Results from a randomised controlled trial of practice nurse led pro-active care for chronic depression in primary care – the ProCEED trial

Marta Buszewicz, Mark Griffin, Elaine M McMahon, Kate Walters and Michael King.

Abstract

Aim: To evaluate whether structured, nurse-led pro-active care of patients with chronic depression in primary care improves outcomes.

Methods: Participants with chronic/recurrent major depression or dysthymia were recruited from 42 UK general practices and randomised to GP treatment as usual or nurse intervention over 2 years.

Results: 282 people received the intervention with 276 controls. At 24 months there was no significant improvement in Beck Depression Inventory (BDI-II) score or quality of life (Euroquol-EQ-VAS), but a significant improvement in functional impairment (Work and Social Activity Schedule) of 2.5(95% CI:0.6,4.3, p=0.010) in intervention patients. Impact per practice nurse intervention session was -0.37(95% CI:-0.68,-0.07,p=0.017) on BDI-II and -0.33(95% CI:-0.55,-0.10,p=0.004) on WSAS scores, indicating that attending all 10 intervention sessions could lead to a BDI-II score reduction of 3.7 points compared to controls.

Conclusion: The intervention improved functioning in these patients, the majority of whom had complex long-term difficulties, but only had a significant impact on depressive symptoms in those engaging with the full intervention.

Declaration of interest: None

Introduction:

Depression is an important public-health problem, and one of the leading causes of disease burden worldwide[1]. The medical outcomes study collated data from 11,242 outpatients in the United States (US) and showed that depressive symptoms, with or without major depressive disorder, impaired functional ability and wellbeing as much as the most common chronic medical conditions such as diabetes, chronic lung disease, hypertension, and heart disease[2,3]. After two years' follow up around 40% of those with major depression were still affected and functionally impaired, while those with chronic minor depression (dysthymia) had the worst outcome. Most had only partial recovery of functional ability[3]. Primary care populations with chronic or recurrent depression, although clinically important, are rarely investigated as a distinct patient group[4]. It is known that chronicity of depression is associated with high mortality, greater psychological and social morbidity and high use of primary care services[5], but there is little consistency regarding longer-term management of this disorder[6]. Studies from the US indicate that organised, enhanced care can have a beneficial effect on outcomes for patients with acute major depression[7], and also those with persistent depression[8] or at high risk of recurrence[9]. However, there are increased costs associated with such an approach and beneficial effects can decline over time, such that a longer-term approach may be indicated, particularly for those with chronic difficulties[10]. Most people with depression are treated in primary care, but there have been few trials of interventions targeted at those with chronic or recurrent depression in either primary or secondary care settings, with most examining interventions for newly diagnosed depression[11]. Collaborative care models include specialist input, which is potentially more costly to deliver than models based solely in primary care. Given the associated unmet needs, significant morbidity and costs there is a need for new approaches to management of this problem in primary care. The aim of this trial was to evaluate the management of chronic depression with regular pro-active contact and follow-up of patients by practice nurses over two years, supported by general practitioners (GPs).

Methods:

Objective:

To establish whether structured, pro-active care of patients with chronic depression in primary care leads to an improvement in medical and social outcomes when compared with usual GP care.

Study design and participants:

Randomised controlled trial comparing GP 'usual care' (control), with a 'pro-active care' approach involving regular follow-up by practice nurses (intervention) in addition to GP usual care, for patients with recurrent or chronic depression (see protocol paper for details[12]). Participants were recruited from 42 general practices throughout the United Kingdom (UK). Inclusion and exclusion criteria are shown below.

Inclusion criteria:
(i) Adults aged 18 and over
(ii) Two or more documented episodes of major depression within the previous 3 years
(iii) Evidence of recurrent and / or chronic depression via CIDI (lifetime) questionnaire[13]
(chronic depression was categorised as an episode of major depression lasting at least 2 years within the 3 years prior to recruitment or chronic dysthymia for the two years prior to recruitment)
(iv) Baseline Beck Depression Inventory score of 14 or above[14]
(v) Sufficient English to be able to complete self-report questionnaires

Exclusion criteria:
(i) Current psychotic symptoms
(ii) Impaired cognitive function

(iii) Incapacitating alcohol or drug dependence

Consent and randomisation:

After a thorough explanation of the study to potential subjects, written informed consent was obtained from those fulfilling the inclusion criteria and agreeing to take part. Consenting participants were individually randomised by telephone, using the independent Medical Research Council computerised randomisation service and a blocked design to maintain a balance of numbers in control and intervention groups. All participants completed baseline questionnaires at the practice prior to being informed about their randomisation result by the research nurse. All study team members apart from the project manager were blind to block size and group allocation.

Trial Intervention:

The intervention, termed 'pro-active' care, involved regular scheduled follow-up appointments with trained nurses over the 24 months of the trial. Intervention participants had a baseline assessment and further sessions were offered after 1 month, 2 months later and then every 3 months for the remainder of the 2 years of the trial, i.e. a total of 10 appointments. Most were face to face, although patients had the option to elect for telephone appointments when attending the surgery was difficult. A joint management plan was formulated between the nurses and each of their patients at the baseline assessment and reviewed during subsequent appointments. If clinically indicated the reviews could be more frequent and if nurses were concerned about a patient, they were asked to discuss them with the relevant GP, who might also see the patient if indicated.

At each session the nurses asked about the patients' current mood and reviewed their social circumstances, current treatment (medication and / or psychological therapy), and any side-effects. They discussed participants' queries about current or past treatments and checked their concordance with treatment, clarifying any reasons for poor concordance. If there were current symptoms of depression, alternative or additional treatments were discussed. The nurses were given brief training in problem solving and motivational interviewing techniques[15,16] and used these to help the participants to identify their own problems, solutions, motivation for change and preferences for care.

The intervention was manualised and has been described in detail elsewhere[12]. All participating nurses received at least one quality assurance visit from a senior, independent MRC GP Research Framework training nurse. Intervention participants were also given an educational booklet designed for the trial, which included information about depression and outlined current evidence based thinking about its treatment (the intervention manual and educational booklet are obtainable on request).

Nurse training and clinical supervision sessions:

The research team provided 3 days training for all participating practice nurses[12]. A further day's training was provided for nurses conducting the outcome assessments. Each nurse was assigned a member of the research team as a 'clinical supervisor' (two were GPs with an interest in mental health and one a clinical psychologist). Nurses had telephone contact every 3 to 4 months with their supervisors and could contact them in between with any patient concerns.

Control arm – 'treatment as usual':

Participants in the control arm received 'treatment as usual' and continued to see their GP on request. They did not see the practice research nurse for any mental health intervention.

Outcome measures:

a) The primary outcome measure was the Beck Depression Inventory (BDI-II)[14].

b) Functional impairment was measured using the Work and Social Activity Scale (WSAS)[17].

c) Diagnostic and Statistical Manual IV (DSM-IV) diagnosis and frequency of depressive episodes assessed using the Composite International Diagnostic Interview (CIDI) questionnaire[13] at recruitment and follow-up.

d) Health-related quality of life measured using the EuroQuol EQ-5D[18] Here we report results from the visual analogue scale (EQ-VAS).

e) Practice service data on number of GP visits, practice nurse contacts, referrals for psychological therapy and prescriptions for psychotropic medication collected for 24 months before recruitment and the 24 months of the trial.

BDI-II results completed by self-complete questionnaire at baseline, 3, 6, 12, 18 and 24 months.
All other measures were collected at baseline and 24 months[12].

The CIDI was completed via face to face interview with a practice research nurse at baseline and 2 years. Final assessment interviews were conducted by research nurses not involved in delivering the intervention who were blind to participants' trial group allocations. As a check on blindness they were asked to estimate which trial arm each participant had been randomised into.

Practice service use data was collected by practice nurses involved in the initial recruitment and delivery of the intervention. All other outcome measures were obtained by self-complete questionnaires.

Sample size and statistical analysis:

Data were double entered and analysed using SPSS for Windows Release 15.0 and STATA Release 10. The sample size was calculated to detect a clinically important difference in BDI-II at 90% power and the 5% (two-sided level) of significance. A pooled standard deviation of 11.0 was assumed and the sample sizes adjusted for clustering using an intra-class correlation (ICC) of 0.02[19]. For a 4-point difference in BDI (assuming an average 10 patients per practice) the required sample size would be 376 (15). Thus 38 practices with 10 patients per practice (total 380) would meet the required sample size. In order to take account of possible attrition, recruiting 12 to 14 patients per practice would allow for 25% attrition, meaning a total of 532 participants would be required.

For continuous variables means and standard deviations were calculated, and for categorical variables numbers and percentages. All analyses were undertaken on an intention to treat (ITT) basis. For the primary (BDI-II) and secondary (WSAS and EQ-VAS) outcomes we used multi-level modelling adjusted for clustering by general practice[20]. For the BDI-II the multi-level modelling included an additional level to take account of repeated measures over time. All models fitted reflected the appropriate hierarchical structure of the data and adjusted for baseline values of the relevant outcome. Practice service use data were analysed using analysis of covariance (ANCOVA), adjusting for baseline values and using robust standard errors to account for clustering[21].

In order to calculate the effect sizes of the main outcome measures we used a method utilising estimates derived from the multi-level models (Hedge's g)[22].
For the BDI-II, WSAS and EQ-VAS the effect of number of "nurse sessions" attended on outcome was also assessed using a contamination adjusted intention to treat analysis (CA ITT)[23]. This was implemented using instrumental variable (IV) regression with the 24 months follow-up score as the outcome, randomisation as the IV, baseline score and number of sessions as explanatory variables and robust standard errors to take account of clustering. A CA ITT analysis allows adjustment for non-adherence, avoiding the biases of as treated and per-protocol analyses and preserving the randomness of allocation by examining how control

4

patients 'would have' behaved were they to have been in the experimental arm. It is similar in principle to a CACE analysis (complier average causal effect

Results:

We approached 3,293 potentially eligible people from 42 general practices throughout the UK, identified predominantly from practice database searches. Participants were recruited between November 2007 and July 2008 and the 2 year follow-up continued until the end of July 2010.

Of 3,293 people initially approached, 959 (29%) expressed an interest in attending for interview and 828 (25%) attended. Following the recruitment interview and assessment 558 people were found eligible and agreed to take part (Figure 1).

Figure 1 about here

Participants' questionnaire responses for the primary outcome the BDI-II were: 99% at baseline; 72% at 3 months; 66% at 6 months; 66% at 12 months; 62% at 18 months and 78% at 24 months. Because of concern about attrition between 3 and 6 months, following discussion at the Trial Steering Group and having obtained ethical approval, we incentivised the return of questionnaires from the 12-month follow-up point with £10 shopping vouchers[24].

The 24 month outcome interviews were completed face to face with a different research nurse from the nurse conducting the initial recruitment and intervention and participant response was 65%. A further 13% of participants returned the final BDI-II by post. A total of 66 participants (12% of the total) formally withdrew over the 24 months of the study; 36 in the intervention group and 30 in the control group. One participant in the intervention arm died of cancer during the trial.

Number of sessions attended: Of the 282 participants in the intervention arm, 77 (27%) were poor attenders and only attended 0-4 intervention sessions, 83 (29%) were moderate attenders and attended 5-8 sessions and 122 (43%) were good attenders, having attended 9-11 intervention sessions. The latter group were considered to have attended for the full intervention as various timing constraints meant that not all could be offered the full 10 sessions initially intended.

Baseline characteristics

The two groups were well balanced with respect to baseline characteristics, with no large differences between the intervention and control groups (Table 1).

Table 1 about here

Outcome results at 24 months

Primary outcome: Scores for the BDI-II at follow-up improved (decreased) in both trial arms over time (Table 2). There was a small but not significantly greater improvement in the intervention arm. The estimated average difference in score, from the multi-level modelling, was lower [better] by 1.2 (95% CI: -0.3, 2.7, p=0.125) in the intervention group when accounting for all time-points.

Table 2 about here

Secondary outcomes: Summary results at 24 months are presented in Table 3. From the multi-level modelling, the WSAS score was found to be significantly lower [better] by 2.5 (95% CI: 0.6, 4.3, p=0.010) in

the intervention group at 24 months, while the EQ-VAS score was higher [better]) by 2.9 (95% CI: -0.8, 6.5, p=0.127) in the intervention group at 24 months.

Table 3 about here

The only statistically significant differences in service use were for practice nurse visits and number of months on antidepressants. Both were higher in the intervention group, with adjusted mean differences (intervention-control) of 1.6 (95% CI: 0.2, 3.0; p=0.026) and 1.4 (95% CI: 0.02, 2.8; p=0.047) respectively. A comparison of the proportions in each diagnostic category (CIDI) between intervention and control groups at follow-up showed no statistically significant difference (p=0.368).
Effect sizes: Using Hedge's g method gave us the effect sizes: BDI-II = 0.09; WSAS = 0.21; EQVAS = 0.14

CA ITT analysis: Results investigating the effect of the number of intervention sessions on BDI-II, WSAS and EQ-VAS scores using the CAITT analysis showed the following "per nurse treatment-session " effects on average score: BDI-II (-0.37, 95% CI: -0.68,-0.07, p=0.017), WSAS (-0.33, 95% CI: -0.55,-0.10, p=0.004) and EQ-VAS (0.38, 95% CI: -0.13,0.88, p=0.142), indicating statistically significant improvements (decreases) per session in BDI-II and WSAS scores of -0.37 and -0.33, respectively. We then multiplied the per session effect by the number of sessions attended, which would lead to a reduction in BDI-II score of 3.7 points and a reduction in WSAS scores of 3.3 points more in intervention patients than controls if all 10 intervention sessions were attended. This assumes from the analysis that each session is likely to have the same effect on outcome and thus the effect of the sessions attended is additive.

Masking of the final assessment: Agreement between the trial arm allocation and guesses of the research nurses undertaking the final patient assessment (n=361) was low (kappa=0.281, p<0.001), indicating successful blinding of the outcome assessments.

Discussion:

Principal findings

There was no significant improvement in depression score (BDI-II) or quality of life (EQ-5D) at 24 months follow-up in the overall sample, but there was an improvement in social functioning (WSAS). The contamination adjusted intention to treat analysis (CA ITT), conducted to assess the effect of the number of sessions received, demonstrated a positive per session effect for both BDI-II and WSAS scores. From this CA ITT analysis it could be inferred that patients attending all 10 intervention sessions might be expected to reduce their BDI-II score by 3.7 points more than control patients.. Given the chronicity of this patient group and the severity of their baseline depression and functional impairment, this improvement is encouraging. The higher level of nurse visits in the intervention group was expected, given the nature of the intervention. Both groups had very high levels of GP contact at baseline, which dropped slightly at follow-up, but were not significantly different between the two groups. Antidepressant usage dropped slightly in both groups over the follow-up period, but was significantly higher in the intervention group. There was no evidence that outcome varied by baseline diagnostic group.

Strengths and limitations

A particular strength was our large, nationally representative sample. The intervention was manualised, straightforward to implement and underwent successful piloting before the trial. Patients were rigorously assessed using standard diagnostic instruments, quality assurance for delivery of the intervention and outcome assessments was ensured and research blinding maintained. The study was conducted across 42 UK general practices, but with fewer practices from deprived ethnically diverse inner city areas resulting in a low proportion of participants from black and minority ethnic groups, so the results may be less applicable to

these populations. Approximately 25% of patients initially approached attended and completed baseline interviews, which might be a limitation as regards generalisability, but analysis of our baseline data indicated that those participating were a severely affected and highly morbid group[25]. This was also reflected in their high rates of GP visits at baseline, which were nearly three times higher than general population figures[26]. There was some attrition over the trial period (74% completed 24 month assessments), although this is reasonable for this population and similar to other studies[10].

In our pilot trial there were no identified issues of contamination. There was very little contact between the practice nurses and control patients, and where this occurred they were reviewed exclusively for physical health problems. There may have been a small risk of contamination in the main trial, which if present would lead to an underestimation of the effectiveness of the intervention.

Implications of these findings with reference to other studies

Our trial focused on the practice nurse as case manager within a chronic care model, with primary care support but, unlike US models of collaborative care, no input from specialist mental health services apart from for individual patients as part of their routine clinical care. This model is similar to that shown to be effective and in widespread use for other long-term conditions such as diabetes and COPD[27], and could be more easily implemented in a primary care setting using existing staff, such as practice nurses with no previous specific training in mental health. Practice nurses are available in many health care systems and achieve good results in managing other long-term conditions[28]. However, their training has been inadequate for working with people with mental health problems[29], which was something we aimed to address with a focused, brief training course and clinical supervision over the study period.

A systematic review of randomised controlled trials of case management for depression in primary care highlighted a range of factors likely to be associated with a positive outcome, several of which were present in this trial[30]. Systematic tracking of patients by a provider other than the doctor was significantly associated with improved depression outcomes and could be further improved by incorporating patient preferences into care, which were both factors we included. Practice nurses in our trial received brief training in simple problem solving and motivational interviewing techniques[15,16]. Our qualitative evaluation indicated they used a problem-solving approach but made little use of motivational interviewing techniques in delivering the intervention[31]. They were encouraged not to consider themselves as therapists delivering a psychological intervention, but to refer patients to local psychological therapy services if indicated. However, they reported that access to psychological therapies was often not readily available for their patients, and their role in facilitating access to such treatments was therefore limited. Increased availability of appropriate, evidence based psychological therapies might have improved patient outcomes.

Our results suggest improvements in functioning were greater than changes in symptoms of depression. This positive impact on functional impairment may be particularly important as there is evidence it is more significant in those with moderate to severe depression[32]. Whilst the functional impairment and disability associated with depression is often noted, there is relatively little emphasis on treatments which may positively impact on this[33,34]. If participants engaged with the intervention and attended all the review sessions they had statistically significant improvements per session in both depressive symptoms and functional impairment. The two are likely to be linked and, although traditionally it is often considered that an improvement in mood leads to improved functioning, the converse may also be the case and it may be that in the context of chronic depression it may be possible to improve functioning without great improvements in depressive symptoms. The absolute difference in functioning (WSAS) score in our study was modest, and its clinical significance is unclear. However the results from our linked qualitative study gives support to some patients reporting meaningful changes in functioning resulting from the intervention[35]. Most participants reported an impact on some aspect of their lifestyle, with potential impacts on diet, increasing exercise and sleep.

Implications for clinicians and policymakers

Systematic reviews of randomised trials involving patients with depression in primary care or community settings have included predominantly acute cases[11]. Our population was more chronic and morbid and potentially more difficult to treat[25], with very high baseline rates of GP consultations. Practice nurses are a widespread resource and in regular contact with such patients for their physical care, but often feel poorly skilled in working with mental health problems[29]. The training we provided was very well received[31] and we would encourage more widespread development of specific, and if possible more intensive, training courses for practice nurses in common mental health problems. We allowed the nurses to decide which approach to take with the patients with reference to the training they had received, but the training was of necessity brief and it would be interesting to see whether a more prescriptive approach to the management of these patients would give different results.

A difficult initial interaction with the nurse, patients who appeared to lack the motivation or time to attend appointments, were reluctant to discuss their difficulties or felt pessimistic that their situation might improve were all factors linked with poor attendance and such patients had poorer outcomes[31]. It may be appropriate for patients who do not engage well with the practice nurse as case manager to see someone with a mental health background in this role. Our trial suggests participants who engaged well and attended all sessions had more positive outcomes, irrespective of the severity or chronicity of their depression at baseline. We obtained useful information from our qualitative work, suggesting early development of rapport with the practice nurse and motivation to change were important features of engagement[31]. This has implications for clinicians considering patient suitability for this type of service.

Our findings indicate that practice nurse-led enhanced care for chronic and recurrent depression shows promise for motivated patients from this highly morbid group in primary care. This model of care may have value in other health care systems with limited access to secondary care psychology or psychiatric services and should be evaluated in these settings.

Conclusions

Patients with chronic or long-term depression are a neglected group as regards both clinical management and research into effective interventions. In our trial, whilst overall improvements in depressive symptoms were small and non-significant for patients receiving the intervention, there were significant improvements in work and social functioning. Further supplementary analysis indicated patients who regularly attended sessions over two years did well, with improvements in both depressive symptoms and functioning. In any implementation, it is key to identify patients more likely to engage with and benefit from such an intervention. The nurses' focus and approach on practical goals and problem solving may have contributed to the improved levels of functioning obtained.

Authors, qualifications, affiliations and addresses

* Marta Buszewicz, MBBS, MRCGP, MRCPsych., Clinical Senior Lecturer[1]; Mark Griffin, MSc, Lecturer[1]; Elaine M McMahon, BA, MPhil, Research Fellow[1]; Kate Walters, MBBS, MSc, PhD, Clinical Senior Lecturer[1], Michael King, MBBS, PhD, FRCPsych., Professor[2]

[1] Research Department of Primary Care & Population Health, University College London (Royal Free Campus), Upper 3rd Level Rowland Hill Street, London NW3 2PF.

[2] Division of Psychiatry, Faculty of Brain Sciences, University College London, Charles Bell House, 67-73, Riding House Street, London W1W 7EH

* Corresponding author m.buszewicz@ucl.ac.uk   (contact address as1 above)

Author contributions:

Ethical Approval

All participants gave written, informed consent. Ethics approval was given by the Royal Free Hospital Ethics Committee – REC reference number 07/Q0501/15

Trial registration:

The trial is registered on the Current Controlled Trials website – ISRCTN number 36610074
http://www.controlled-trials.com/ISRCTN36610074http://www.controlled-trials.com/ISRCTN36610074

Acknowledgements

Role of the funding source

Role of the sponsor:

Declaration of interest:

All authors declare no competing interests

References:
*Indicates references describing psychometric tests and statistical procedures (13, 14 and 17 – 23

1. Murray CJL, Lopez AD. *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries and Risk Factors in 1990 and Projected to 2020.* Geneva, Switzerland; World Health Organization, 1996.

2. Wells KB, Stewart A, Hays RD, Burnam A, Rogers W, Daniels M et al., The functioning and well-being of depressed patients. Results from the medical outcomes study. *JAMA* 1989; 262: 914–9.

3. Wells KB, Burnam MA, Rogers W, Hays R, Camp P. The course of depression in adult outpatients. Results from the medical outcomes study. *Archives General Psychiatry* 1992; 49: 788–94.

4. Conradi, HJ, de Jonge P, Ormel J. Prediction of the three-year course of recurrent depression in primary care patients: different risk factors for different outcomes. *Journal of Affective Disorders* 2008; vol. 105, no. 1–3, pp. 267–271.

5. Lloyd KR, Jenkins R, Mann A. Long term outcome of patients with neurotic illness in general practice. *British Medical Journal* 1996; vol. 313, no. 7048, pp. 26–28.

6. Arroll B, Moir F. Time for a rethink of treatment for patients with depression in primary care. *British Journal of General Practice* 2010; 60 (578): 641-2

7. Katon W, Robinson P, Von Korff M, Lin E, Bush T, Ludman E et al., 'A multifaceted intervention to improve treatment of depression in primary care', *Archives of General Psychiatry* 1996; 53: 924-32

8. Simon GE, Katon WJ, VonKorff M, Unützer J, Lin EH, Walker EA et al. Cost-effectiveness of a collaborative care program for primary care patients with persistent depression. *American Journal of Psychiatry* 2001; Oct; 158(10): 1638-44.

9. Katon WJ, Rutter C, Ludman E, von Korff M, Lin E, Simon G et al. A Randomised Trial of Relapse Prevention of Depression in Primary Care. *Archives of General Psychiatry* 2001; 58: 241-247

10. Rost K, Nutting P, Smith JL, Elliott CE, Dickinson M. Managing depression as a chronic disease: a randomised trial of ongoing treatment in primary care. *British Medical Journal* 2003; 325: 934

11. Gilbody S, Bower P, Fletcher J, Richards D, Sutton A. Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. *Archives of Internal Medicine* 2006; 166 : 2314-21

12. Buszewicz, Griffin M, McMahon E, Beecham J, King M. Randomised controlled trial of structured, proactive nurse-led care for chronic depression in primary care: the ProCEED trial. *BMC Psychiatry* 2010, 10:61 (4 August 2010)

13. Kessler RC, Abelson J, Demler O, Escobar JI, Gibbon M, Guyer ME et al. Clinical calibration of DSM-IV diagnoses in the World Mental Health (WMH) version of the World Health Organization (WHO) Composite International Diagnostic Interview (WMH-CIDI). *International Journal of Methods in Psychiatric Research* 2004; 13(2): 122-139.*

14. Arnau R, Meagher MW, Norris MP, Bramson R. Psychometric Evaluation of the Beck Depression Inventory-II with Primary Care Medical Patients. *Health Psychology* 2001, 20(2):112-119.*

15. Mynors-Wallis LM, Gath DH, Day A, Baker F. Randomised controlled trial of problem solving treatment, antidepressant medication, and combined treatment for depression in primary care. *British Medical Journal,* 2000; 320(7226):26-30.

16. Rollnick S, Heather N, Bell A. Negotiating behaviour change in medical settings: The development of brief motivational interviewing. *Journal of Mental Health* 1992, 1:25-37.

17. Mundt JC, Marks IM, Shear MK, Greist JM. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. *British Journal of Psychiatry* 2002; 180(5): 461.*

18. Brooks R. EuroQol: the current state of play. *Health Policy* 1995; 37: 53-72.*

19. King M, Davidson O, Taylor F, Haines A, Sharp D, Turner R. Effectiveness of teaching general practitioners skills in brief cognitive behaviour therapy to treat patients with depression: randomised controlled trial. *British Medical Journal* 2002; 324: 947.*

20. Rabe-Hesketh S, Skrondal A. *Multilevel and Longitudinal Modelling using STATA* (Second Edition) 2008 ; STATA Press.*

21. Vickers AJ, Altman DG. Analysing controlled trials with baseline and follow up measurements. *British Medical Journal* 2001; 323: 1123-1124.*

22. Hedges LV. Distribution theory for Glass's estimator of effect size and related estimators. *Journal of Educational Statistics* 1981; 6 (2): 107–128. doi:10.3102/10769986006002107.*

23. Sussman J, Hayward R. Using instrumental variables to adjust for treatment contamination in randomised controlled trials. *British Medical Journal* 2010; Volume 340: 1181-84, c2073 doi: 10.1136/bmj.c2073.*

24. Edwards PJ, Roberts IG, Clarke MJ, DiGuiseppi C, Wentz R, Kwan I et al. Methods to increase response rates to postal questionnaires. *Cochrane Library* 2008, 4, (Review).

25. McMahon EM, Buszewicz M, Griffin M, Beecham J, Bonin E, Rost F et al. Chronic and recurrent depression in primary care: socio-demographic features, morbidity and costs. *International Journal of Family Medicine* 2012; 316409. Published online 2012 June 6. doi: 10.1155/2012/316409

26. *Trends in Consultation Rates in General Practice - 1995-2009*, Health and Social Care Information Centre, 2009, http://www.hscic.gov.uk/pubs/gpcons95-09 (last accessed 12th June 2014)

27. Wagner EH, Austin BT, Von Korff M. Organising care for patients with chronic illness. *Millbank Quarterly* 1996; 74: 511-544.

28. Bodenheimer T, MacGregor K, Stothart N. Nurses as leaders in chronic care. *British Medical Journal* 2005; 330: 612-3.

29. Crosland A, Kai J. They think they can talk to nurses: practice nurses' views of their roles in caring for mental health problems. *British Journal of General Practice* 1998; 48: 1383-1386.

30. Christensen H, Griffiths K, Gulliver A, Clack D, Kljakovic, Wells L. Models in the delivery of depression care: a systematic review of randomised and controlled intervention trials. *BMC Family Practice* 2008; 9:25

31. Bennett M, Walters K, Drennan V, Buszewicz M. Structured Pro-Active Care for Chronic Depression by Practice Nurses in Primary Care: a Qualitative Evaluation. *PLOS ONE* 12 Sep 2013; 10.1371/journal.pone.0075810

32. Mintz J, Mintz LI, Arruda MJ, Hwang SS. Treatments of depression and the functional capacity to work. *Archives General Psychiatry* 1992 Oct; 49 (10): 761-8.

33. Greer TL, Kurian BT, Trivedi MH. Defining and measuring functional recovery from depression. *CNS Drugs* 2010 Apr; 24(4):267-84. doi: 10.2165/11530230-000000000-00000.

34. McKnight PE, Kashdan TB. The importance of functional impairment to mental health outcomes: a case for reassessing our goals in depression treatment research. *Clinical Psychology Review* 2009 April; 29(3): 243. doi:10.1016/j.cpr.2009.01.005.

35. Buszewicz M, Griffin M, Beecham J, Bonin E, Hutson M. *ProCEED, Report of a study of pro- active care by practice nurses for people with anxiety and depression* 2011, Mind publications: London.

Figure 1: Consort Diagram: Recruitment and treatment group allocation

Enrolment

Potential participants identified (n = 3,293)
-Computer search (n=2,974)
-GP (n=188)
-Poster/ self-referral (n=34)
-No information (n=97)

Invited to participate (n = 3,293)

Scheduled for recruitment interview (n = 959)

Attended recruitment interview (n = 828)

Excluded (n = 270)
-Ineligible (score below 14 on BDI-II n=157)
-Ineligible (not meeting CIDI criteria n = 83)
- Chose not to participate (n= 30)

Allocation

Allocated to control group (n=276)

Follow-up

Withdrawals (n = 30)
- Felt better (1)
- No reason given (13)
- Upset by study (8)
- Study not useful (3)
- Physical illness (5)

Drop-outs (n=11)

Died (n = 0)

Withdrawals (n = 36)
- Felt better (2)
- No reason given (16)
- Upset by study (11)
- Study not useful (3)
- Physical illness (4)

Drop-outs (n=14)

Died (n = 1)

Analysis

Included in primary analysis (n = 235)

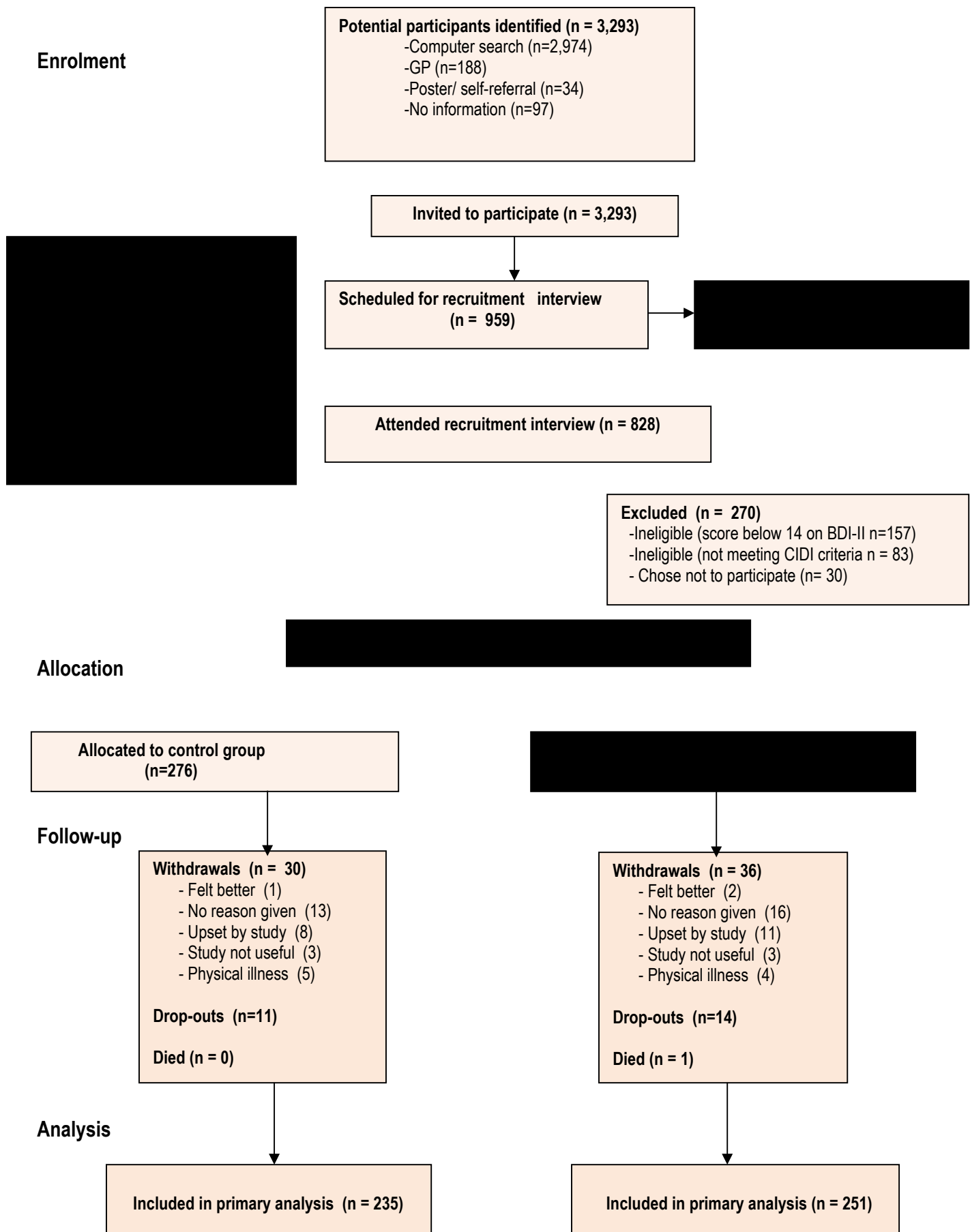**Included in primary analysis (n = 251)**

Table 1 - Baseline socio-demographic characteristics, diagnoses, symptoms, function and health services utilisation. (Service use data refers to the 24 months prior to the baseline assessment).

		Intervention	Control
Age (years)	Mean (StandardDeviation : S.D)	48.3 (12.3)	48.4 (13.4)
Gender	Female	217 (77.0%)	201 (72.8%)
Marital Status	Married	133 (47.7%)	127 (46.9%)
Living with	Partner/children	212 (76.3%)	188 (69.1%)
Accommodation	Owner-occupied	188 (68.6%)	179 (66.1%)
Ethnicity	White UK	251 (90.6%)	241 (89.3%)
Employment	Paid	137 (48.9%)	121 (44.8%)
Diagnosis (CIDI)	Chronic major depression	78 (28.1%)	86 (31.6%)
	Recurrent depression	155 (55.8%)	142 (52.2%)
	Dysthymia	45 (16.2%)	44 (16.2%)
BDI-II	Mean (S.D.) Number (N)	31.9 (9.8) 278	33.1 (10.6) 272
WSAS	Mean (S.D.) N	22.1 (9.6) 280	22.4 (9.4) 272
EQ-VAS	Mean (S.D.) N	54.5 (19.5) 281	52.8 (20.1) 269
GP visits	Mean (S.D.) N	15.5 (9.9) 270	15.8 (9.7) 271
GP home visits	Mean (S.D.) N	0.2 (1.2) 236	0.2 (0.9) 224
Practice nurse visits	Mean (S.D.) N	3.9 (4.7) 258	4.5 (5.1) 254
Practice counsellor visits	Mean (S.D.) N	0.7 (2.6) 258	0.4 (1.4) 254
Referrals to psychological therapy/psychotherapy	Mean (S.D.) N	0.4 (0.9) 155	0.3 (0.6) 145
Referrals to psychiatrist /community mental health team	Mean (S.D.) N	0.4 (0.7) 154	0.6 (1.8) 154
Number of months on antidepressants	Mean (S.D.) N	14.1 (8.8) 267	12.7 (8.3) 269

CIDI : Composite International Diagnostic Interview; BDI-II : Beck Depression Inventory; WSAS : Work and Social Activity Scale; EQ-VAS : Euroquol Visual Analogue Scale

Table 2 - BDI-II scores across follow-up times

		3 months	6 months	12 months	18 months	24 months
Control (n = Number)	Mean (S.D.) n	29.2 (12.8) 180	28.8 (13.8) 167	27.9 (13.6) 166	27.3 (13.6) 152	26.0 (14.9) 206
Intervention (n = Number)	Mean (S.D.) n	28.1 (12.3) 221	25.8 (12.7) 201	25.2 (12.8) 201	25.1 (14.4) 196	22.1 (14.2) 224

S.D. : Standard Deviation

Table 3 – Outcomes at 24 months follow-up
(Service use data refers to the 24 months prior to the 24 month follow-up assessment).

		Intervention	Control
WSAS	Mean (S.D.) n	16.2 (12.1) 224	18.8 (12.1) 205
EQ-VAS	Mean (S.D.) n	61.7 (21.6) 214	58.0 (21.4) 201
GP visits	Mean (S.D.) n	13.7 (9.5) 234	13.4 (9.1) 226
GP home visits	Mean (S.D.) n	0.1 (0.6) 193	0.1 (0.5) 190
Practice nurse visits	Mean (S.D.) n	5.5 (6.6) 234	4.8 (6.6) 226
Practice counsellor visits	Mean (S.D.) n	0.7 (2.1) 234	0.4 (1.6) 226
Referrals to psychological therapy/psychotherapy	Mean (S.D.) n	0.6 (1.2) 133	0.3 (0.6) 119
Referrals to psychiatrist /community mental health team	Mean (S.D.) n	0.6 (1.4) 117	0.4 (0.8) 126
Number of months on antidepressants	Mean (S.D.) N	13.6 (9.7) 261	11.7 (9.6) 250
Diagnosis (CIDI)	Chronic major depression	27 (13.8%)	28 (16.6%)
	Recurrent depression	87 (44.4%)	60 (35.5%)
	Dysthymia	25 (12.8%)	27 (16.0%)
	No episodes of depression	57 (29.1%)	54 (32.0%)

WSAS : Work and Social Activity Scale; EQ-VAS : Euroquol Visual Analogue Scale