No | Patient and professional manuals (Foundations for Integrated Care) | • If patient more symptomatic >10 reassess to determine if relapsing.<br>• Formal relapse planning.<br>• Patients educated about early warning signs.<br>• Risk stratification. | • Structured management plan<br>• Scheduled patient follow-up |
| **Rost 2002** | Major depression | 211 (84) | 43 | Practice nurse-led care management (usual care) | US, Primary care | 24 months | No | Professional manual | • Medication adherence<br>• Explanation of risk of relapse in manual | • Structured management plan<br>• |
| **Rubenstein 2006** | Depression | 567 (59) | 48.2 | Collaborative care (usual care) | US, Primary care | Unclear | No | Professional manual (Partners in Care) | Relapse prevention not reported. | |
| **Salisbury 2015** | Depression | 417 (69) | 50 | Integrated telehealth service (usual care) | UK, Primary care | 4 months | No | Patient and professional manuals: "Living life to the full" | • After an initial assessment and goal-setting telephone call, the advisers called each participant on six occasions roughly equally spaced over 4 months, and then made up to three more calls at roughly | • Structured management plan<br>• Scheduled patient follow-up |

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| | | | | | | | | | two month intervals to provide reinforcement and to detect relapse.<br>• Support in use of the CBT programme (online or in book form), the telephone scripts included modules covering the monitoring of depression symptoms, drug treatment, medication adherence, exercise, and alcohol use. | |
| **Sharpe 2014** | Co-morbid depression in cancer patients | 449 (90) | 56 | Integrated collaborative care (usual care) | UK, Cancer centres | 6 months | No | None | The initial treatment phase comprises a maximum of ten sessions with the nurse (at the cancer or primary care clinic, or if necessary by telephone) over a 4-month period. After this initial treatment period, PHQ-9 scores are monitored monthly by telephone (through an automated system supplemented by nurse calls). Details of response to this not reported. | • Structured management plan<br>• Scheduled patient follow-up |
| **Simon 2000** | Depression | 613 (71.6) | 46.5 | Telephone collaborative care (usual care) | US, Primary care | 6 months | No | Care manager manuals | From Care manager manual: "If depression is in remission, discuss self-monitoring for signs of relapse" | • Structured management plan |
| **Simon 2004** | Depression and starting antidepressants | 600 (74.3) | 44.5 | Telephone care management (usual care) | US, Primary care | 6 months | No | Care manager manuals | • Self-care and booster plan for maintaining | • Structured management plan |

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| | | | | | | | | | program gains and preventing relapse.<br>• An 8-session manualized cognitive-behavioural program followed by 3 - 4 telephone relapse-prevention sessions. | • Scheduled patient follow-up |
| **Simon 2011** | Depression | 208 (72) | 46 | Online messaging – based intervention (usual care) | US, Primary care | 5 months | No | Care manager manuals | No approach to relapse reported | |
| **Smit 2006** | Depression | 267 (66) | 42 | Enhanced treatment (usual care) | Netherlands, Primary care | 6 months | No | Full details as published in companion paper (Smit, 2005) | Patient-tailored depression prevention plan (early warning signs, stress reduction, medication plan, emergency plan, copy to Primary Care Physician) | • Structured management plan |
| **Strong 2008** | Depression in patients with cancer | 200 (71) | 56.6 | Cancer nurse-led intervention (usual care) | UK, Cancer clinics | 3 months | No | None | Monitored for 3 months after treatment (using PHQ-9) and if scored highly offered further appointments | • Structured management plan<br>• Scheduled patient follow-up |
| **Swindle 2003** | Depression | 268 (3) | 56.2 | Specialist nurse-led intervention (usual care) | US, General medicine clinic | 12 months | No | None | • Monitoring for up to two months<br>• Focus on medication adherence | • Structured management plan<br>• Scheduled patient follow-up |
| **Uebelacker 2011** | Latino Medicaid Health Plan members | 38 (95) | 39.1 | Telephone Depression Care management (usual care) | US, Primary care | 3 months | No | Professional manual | Focuses on medication adherence and not stopping medications without discussing with doctor | • Structured management plan |
| **Unutzer 2002** | Late-life depression | 1801 (65) | 71.2 | Collaborative Care management (usual care) | US, Primary care | 12 months | No | Patient workbook and professional manuals | Patients who recovered made personalised relapse prevention plan and were followed up monthly | • Structured management plan<br>• Scheduled patient follow-up |

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| **Vera 2010** | Depression and chronic medical conditions | 179 (76) | 55 | Collaborative care (usual care) | Puerto Rico, Primary care | 6 months | No | None | Care managers contacted patients in person or by phone at least every two weeks initially and then monthly, for up to six months. Additional contacts could be scheduled as needed to help patients overcome barriers and provide treatment adherence support. | • Structured management plan<br>• Scheduled patient follow-up |
| **Vlasveld 2011** | Depressive disorder in Occupational Health Setting | 126 (54) | 44.8 | Multidisciplinary collaborative care (usual care) | Netherlands, Primary care | 3 months | No | Patient workbook | The treatment will be monitored every two weeks and, when needed, will be intensified by adding an extra 6 sessions of PST, or by adding antidepressant medication to the treatment plan or by increasing or changing the antidepressant medication. Patient workbook with Chapter dedicated to relapse prevention | • Structured management plan<br>• Scheduled patient follow-up |
| **Walker 2014** | Major depression and poor-prognosis cancer | 92 (65) | 64 | Integrated collaborative care (usual care) | UK, Cancer clinics | 32 weeks | No | None | The initial treatment phase comprises a maximum of ten structured sessions with the nurse (usually at the patient's home), starting as soon as possible after a diagnosis of depression and given over a 4-month period. The nurse then monitors the patient's PHQ-9 scores monthly by telephone for a further 4 months and provides additional sessions for patients who do not meet treatment targets. | • Structured management plan<br>• Scheduled patient follow-up |
| **Wells 2000** | Depression | 1356 (70.7) | 43.7 | Collaborative care (usual care) | US, Primary care | 12 months | No | Partners in Care professional | Relapse prevention not specifically reported. | |

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| | | | | | | | | manuals | | |
| **Wilkinson 1993** | Depression | 61 (74) | 46 | Practice nurse-led intervention (usual care) | UK, Primary care | 2 months | No | None | No focus on relapse prevention reported. Medication maintenance focussed on recovery rather than relapse prevention | |
| **Williams 2007** | Post-stroke depression | 182 (54) | 60 | Care management (usual care) | US, Hospital and community | 3 months | No | Email correspondence with author – follow up 12 weeks, minimal focus on relapse | Did not focus on relapse prevention | |
| **Yeung 2010** | Depressed Chinese Americans | 100 (69) | 49.7 | Culturally sensitive collaborative treatment (usual care) | US, Primary care | 6 months | No | | Subsequent contacts, which occurred at the 2nd, 4th, 8th, 12th, 16th, 20th, and 24th weeks through telephone calls, focused on monitoring of depressive symptoms, adherence to medication treatment, management of adverse events, and knowledge of self-management strategies. | • Structured management plan<br>• Scheduled patient follow-up |
| **Zimmerman 2016** | Anxiety depressive or somatic symptoms | 325 (66.8) | 40.2 | Collaborative nurse-led self-management support (usual care) | Germany, Primary care | 12 months | No | None | No approach to relapse reported. | |

**Declarations of Interest:**

None

## Author contributions

ASM, PAC, SG and DM conceived the design of the study, developed the protocol and have interpreted the findings. JLH, RC, PAC selected the articles. ASM, NC and OJF extracted the data. All authors contributed to data interpretation. ASM, PAC and DM wrote the first draft of the manuscript. All remaining authors aided with the interpretation of the results, commented critically on the introduction and discussion, approved the final version of the manuscript and agree to be accountable for all aspects of the work.


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