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1 **Effect of collaborative care vs usual care on depressive symptoms among older adults with sub-**
2 **threshold depression: the CASPER randomized clinical trial**
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4

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38

39 **KEY POINTS**

40

41 **Question:** Is collaborative care an effective method to reduce depressive symptoms in older people

42 with low severity depression?

43

44 **Findings:** : In the CASPER randomized trial of 705 participants age 65 and older with sub-threshold

45 depression, those randomized to a collaborative care intervention had lower depression scores,

46 measured by the Patient Health 9-item questionnaire at 4 month follow-up, compared to usual care.

47

48 **Meaning:** Among older adults with subthreshold depression, a collaborative care intervention

49 reduced depressive symptoms at 4-month follow-up, compared to usual care. The long term efficacy

50 of this intervention is unclear.

51

52 **ABSTRACT (350 words)**

53 **Importance:** There is little evidence to guide management of depressive symptoms in older people.

54 **Objective:** To evaluate whether a collaborative care intervention can reduce depressive symptoms

55 and prevent more severe depression in older people.

56 **Design, Setting, Participants:** Randomized clinical trial, conducted from 24th May 2011 to 14th Nov

57 2014 in 32 primary care centers in United Kingdom. 705 participants aged 65 and over with DSM-IV

58 sub-threshold depression were randomized (1:1).

59 **Intervention:** Collaborative care was coordinated by a case manager who assessed functional

60 impairments relating to mood symptoms. Participants were offered behavioural activation and

61 completed an average of 6 weekly sessions. The control group received usual primary care.

62 **Main Outcomes:** Participants were followed up for 12 months. Primary outcome was self-reported

63 depression severity at 4 month follow-up, measured by the Patient Health Questionnaire-9 item

64 (PHQ-9, range 0-27). Included among 10 pre-specified secondary outcomes were the PHQ 9 score at

65 12-month follow-up and the proportion meeting criteria for depressive disorder (defined as PHQ9

66 score >/= 10) at 4 and 12 month follow-up.

67 **Results:** 705 participants were randomised (344 intervention vs 361 usual care) (58% female, mean

68 age 77 (SD 7.1)). 4 month retention was 83% with higher loss to follow-up in collaborative care

69 (82/344 - 24%) compared to usual care (37/361 - 10%). Collaborative care resulted in lower PHQ-9

70 scores as compared to usual care at four month follow-up (mean PHQ-9 collaborative care: 5.36;

71 mean usual care: 6.67; mean difference: -1.31, 95% CI: -1.95 to -0.67, p<.001). Treatment

72 differences remained at twelve months (mean PHQ-9 collaborative care = 5.93, mean PHQ-9 usual

73 care = 7.25; mean difference: -1.33 points, 95% CI: -2.10 to -0.55). The proportions of participants

74 meeting criteria for depression at four month follow-up were 17.2% (45/262) vs 23.5% (76/324),

75 respectively (difference = -6.3%. 95%CI -12.8, 0.2, Relative Risk 0.83, 95% CI: 0.61 to 1.27, p=0.247)

76 and at 12-month follow-up were 15.7% (37/235) vs. 27.8% (79/284) (difference = -12.1%, 95%CI -

77 19.1, -5.1, Relative Risk 0.65, 95%CI 0.46 to 0.91, p=0.013).

78 **Conclusion and Relevance:** Among older adults with sub-threshold depression, collaborative care

79 compared with usual care resulted in a statistically significant difference in depressive symptoms at

80 4-month follow-up, of uncertain clinical importance. Although differences persisted through 12

81 months, findings are limited by attrition, and further research is needed to assess longer-term

82 efficacy.

83 Trial Registration: Current Controlled Trials ISRCTN02202951

84 http://www.isrctn.com/ISRCTN02202951

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87

88 **BACKGROUND**

89 Depression is the second leading cause of disability worldwide.(1) One in seven older people meet

90 criteria for depression (2). Effective therapeutic strategies are needed in older people with

91 depressive symptoms who also have comorbid diseases and impaired quality of life.(2)(3)(4) There is

92 limited research about older people with mild depressive disorders who have insufficient levels of

93 depressive symptoms to meet diagnostic criteria (called 'sub-clinical', 'sub-threshold' or 'sub-

94 syndromal' depression) (5) but also reduced quality of life and function.(4) Sub-threshold

95 depression is a risk factor for more severe depressive illness.(6) With increased interest in

96 preventive approaches to depression (7), trials have focused on adults with sub-threshold

97 disorders.(8) The focus of this research was older people with low level depressive symptoms.

98

99 The prescription of anti-depressants is not recommended as a first line treatment for sub-threshold

100 depression since there is little evidence they are effective. Psychological therapies may be more

101 appropriate, but higher intensity forms of therapy such as Cognitive Behaviour Therapy,

102 Interpersonal Therapy or Behavioural Activation (BA) are generally reserved for people with more

103 severe disorders.(9) Collaborative care involves the provision of care by a trained case manager

104 under the principles of chronic disease management.(10) A meta-analysis reported that

105 collaborative care is effective for people with depression meeting diagnostic thresholds (11), but its

106 ability to prevent depression in high risk populations has not been examined. The objective of this

107 study was to evaluate the effect of a collaborative care intervention in older people with sub-

108 threshold depression in a UK primary care setting.

109

110 **METHODS**

111 This trial was a pragmatic, multi-centre, two-group, parallel, randomized clinical trial. Older adults

112 with lower severity depressive symptoms recruited in primary care were randomized to receive

113 either usual care from their primary care physician or a collaborative care intervention in addition to

114 their usual primary care.

115

116 **Recruitment of participants and eligibility criteria**

117 This study was approved by the NHS Leeds East Ethics Committee on 28 September 2010

118 (10/H1306/61). Participants age 65 and older from 32 primary care practices gave written informed

119 consent between March 2011 and July 2013 in the North of England, UK. Prior to the definitive trial

120 an internal pilot was conducted with 100 participants where the age of participants was 75 years and

121 above. The age cut point was reduced from 75 to 65 following advice from the Trial Steering

122   Committee to align the trial population with an age-specific demarcation in the UK where patients

123   aged 65 and older are treated by older persons' mental health services.

124

125   Potential participants were identified by postal questionnaire and were eligible if they reported

126   depressive symptoms on a standardised brief 2 item case-finding tool (the Whooley questions - *Q1:*

127   *Over the past month have you been bothered by feeling down, depressed or hopeless? Q2: Over the*

128   *past month have you been bothered by having little or no interest or pleasure in doing things?*) (12)

129   and were found to have sub-threshold depression according to DSM-IV criteria using the Mini

130   International Neuropsychiatric Interview (MINI v5.0) (13), conducted over the phone by researchers

131   trained by clinical co-investigators. The participants' Primary Care Physician excluded people with

132   known alcohol dependency; psychosis; recent suicidal risk; significant cognitive impairment; recent

133   bereavement or terminal illness on clinical grounds (based on their knowledge of the patient).

134   People receiving psychological therapy were excluded. Participants receiving antidepressants

135   remained eligible. Ethnicity was recorded by self-report to describe the diversity of participants.

136

137   **Randomisation, concealment and blinding**

138   Participants were allocated to collaborative care or usual care by a computer in a 1:1 ratio by simple

139   randomization without blocking or stratification. Treatment allocation was concealed from study

140   researchers at the point of recruitment using an automated computer data entry system,

141   administered remotely by the York Trials Unit which employed a computer-generated code. None of

142   the participants, primary care practices or clinicians were blinded to treatment allocation.

143   Researchers who assessed outcomes were blind to treatment allocation.

144

145   **Intervention (collaborative care) and comparator (usual GP care)**

146   Participants in the intervention group received a programme of collaborative care, designed

147   specifically for older people with sub-threshold depression and to accommodate long term physical

148   health problems (see (15) for an extended description). Collaborative care was delivered by a case

149   manager (with a background in mental health nursing or a graduate psychologist) over eight weekly

150   sessions.(16) The intervention consisted of telephone support and session by session symptom

151   monitoring to track treatment response. The case managers were supervised and corresponded

152   with the primary care physician or older-age psychiatrist where necessary. The first session was

153   delivered face-to-face and subsequent sessions via telephone. A computer system was used to

154   monitor care and supervision of case managers was offered by DB, DF, DE, DM, JD and SG.

155   Participants were offered a structured programme of behavioural activation.(17) This brief

156 psychological intervention addressed the behavioural deficits of depression such as avoidance of

157 social interaction and the absence of rewarding activities.(18) Participants already prescribed anti-

158 depressants were encouraged to continue medication and primary care physicians were only

159 encouraged to initiate medication in response to increasing depressive symptoms.(9)

160

161 Participants in the control group were allocated to receive usual primary care. They received no

162 additional care to the usual primary care management of sub-threshold depression.

163

164 **Outcomes**

165 The primary outcome was self-reported severity and symptoms of depression, assessed by the

166 Patient Health Questionnaire-9 items (PHQ-9),(19) at four months. The PHQ-9 has a score range 0

167 (least depressed) to 27 (most depressed). Secondary exploratory outcomes included the PHQ-9

168 depression severity at 12 months; and at 4 and 12 months: dichotomised depression according to

169 'depression diagnosis', defined using an optimum cut point of PHQ-9≥10, which has been validated

170 as a sensitive and specific criterion for DSM-IV Major Depressive Disorder.(19) We also studied a

171 limited range of secondary exploratory outcomes of decrements and comorbidities associated with

172 depression, including health-related quality of life measured by the 12 item short form survey (SF-

173 12) mental component scale and physical component scale, score range 0 (lowest level of health) to

174 100 (highest level of health) (20); anxiety, measured by the Generalized Anxiety Disorder

175 Assessment (GAD-7), score range 0 (no anxiety) to 21 (severe anxiety) (21) and self-reported

176 prescribed mental health medication. Data were also collected on somatoform complaints,

177 measured by the Patient Health Questionnaire-15 items (PHQ-15), score range 0 to 28 (higher scores

178 indicate greater physical impairment, item on menstrual problems was excluded) (22); and

179 psychological resilience, measured by the two-item Connor-Davidson Resilience Scale (CD-RISC2)

180 which has a score range of 0 to 8, a higher score indicating greater psychological resilience (23), but

181 these were not statistically evaluated. Questionnaires were administered by researchers blinded to

182 treatment allocation. Resource use was ascertained from primary care records, and Quality

183 Adjusted Life Years (QALYs) were measured using the EuroQol (EQ-5D-3L), score range 0 (death) to 1

184 (perfect health)(24) though the cost-effectiveness analysis is not reported here. Death during

185 follow-up was pre-specified as an outcome and measured via linkage to mortality data from the UK

186 Office for National Statistics (ONS). In our trial protocol we indicated that the number of falls would

187 be recorded, but we decided not collect these data before the first participant was randomised.

188

189 **Sample size**

190   In order to detect a small to medium standardised minimum effect size of 0.3 (based on a meta-

191   analysis of previous trials of collaborative care,(25), corresponding to approximately 1.3 PHQ-9 score

192   points) with 80% power and a two-sided 5% significance level, 352 patients were required (176 in

193   each group). Although this was an individually-randomised trial, the sample size was inflated to

194   account for potential clustering around case managers and potential loss to follow-up of 25%. The

195   final sample size to be recruited was 658 patients, 329 in each group.

196

197   **Statistical analysis**

198   **Primary analysis:** Patients were analysed as part of the group to which they had been randomised

199   (intention-to-treat) using a linear mixed model if they had valid primary outcome data at 4 or 12

200   months follow-up and a baseline PHQ-9 and SF-12 physical component score. The primary analysis

201   model included as fixed effects: time (4 or 12 months), treatment group and time-by-treatment

202   interaction, adjusting for PHQ-9 depression at randomization and physical/functional limitations (SF-

203   12 physical component score) at baseline.   The primary endpoint was the estimate of the

204   intervention effect at 4 months.

205

206   **Secondary exploratory Analyses of the Primary Outcome:** To quantify the effect of the grouping by

207   case managers, these were modelled separately in each treatment group. Additional variables

208   associated with PHQ-9 scores at 4 months (age, gender, GAD-7, PHQ-15, mental health medication

209   use and previous history of depression based on M.I.N.I. responses) were included as covariates in

210   the primary analysis model. To investigate the effect of missing data on the treatment effect, any

211   baseline variables associated with non-response at four months follow-up (i.e. no valid PHQ-9 score)

212   were identified and included as covariates in the primary analysis model. In light of the observed

213   differential dropout a multiple imputation model of the primary analysis was additionally included.

214

215   **Secondary exploratory Outcomes:** Analysis of secondary outcomes was exploratory, and no

216   adjustments for multiple testing were applied. The estimate of the effect of the intervention on

217   PHQ-9 scores at 12 months was extracted from the primary analysis model. For the dichotomous

218   outcome of depression diagnosis' at follow-up (PHQ-9 ≥ 10), data were analysed by logistic

219   regression with Poisson regression models to calculate adjusted relative risks. For other exploratory

220   continuous secondary outcomes (SF-12, GAD-7), statistical analyses were conducted using a similar

221   model to the primary analysis. Other collected data (PHQ-15 and CD-RISC2) were summarized

222   descriptively.

223

224   Analyses used two-sided significance at the 5% level, and no adjustments for multiple comparisons

225   were made. All analyses were conducted in Stata version 13.1. The statistical analysis and reporting

226   of the trial followed the Consolidated Standards of Reporting Trial (CONSORT) guidelines.(26). The

227   study followed a trial protocol and all analyses followed a pre-specified statistical analysis plan (see

228   online supplement for (i) our study protocol and (ii) a detailed description of statistical analysis, with

229   a description of any amendments to protocol).

230

231

232   **RESULTS**

233   37,134 patients from 38 primary care centres were invited to participate by letter between March

234   2011 and May 2013. Of 6,693 patients who consented to be contacted and provided information

235   about depressive symptoms, 4,259 were excluded (largely on the basis of negative results on the

236   two-item depression screen), and 2,434 patients were assessed for eligibility by the MINI diagnostic

237   interview.   705 (29%) patients were identified to have sub-threshold depression and were

238   randomized into the trial; 58% female, mean age 77 (SD 7.1). 344 were allocated to collaborative

239   care and 361 to usual care. The remaining patients were either classified as fulfilling no criteria for

240   depression (n=1,558, 64%) or as meeting criteria for major depressive disorder (MDD) (n=171, 7%)

241   (see CONSORT diagram in Figure 1). The primary outcome (PHQ-9 depression severity at 4 months)

242   was available for 586 patients, representing a loss to follow-up of 16.9% (23.8% in the collaborative

243   care group and 10.2% in the usual care group). At 12 month follow-up, 519 patients were retained,

244   with loss to follow up of 26.4% at 12 months (31.7% in the collaborative care group and 21.3% in the

245   usual care group).

246

247

248   **<Figure 1> CONSORT diagram**

249

250   The two groups were comparable at baseline (Table 1). The median depression severity in both

251   groups based on the PHQ-9 was 7, consistent with a low severity depression.(19) Prescription rates

252   of antidepressants were low at baseline (collaborative care 10%, usual care 14%).

253

254   <Table 1>

255

256   **Delivery of collaborative care intervention**

257   Collaborative care was delivered by 18 case mangers (mean case load of 19.1 randomised patients).

258   Participants received on average six sessions (median: 7, minimum 1, maximum 15) over seven to

259   eight weeks, of which two were delivered face-to-face, and four were delivered over the phone. The

260   average session duration was half an hour.

261

262

Depression severity at follow-up

At four month follow-up (primary outcome) there was a between-group difference of -1.31 PHQ-9

score points (95% CI: -1.95 to -0.67, p<.001) equivalent to a standard effect size of 0.3 in favour of

collaborative care. At 12 month follow-up (exploratory outcome) a between group difference

remained (-1.33 PHQ-9 score points; 95% CI: -2.10 to -0.55, p=.001). See Table 2 for full results,

including sensitivity analyses.

<Table 2>

Depression diagnosis (PHQ9>=10) at follow-up

In secondary exploratory analyses, the proportion of participants with a new depression diagnosis

(PHQ-9 ≥ 10) was lower in the collaborative care group at 12-month follow-up, but not at 4-month

follow-up , (four months: 17.2% vs 23.5%, difference = -6.3%. 95%CI -12.8, 0.2, Relative Risk = 0.83 ,

95% CI: 0.61 to 1.27, p=0.247; 12 months: 15.7% vs. 27.8%, difference = -12.1%, 95%CI -19.1, -5.1,

Relative Risk 0.65, 95%CI 0.46 to 0.91, p=0.013). See Table 2.

Antidepressant use

In secondary exploratory analyses, the relative risk of being prescribed antidepressants was not

different between the two groups at four months follow-up (Relative Risk: 0.73, 95% CI: 0.51 to 1.04,

p=0.083) or at twelve months follow-up (Relative Risk: 0.84, 95% CI: 0.60 to 1.19, p=0.327).

Health Related Quality of Life

In secondary exploratory analyses, the physical health of patients was better for collaborative care

at4 and 12-month follow-up (mean score differences: -2.83 at 4 months, 95% CI: -4.03 to -1.62,

standard effect size *d*=0.2, p <.001; -1.67 at 12 months, 95% CI: -3.06 to -0.27, *d*=0.1, p=.020 – see

Figure 2 and table 2). The mental health of patients was better for collaborative care at 4 and 12

months in exploratory analyses (mean score differences: -1.88 at 4 months, 95% CI: -3.29 to -0.47 ,

d=0.2, p =.009; -2.15 at 12 months, 95% CI: -3.70 to -0.59, *d*=0.2, p=.007 – see Figure 2 and table 2).

Anxiety

Significant exploratory between group differences in anxiety symptoms (GAD-7) were observed in

favour of collaborative care at four month follow up (mean score difference: -1.08, 95% CI: -1.64 to -

0.52, *d*=0.3, p<.001) and at twelve month follow-up (mean score difference: -1.01, 95% CI: -1.61 to -

0.42, *d*=0.2, p=.001). See Figure 2 and Table 2.

297

298   **Somatoform complaints**

299   Physical health problems (PHQ-15) mean scores at 4 months were: collaborative care = 7.4, SD 3.99,

300   usual care = 9.1 SD 4.28. At 12 months PHQ-15 mean scores were: collaborative care = 8.1 SD 4.03,

301   usual care 9.2 SD 4.53. No statistical comparison was made. See Figure 2.

302

303   **Resilience**

304   Resilience scores at 4 and 12 months were as follows: 4month mean CD-RISC2 score, collaborative

305   care = 6.2, SD 1.71, usual care = 5.7 SD 1.71; 12 months CD-RISC2 score collaborative care = 6.1 SD

306   1.71, usual care 5.7 SD 1.77. No statistical comparison was made.

307

308   <Figure 2>

309

310   **Adverse events - mortality**

311   A total of 23 participants died during 12-month follow-up-, 5 patients in the collaborative care group

312   (1.5% of randomised patients) and 18 patients in the usual care group (5.0% of randomised patients)

313   which was statistically significant (χ_1=6.97, p =.008). All causes of death and their potential

314   relatedness to the trial treatment were assessed independently and presented to the Data

315   Monitoring and Ethics Committee (DMEC) in line with our procedures for serious adverse events.

316   Approximately 81% of deaths were categorised as unrelated to treatment, and 18% as unlikely to be

317   related to treatment. The DMEC committee assessed that the recorded causes of death could not

318   be reasonably attributed to either the intervention or control treatment. The exploratory observed

319   group difference in mortality is therefore treated as a chance result.

320

321   **DISCUSSION**

322   The main finding from this randomized trial is that a collaborative care intervention reduced the

323   PHQ-9 score at four month follow-up, compared to usual care. In secondary exploratory analyses,

324   the PHQ-9 score was also lower at 12-month follow-up in the collaborative care group, but high

325   attrition rates reduce confidence in this result. For populations with case level depression a

326   successful treatment outcome has been defined as five points on the PHQ9.(28) We did not observe

327   this magnitude of benefit in either group of the trial when comparing scores before and after

328   treatment, although this result would be anticipated given the lower baseline PHQ9 scores in

329   populations with subthreshold depression. The between-group difference was 1.31 PHQ9 points

330   which is a small to medium effect size according to Cohen (9, 27) and consistent with the Cochrane

331   meta-analysis of collaborative care(11), but is not large when judged against a clinical difference of 5

332   points advocated in more severe disorders (see (29)). In additional secondary exploratory analyses,

333   collaborative care prevented the onset of depression diagnosis (as ascertained by the PHQ9) by

334   12.1% at 12 months, but was non-significant at 4 months in an exploratory analysis.

335

336   The treatment of older people with subthreshold depression has been insufficiently studied. The

337   results of the trial are consistent with other research regarding collaborative care for depression in

338   older people.(11, 17, 30) However few studies to date have examined the effectiveness of

339   collaborative care in older people and explored the ability to prevent lower severity depression

340   symptoms progressing to the point of case level depression. Behavioural activation is a relatively

341   simple type of treatment that could be taught to and administered by a wide range of health care

342   professionals.(31)

343

344   We noted a reduction in mortality for people who received collaborative care, but independent case

345   by case review of deaths was not thought to be linked to the intervention. This was an unexpected

346   finding and one which deserves further study in future trials. We have considered the possibility

347   that people randomized to the control group were more unwell and that this might have influenced

348   the primary outcome. We think this explanation unlikely since the numbers who died were small in

349   relation to the size of the trial and there was evidence of balance between groups at baseline on

350   measures of symptoms severity and quality of life. We note that all secondary outcomes are also

351   exploratory.

352

353   There were several limitations to the study. First, the ascertainment of depression diagnosis was

354   exploratory and not ascertained using a standardised diagnostic interview (32) Second, there was

355   differential retention and attrition between the two groups. Participants who wished to discontinue

356   the collaborative care intervention fully withdrew from the trial at the same time, including follow-

357   up. It is possible that participants who withdrew may have presented a different outcome profile to

358   those who continued, which may have biased the treatment effect.   Third, there was no follow-up

359   after 12 months.

360

361   **Conclusions and relevance**

362   Among older adults with sub-threshold depression, collaborative care compared with usual care

363   resulted in a statistically significant difference in depressive symptoms at 4-month follow-up, of

364   uncertain clinical importance. Although differences persisted through 12 months, findings are

365   limited by attrition, and further research is needed to assess longer-term efficacy.

366

367

368

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376
377 **Acknowledgements**

383

Contributions of authors

Joy Adamson (Senior Research Fellow, Health Sciences) contributed to the development of the grant application and trial protocol. Supervised the conduct of qualitative research. Involved in qualitative analysis and writing the report.

Katie Atherton (Clinical Studies Officer, Health Sciences) case manager and contributed to the day-to-day running of the trial.

Della Bailey (Research Fellow, Health Sciences) developed manual/intervention post pilot phase. A case manager who also supervised case managers and trained them. Involved in writing the report.

Jacqueline Birtwistle (Research Assistant, Health Sciences) contributed to the day-to-day running of the trial.

Katharine Bosanquet (Research Fellow, Health Sciences) coordinated recruitment and the running of the core site, York. Managed the collection of objective data from all GP practices. Involved in writing the report; drafted the report.

Emily Clare (Clinical Studies Officer, CRN) coordinated recruitment and the running of the trial at the Newcastle site.

Jaime Delgadillo (Researcher and Cognitive Behavioural Psychotherapist, Leeds Community Healthcare NHS Trust) supervised case managers. Gave clinical input and advice during the trial.

David Ekers (Senior Clinical Lecturer, Health Sciences) contributed to the development of the grant application and trial protocol. Provided expertise and training in behavioural activation. Gave clinical input and advice during the trial. Local principal investigator.

Deborah Foster (Research Fellow, Health Sciences) developed manual/intervention post pilot phase. A case manager who also supervised case managers and trained them.

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Samantha Gascoyne (Trial Support Officer, Health Sciences) contributed to the day-to-day running of the trial. Involved in writing the report.

Simon Gilbody (Professor, Psychological Medicine and Health Services Research) contributed to the development of the grant application and trial protocol. Gave clinical input and advice during the trial. Chief Investigator who oversaw the study. Led the writing the report and is guarantor of this paper.

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Jodi Meredith (Trial Support Officer, Health Sciences) case manager and contributed to the day-to-day running of the trial.

Natasha Mitchell (Research Fellow, Health Sciences) contributed to the trial protocol and setting up of CASPER study. Initial CASPER study manager.

Karen Overend (Trial Support Officer, Health Sciences) contributed to the day-to-day running of the trial.

Madeline Pasterfield (Research Assistant, Health Sciences) case manager; tailored the training manual to be appropriate for older adults.

David Richards (Professor, Mental Health Services Research) contributed to the development of the grant application and trial protocol. Provided content expertise in the design of low intensity Collaborative Care.

Karen Spilsbury (Professor, Nursing) contributed to the development of the grant application and trial protocol. Supervised the conduct of qualitative research. Involved in qualitative analysis and writing of report.

Gemma Traviss-Turner (Senior Research Fellow, Health Sciences) coordinated recruitment and the running of the trial at the Leeds site.

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Rebecca Woodhouse (Trial Support Officer, Health Sciences) contributed to the day-to-day running of the trial. Involved in writing the report.

Friederike Ziegler (research fellow at the University of York) established a public and patient involvement (PPI) group which advised on the development of study materials

All authors approved and/or commented on the final manuscript.

Ethical Approval

This project received ethical approval from the UK National Research Ethics Service (Leeds West) review board on 28th September 2010 (approval reference 10/H1306/61)

Access to Data

Professor Simon Gilbody (Chief Investigator) and Ada Keding (trial statistician) had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclaimer

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Patient and Public Involvement (PPI) in Research

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Declaration of interests

The authors have no conflicts of interest to declare.

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Table 1: Baseline characteristics

Characteristic	As Randomised		As Analysed*	
	Collaborative Care (N=344)	Usual Care (N=361)	Collaborative Care (N=274)	Usual Care (N=327)
Age at consent (in years)				
N	344 (100.0%)	361 (100.0%)	274 (100.0%)	327 (100.0%)
Mean (SD)	77.1 (7.08)	77.5 (7.18)	76.6 (7.21)	77.4 (7.13)
Median (min, max)	77 (65, 96)	78 (64, 93)	77 (65, 93)	78 (64, 93)
Gender				
Male	159 (46.2%)	139 (38.5%)	122 (44.5%)	123 (37.6%)
Female	185 (53.8%)	222 (61.5%)	152 (55.5%)	204 (62.4%)
Educated past 16 years of age	180 (52.3%)	186 (51.5%)	146 (53.3%)	168 (51.4%)
Degree or equivalent professional qualification	115 (33.4%)	106 (29.4%)	95 (34.7%)	96 (29.4%)
Smoking (yes)	16 (4.7%)	29 (8.0%)	12 (4.4%)	25 (7.6%)
Three or more alcohol units/day (one unit equals 10ml of pure alcohol)	32 (9.3%)	21 (5.8%)	26 (9.5%)	16 (4.9%)
Ethnicity				
White	340 (98.8%)	358 (99.2%)	271 (98.9%)	324 (99.1%)
Asian or Asian British	2 (0.6%)	0 (0.0%)	2 (0.7%)	0 (0.0%)
Black or Black British	0 (0.0%)	2 (0.6%)	0 (0.0%)	2 (0.6%)
Other	1 (0.3%)	0 (0.0%)	1 (0.4%)	0 (0.0%)
Fallen in the last 12 months				
Yes	110 (32.0%)	142 (39.3%)	89 (32.5%)	131 (40.1%)
No	224 (65.1%)	212 (58.7%)	176 (64.2%)	190 (58.1%)
Can't recall	8 (2.3%)	5 (1.4%)	8 (2.9%)	4 (1.2%)
Health problems				
Diabetes	55 (16.0%)	66 (18.3%)	43 (15.7%)	64 (19.6%)
Osteoporosis	33 (9.6%)	42 (11.6%)	27 (9.9%)	40 (12.2%)
High blood pressure	157 (45.6%)	174 (48.2%)	131 (47.8%)	160 (48.9%)
Rheumatoid arthritis	38 (11.0%)	57 (15.8%)	31 (11.3%)	53 (16.2%)
Osteoarthritis	98 (28.5%)	114 (31.6%)	81 (29.6%)	106 (32.4%)
Stroke	28 (8.1%)	31 (8.6%)	22 (8.0%)	27 (8.3%)
Cancer	49 (14.2%)	37 (10.2%)	38 (13.9%)	34 (10.4%)
Respiratory conditions	65 (18.9%)	81 (22.4%)	51 (18.6%)	73 (22.3%)

Characteristic	As Randomised		As Analysed*	
	Collaborative Care (N=344)	Usual Care (N=361)	Collaborative Care (N=274)	Usual Care (N=327)
Eye condition	130 (37.8%)	136 (37.7%)	98 (35.8%)	117 (35.8%)
Heart disease	88 (25.6%)	86 (23.8%)	66 (24.1%)	75 (22.9%)
Other	74 (21.5%)	74 (20.5%)	64 (23.4%)	65 (19.9%)
PHQ-9 (0-27, higher score indicates worse depression)				
N	340 (98.8%)	358 (99.2%)	274 (100.0%)	327 (100.0%)
Mean (SD)	7.8 (4.71)	7.8 (4.64)	7.6 (4.32)	7.6 (4.55)
Median (min, max)	7 (0, 27)	7 (0, 25)	7 (0, 27)	7 (0, 25)
PHQ-15 (0-28, higher score indicates worse physical symptoms)				
N	339 (98.5%)	356 (98.6%)	274 (100.0%)	326 (99.7%)
Mean (SD)	9.1 (4.12)	9.5 (3.94)	9.1 (4.17)	9.4 (3.93)
Median (min, max)	9 (0, 25)	9 (0, 20)	9 (0, 25)	9 (0, 20)
SF-12 (Physical Component, 0-100, higher score indicates better physical health)				
N	337 (98.0%)	356 (98.6%)	274 (100.0%)	327 (100.0%)
Mean (SD)	38.0 (13.37)	36.5 (13.02)	38.5 (13.15)	36.6 (13.11)
Median (min, max)	37.5 (4.6, 69.9)	35.1 (5.7, 66.6)	38.1 (4.6, 69.9)	35 (5.7, 66.6)
SF-12 (Mental Component, 0-100, higher score indicates better mental health)				
N	337 (98.0%)	356 (98.6%)	274 (100.0%)	327 (100.0%)
Mean (SD)	44.3 (10.96)	45.1 (10.02)	44.5 (10.97)	45.2 (10.04)
Median (min, max)	44.9 (12.5, 66.0)	46.3 (9.6, 67.0)	45.1 (12.5, 66.0)	46.5 (9.6, 67.0)
GAD-7 (0-21, higher score indicates worse anxiety)				
N	340 (98.8%)	358 (99.2%)	274 (100.0%)	327 (100.0%)
Mean (SD)	5.7 (4.82)	5.7 (4.45)	5.5 (4.58)	5.6 (4.38)
Self-report of any prescribed mental health medication	35 (10.2%)	51 (14.1%)	29 (10.6%)	46 (14.1%)

* As analysed: All patients included in the primary analysis, i.e. patients with a valid PHQ-9 score at 4 or 12 months follow-up and valid covariate data (PHQ-9 score at randomisation and baseline SF-12 Physical Component Score)

Table 2: Summary of between-group differences

Estimate at	Collaborative Care			Usual Care			Group Difference		
	N	Mean	(95% CI)	N	Mean	(95% CI)	Mean	(95% CI)	p
PHQ-9: Primary analysis[1] (0-27, higher score indicates worse depression)									
4 months*	274	5.36	(4.89, 5.83)	327	6.67	(6.24, 7.10)	-1.31	(-1.95, -0.67)	<.001
12 months	274	5.93	(5.35, 6.50)	327	7.25	(6.73, 7.77)	-1.33	(-2.10, -0.55)	.001
PHQ-9: Analysis adjusted for clustering by case manager[2,] (0-27, higher score indicates worse depression)									
4 months	274	5.46	(4.80, 6.11)	327	6.67	(6.23, 7.11)	-1.21	(-1.99, -0.42)	.003
12 months	274	6.03	(5.30, 6.76)	327	7.24	(6.71, 7.78)	-1.21	(-2.12, -0.31)	.008
PHQ-9: Analysis using multiply imputed data[3] (0-27, higher score indicates worse depression)									
4 months	344	5.40	(4.94, 5.85)	361	6.80	(6.36, 7.23)	-1.40	(-2.04, -0.76)	<.001
12 months	344	6.01	(5.43, 6.60)	361	7.26	(6.73, 7.79)	-1.25	(-1.99, -0.50)	.001
PHQ-9: Unadjusted means (0-27, higher score indicates worse depression)									
4 months	262	5.17	(4.67, 5.68)	324	6.75	(6.26, 7.24)	-1.58	-	-
12 months	235	5.67	(5.09, 6.24)	284	7.23	(6.65, 7.82)	-1.57	-	-
	N	Total	%	N	Total	%	RR[5]	(95% CI)	p
Proportion of patients with moderate to severe PHQ-9 depression[4,5,] (Exploratory) (PHQ9 score ≥10)									
4 months	45	262	17.2	76	324	23.5	0.83	(0.61, 1.27)	.247
12 months	37	235	15.7	79	284	27.8	0.65	(0.46, 0.91)	.013
Proportion of patients with prescribed antidepressants[6] (Exploratory)									
4 months	26	264	9.9	46	321	14.3	0.73	(0.51, 1.04)	.083
12 months	23	234	9.8	44	281	15.7	0.84	(0.60, 1.19)	.327
	N	Mean	(95% CI)	N	Mean	(95% CI)	Mean	(95% CI)	p
SF-12 Physical Component Score (PCS)[7] (Exploratory) (0-100, higher score indicates better physical health)									
4 months	263	38.8	(37.7, 39.9)	316	36.0	(35.0, 37.0)	2.83	(1.62, 4.03)	<.001
12 months	263	37.8	(36.6, 39.0)	316	36.1	(35.0, 37.2)	1.67	(0.27, 3.06)	.020
SF-12 Mental Component Score (MCS)[7] (Exploratory) (0-100, higher score indicates better mental health)									
4 months	263	47.6	(46.3, 48.9)	316	45.7	(44.6, 46.9)	1.88	(0.47, 3.29)	.009
12 months	263	46.8	(45.4, 48.1)	316	44.6	(43.4, 45.9)	2.15	(0.59, 3.70)	.007
GAD-7 Anxiety[8] (Exploratory) (0-21, higher score indicates worse anxiety)									
4 months	264	4.05	(3.54, 4.55)	315	5.13	(4.67, 5.59)	-1.08	(-1.64, -0.52)	<.001
12 months	264	4.18	(3.66, 4.71)	315	5.20	(4.72, 5.67)	-1.01	(-1.61, -0.42)	.001

* Primary endpoint

[1] Primary analysis: Linear mixed effects model adjusted for treatment group, time (4 & 12 months), group x time interaction, PHQ-9 at randomisation and baseline SF-12 Physical Component Score, including unstructured residual variances and covariance over time

[2] As primary analysis model, additionally including case manager as random effect

[3] As primary analysis model, using data derived by multiple imputation based on predictors: allocation, age at consent, PHQ-9 at randomisation, baseline SF-12 Physical Component Score, baseline SF-12 Mental Component Score, baseline GAD-7, prescribed antidepressants at baseline (yes/no) and baseline PHQ-15

[4] Relative risk (RR) of the outcome for collaborative care compared with usual care. RR > 1 indicates collaborative care increases risk of event; RR < 1 indicates collaborative care decreases risk of event.

[5] PHQ-9 self-reported depression severity, score range 0-27, moderate to severe depression defined as scores ≥10

[6] Individual logistic regressions, adjusted for treatment group, PHQ-9 at randomisation, baseline SF-12 Physical Component Score, prescribed antidepressants at baseline (yes/no), baseline GAD-7 and baseline PHQ-15

[7] Linear mixed effects model adjusted for treatment group, time (4 & 12 months), group x time interaction, PHQ-9 at randomisation, baseline SF-12 mental component score, baseline SF-12 physical component score, prescribed antidepressants at baseline (yes/no), baseline GAD-7 and baseline PHQ-15, including unstructured residual variances and covariance over time

[8] Linear mixed effects model adjusted for treatment group, time (4 & 12 months), group x time interaction, PHQ-9 at randomisation, baseline GAD-7, baseline SF-12 physical component score, prescribed antidepressants at baseline (yes/no) and baseline PHQ-15, including unstructured residual variances and covariance over time