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Research paper

Effectiveness of a task-sharing collaborative care model for identification and management of depressive symptoms in patients with hypertension attending public sector primary care clinics in South Africa: pragmatic parallel cluster randomised controlled trial.

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ABSTRACT

Background: We tested the real-world effectiveness of a collaborative task-sharing model on depressive symptom reduction in hypertensive Primary Health Care (PHC) patients in South Africa.

Method: A pragmatic parallel cluster randomised trial in 20 clinics in the Dr Kenneth Kaunda district, North West province. PHC clinics were stratified by sub-district and randomised in a 1:1 ratio. Control clinics received care as usual (CAU), involving referral to PHC doctors and/or mental health specialists. Intervention clinics received CAU plus enhanced mental health training and a lay counselling referral service. Participant inclusion criteria were ≥ 18 years old, Patient Health Questionnaire-9 (PHQ-9) score ≥ 9 and receiving hypertension medication. Primary superiority outcome was ≥ 50% reduction in PHQ-9 score at 6 months. Statistical analyses comprised mixed effects regression models and a non-inferiority analysis. Trial registration number: NCT 02425124.

Results: Between April 2015 and October 2015, 1043 participants were enrolled (504 intervention and 539 control); 82% were women; half were ≥ 55 years. At 6 and 12 months follow-up, 91% and 89% of participants were interviewed respectively. One control group participant committed suicide. There was no significant difference in the primary outcome between intervention (N=256/456) and control (N=232/492) groups (55.9% versus 50.9%; adjusted risk difference = -0.04 ([95% CI = -0.19; 0.11], p = 0.6). The difference in PHQ-9 scores was within the defined equivalence limits at 6 and 12 months for the non-inferiority analysis.

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Limitations: The trial was limited by low exposure to depression treatment by trial participants and by observed co-intervention in control clinics

Conclusions: Incorporating lay counselling services within collaborative care models does not produce superior nor inferior outcomes to models with specialist only counselling services.

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Abbreviations

BREC	Biomedical Research Ethics Committee
CAU	Care As Usual
CCS	Clinical Communication Skills
CVD	Cardiovascular Disease
DKK	Dr Kenneth Kaunda District
DOH	Department of Health
DSMB	Data Safety and Monitoring Board
HIV	Human Immunodeficiency Virus
ICSM	Integrated Clinical Services Management
LMICs	Low-and-Middle-Income-Countries
NHI	National Health Insurance
PACK	Practical Approach to Care Kit
PC101	Primary Care 101
PHC	Primary Health Care
PHQ-9	Patient Health Questionnaire-9
PRIME	PRogramme for Improving Mental health carE
WHODAS 2.0	World Health Organization Disability Assessment Schedule 2.0

Introduction

While South Africa's health care system has been severely constrained by the HIV crisis over the past decade, a silent non-communicable disease epidemic has been growing. Hypertension is estimated to affect 20% of the adult population (Steyn et al., 2001). This is concerning given that uncontrolled hypertension is a risk for cardiovascular disease (CVD) (Zhou et al., 2018), and is the leading cause of death globally, with three-quarters of deaths due to CVD occurring in low- and middle-income countries (LMICs) (World Health Organization, 2017). Comorbid depression independently increases risk of cardiovascular events in at-risk populations (Jackson et al., 2018). In the context of high rates of hypertension, and depression being the most common individual common mental disorder

(Tomlinson et al., 2009); identification and management of comorbid depressive symptoms in patients with hypertension attending primary health care (PHC) services could help improve health outcomes of this population.

The PRogramme for Improving Mental health carE (PRIME) was a multinational research consortium focused on the development, implementation and scaling up of integrated primary mental health care at the district level in five LMICs (Lund et al., 2012). Working in partnership with the South African Department of Health, patients and community representatives, PRIME co-developed a collaborative care model that included a lay-counselling service within PHC clinics for treating depressive symptoms in patients with chronic conditions. Collaborative care for comorbid depressive symptoms in patients with chronic conditions is effective in improving mental and physical health outcomes in high-income countries (Katon et al., 2010). There is a need for evidence of the effectiveness of such models in real-world LMIC settings.

The PRIME model in South Africa, described elsewhere (Petersen et al., 2016), entailed strengthening of i) PHC nurses' capacity to identify depressive symptoms in chronic care patients through additional training; and ii) referral systems to include facility-based lay counsellors trained and supervised to deliver manualized evidence-based counselling using cognitive behavioural techniques and problem solving (Dua et al., 2011). The latter was in addition to care as usual (CAU) which comprised established, albeit limited, referral pathways to doctors responsible for initiating antidepressant medication, and mental health specialists (sessional psychiatrists and district-based psychologists), who provided specialist referral services. A pilot study involving a repeat cross-sectional survey in four clinics, as well as a comparison group cohort study, found greater identification and referral of patients with comorbid depressive symptoms after the intervention; and an improvement in patient-level depressive symptoms in referred patients (Petersen et al., 2019).

We report on a pragmatic cluster randomised controlled trial of the scale-up of this model as part of routine PHC. The primary aim of the study was to test the hypothesis that the PRIME collaborative model would be more effective than CAU for patients with hypertension and comorbid depressive symptoms and would improve both depressive symptoms and blood pressure control. Administrative and funding information required by the SPIRIT checklist (Chan et al., 2013) can be found in the protocol (Petersen et al., 2018) (https://doi.org/10.1186/s13063-018-2518-6).

Methods

Study setting

The study site was the Dr Kenneth Kaunda (DKK) district in the North West province of South Africa, west of the Gauteng industrial hub of South Africa. DKK was a National Health Insurance pilot site where a number of health system reforms were initiated including the Ideal Clinic which included Integrated Clinical Services Management (ICSM) for patients with chronic conditions (Department of Health, 2016). The formative evaluation and piloting of the collaborative care model also occurred in DKK and was used by the district to inform the development of a district mental health care plan that foregrounded decentralizing and increasing access to mental health care at PHC facilities. DKK is fairly representative of districts in South Africa, with a combination of smaller cities, towns and rural areas, and has a population of 796,823 (Petersen et al., 2016), with the main economic activities being gold and platinum mining and agriculture.

Study Design

A pragmatic two-group parallel cluster randomised controlled trial was undertaken between April 2015 and October 2016. The cluster randomised design was adopted to avoid contamination between intervention and control group participants, as the intervention was implemented at the level of the PHC clinics. Data were collected in parallel with a sister trial, (CobALT - Comorbid Affective Disorders, AIDS/HIV, and Long Term Health), which evaluated the impact of the same intervention on depressive symptoms and viral load outcomes in HIV-positive patients on antiretroviral treatment in DKK as well as in the neighbouring Bojanala Platinum district (Fairall et al., 2018). Participant recruitment and baseline data collection began in the control clinics 3 months prior to the intervention clinics to provide for a short

embedding period of the model in the intervention clinics.

The clinics were the unit of randomisation, with data collected on individual participants. Patient participants were recruited independently of the trial intervention being tested, in line with the highly pragmatic orientation of the trial - which aimed to test the model in its completion, from identification through to management of depressive symptoms.

In addition to the primary analysis assessing superiority, and before completion of data collection and analysis, ethics approval was obtained to conduct a secondary non-inferiority analysis of the main outcome findings. This was added in the event of a null finding of the superiority analysis to assess whether the intervention did not cause harm. The criteria for interpreting a superiority trial as a non-inferiority trial (Lewis, 2001) were met, namely: i) known effectiveness of the comparator, where referral was to doctors for antidepressant medication initiation, and mental health specialists (the model of CAU in the control group) (Archer et al., 2012); and ii) the choice of the non-inferiority margin being objective and widely accepted (Lewis, 2001), with Patient Health Questionnaire-9 (PHQ-9), (the main outcome measure), having established non-inferiority margins (Richards et al., 2016; Saxon et al., 2017). Ethical approval for the study was obtained from the University of KwaZulu-Natal's Biomedical Research Ethics Committee (BREC) (BFC049/15); the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (HREC: 412/2011); as well as the North West Department of Health. Data safety and monitoring was overseen by the Data Safety and Monitoring Board (DSMB) established for the sister CobALT trial (Fairall et al., 2018). All amendments to the protocol were approved by BREC and amended on the trial registries. More details on approval, consent processes, data safety and monitoring have been published (Petersen et al., 2018).

Description of services at intervention and control clinics

Care as usual clinics

All clinics were exposed to CAU. This was an integrated chronic care approach that included reorganization of chronic care services from verticalized to integrated services as part of South Africa's national ICSM strategy (Mahomed et al., 2014). This included the introduction of a clinical decision support tool called Primary Care 101 (PC101) [later called Adult Primary Care (APC) and internationally, the Practical Approach to Care Kit (PACK)] (Fairall et al., 2018). This tool integrates the management of communicable and non-communicable diseases, mental illness, and women's health. APC was rolled out to all NHI pilot districts, including DKK through 12 facility-based, short (1.5-2 hours) interactive training sessions (including two sessions on mental health). Patients identified with depressive symptoms were referred for treatment to: i) PHC doctors for antidepressant medication initiation; ii) two district-based psychologists providing outreach counselling services to PHC clinics; and iii) the Psychology Outpatient Clinic based at the district hospitals serviced by four psychologists at the time of the trial. A 982-bed provincial tertiary specialist psychiatric hospital was also available for patients with severe mental illness requiring hospitalisation.

Intervention clinics

In addition to CAU, intervention clinics were exposed to i) Supplementary training provided to PHC nurses comprising four additional APC sessions on mental health content, and four sessions on clinical communication skills (CCS). The APC mental health training mirrored the DoH cascade model of training, whereby master trainers trained facility-based trainers to provide on-site training to PHC nurses, while CCS training was provided by external CCS specialists; ii) Two workshops held with PHC doctors (appointed to PHC clinics as part of the NHI piloting process) responsible for initiating antidepressant treatment, to orientate them to the importance of treatment for depressive symptoms; and iii) Referral pathways that were strengthened through the introduction of lay counselling services in each of the 10 intervention clinics. The lay counsellors (N=14, including replacement counsellors) were trained and supervised to provide manualized evidence-based counselling for patients with depressive symptoms under the supervision of a project-employed clinical psychologist. Lay counsellors, with a minimum of 12 years of schooling, were consequently selected, trained and employed to provide this service for the duration of the trial.

Randomisation and blinding

The largest 20 primary care clinics (excluding the four clinics involved in the PRIME pilot study) out of all 60 clinics in the DKK district were enrolled in the trial (Fig. 1). All the enrolled clinics reported more than 10 000 patient attendances annually. Randomisation of the clinics was done by the trial statistician using nQuery Advisor before intervention implementation or data collection. Clinics were stratified by sub-district into two strata to avoid bias arising from differences in sub-districts; and then randomised in each stratum into one of two parallel groups, with ten in each group. Staff in the intervention clinics were not blinded to intervention status because they were recipients of the training intervention. Blinding of fieldworkers could also not be guaranteed given implementation activities of the intervention even though they were not in informed of clinic status. All fieldwork activities were standardised across both groups with training manuals, standard operating procedures and daily supervision (Petersen et al., 2018).

Enrolment procedure

Patients attending the clinics for chronic conditions were invited to be assessed for eligibility for the study through information provided verbally in waiting rooms (with no mention of mental health or hypertension). These volunteers were asked, in a private space, if they were $\geq$18 years, and were on hypertension treatment. Patients who met these eligibility criteria were then administered the PHQ-9 following verbal pre-consent to be screened in a private room. Those screening positive, using a locally validated cut-off for chronic care patients of $\geq$ 9 on the PHQ-9 (Bhana et al., 2015), were provided with verbal and written information about the study in either Setswana, English or Afrikaans, and signed consent/ used a thumbprint as their signature. Patients were excluded if they needed urgent medical attention; were too ill to provide informed consent; or planned to move outside the area during the 12-month follow-up period (Petersen et al., 2018). Patients scoring positive on item 9 of the PHQ-9 (that explores thoughts in the past two weeks of being better off dead or of self-harm), received psycho-educational material on suicidality and where to get help. In addition, at baseline and 6 months follow-up, participants were referred to a PHC nurse for further assessment and treatment if they reported having these thoughts for $\geq$ 8 days over two weeks. These referrals rules were changed at 12 months follow-up to improve accuracy. Participants who reported having these thoughts >0 days were asked an additional 5 questions (whether they had a suicide plan, had deliberately injured themselves without intending to kill themselves, had attempted suicide in the past month and/or in their lifetime). If they answered yes to $\geq$1 of these questions they were given a referral.

Sample size

An intra-clinic correlation coefficient of 0.04 was used for the primary outcome of a 50% improvement in PHQ-9 score at 6 months compared with enrolment. This was based on a similar trial in a LMIC (Rahman et al., 2008); significance level of 0.05; and estimated loss to follow-up of 20%. For the superiority analysis, a sample size comprising 50 patients in each of the 20 clinics making up 1000 patients (500 patients in the intervention group and 500 patients in the control group) was estimated to provide 90% power to detect a risk difference of 17% (60% control versus 77% intervention), and 80% power to detect a risk

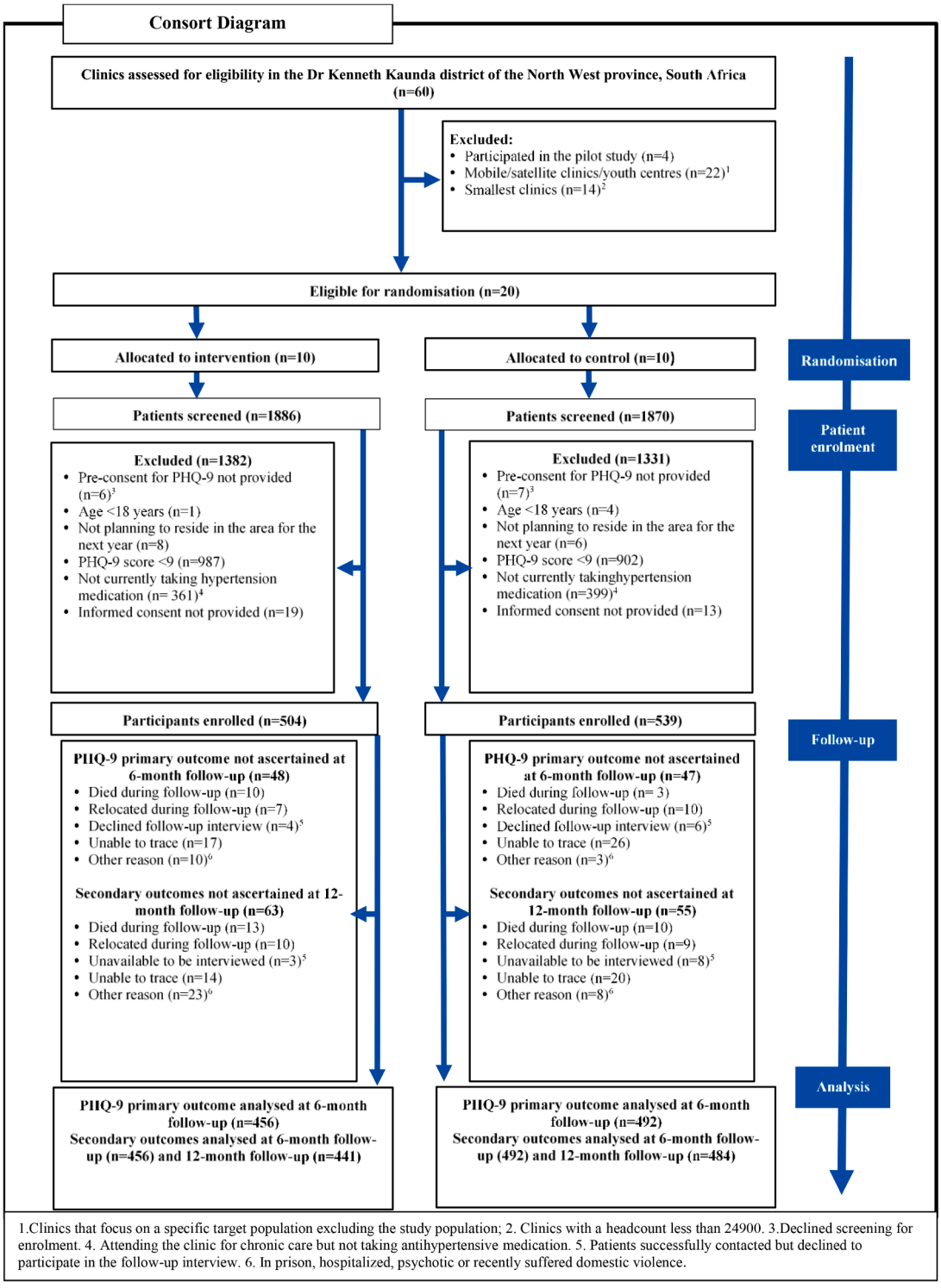

Fig. 1. Consort Diagram.

difference of 15% (60% control versus 75% intervention). This cluster based sample size was also sufficient to power the equivalence analysis, with at least 80% power for a two-one-sided test for equivalence of the mean PHQ-9 scores at 6 and 12 months based on the margins of -1.9 to 1.9 units; a standard deviation of 5 units; and inflation factor (IF) of 2.96 (IF=1+(50-1)x0.04). For the non-inferiority sample size assumptions, the individual randomised sample size was 151 per group, and hence applying the IF the required sample size was 447 per group. Further sample size estimates are reported in the protocol (Petersen et al., 2018).

Data collection and outcome measures

Enrolled participants were administered the baseline questionnaire in either Setswana, Afrikaans or English. Fieldworkers used tablets to collect data electronically that were uploaded daily onto a secure server. Details of the selection, training and supervision of the fieldworkers, data management and participant stipends are reported in the protocol (Petersen et al., 2018). In addition to the PHQ-9, the baseline questionnaire included demographic questions, anthropometric

measurements (height, weight, waist circumference and blood pressure), World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0), Perceived Stress Scale, healthcare utilisation including clinic visits, and hospital admissions. Mortality data were acquired through families of participants once participants had defaulted on follow-up interviews. Detailed information on these measures have been reported in the protocol (Petersen et al., 2018). Independently of the trial outcomes, process indicators monitoring the intervention implementation were collected through clinical and project records, irrespective of whether patients were enrolled in the trial.

Outcomes

The primary outcome was the proportion of patients with at least 50% reduction in PHQ-9 scores at 6 months follow-up compared to baseline. This primary outcome was adopted as per the protocol (Petersen et al., 2018) on the basis of being recommended and widely used as a measure of a clinically significant change (Kroenke et al., 2001; Huijbregts et al., 2013; IJff et al., 2007; Wernher et al., 2014; Unützer et al., 2002). Secondary outcomes were: other PHQ-9 outcomes (difference in mean scores, recovery, remission) at both 6 and 12 months (see Table 2); receipt of counselling (yes/no and from whom); receipt of antidepressant treatment; blood pressure measured by fieldworkers at 6 and 12 months; and other risk factors for CVD including body mass index, waist circumference and smoking history.

Statistical analyses

The statistician was blinded to all data pertaining to the primary and secondary outcomes until the analysis was finalized. Analyses were conducted in Stata 13. Analyses comparing outcomes were by intention to treat. Missing data were not imputed, and participants with missing data were excluded from the analyses of those variables. Mixed effect regression models, in which stratum was included as a covariate and intra-cluster correlation of outcomes was accounted for by treating clinics as random effects. Binomial regression was used to estimate differences in proportions of participants considered having at least 50% reduction in depressive symptoms, measured using PHQ-9 at 6 months for the primary outcome and adjusted for baseline PHQ-9 scores. Secondary outcomes were analysed using binomial regression for binary outcomes, linear regression for numerical outcomes comparing values at follow-up adjusted for baseline values, and Poisson regression for count outcomes.

For the non-inferiority analysis, the non-inferior clinical outcome was defined as the difference between groups in mean PHQ-9 symptom scores at 6 and 12 months within the equivalence limits of -1.9 to 1.9 (90% confidence interval). As suggested by the Committee for Proprietary Medicinal Products (2001), this was derived from previous non-inferiority trials using the PHQ-9 as the outcome measure (Richards et al., 2016; Saxon et al., 2017), and where a change difference of less than 2 on the PHQ-9 is not regarded to be clinically important (Saxon et al., 2017). We used mixed effect linear regression models adjusted for stratum, baseline PHQ-9 scores and for the cluster design to test for equivalence of differences in mean PHQ-9 scores between the two groups at 6 and 12 months.

Results

At enrolment, 3756 patients were screened and 1043 enrolled; 504 in 10 intervention clinics and 539 in 10 control clinics. Excluded patients were either younger than 18 (5), not planning to reside in the study area during follow-up (14), did not give pre-consent (13), were not taking hypertension medication (760) or did not provide informed consent (32) (Fig. 1). All 20 clusters were followed up to the end of the trial: 456 (90%) and 492 (91%) patients at 6 months; and 441 (88%) and 484 (90%) patients at 12 months in the intervention and control groups, respectively. There were 23 (5%) deaths in the intervention group and 14 (3%) in the control group at follow-up, with one suicide reported in the control group at 12-month follow-up. This suicide was not deemed to be related to the study procedure by the DSMB and BREC.

The enrolment socio-demographic and clinical characteristics of the intervention and control groups are displayed in Table 1. The clinic baseline table is contained in the online supplementary File S1.

The trial population was predominantly women in both intervention (85%) and control groups (79%), with 25% of participants in both groups reporting having never attended school. Employment levels were low (22% and 23% in the intervention and control groups respectively), with over half the sample in receipt of social grants (52% and 62% in the intervention and control groups respectively). At baseline, there were high levels of multimorbidity: 63% and 58% of participants had other chronic conditions in addition to depressive symptoms and hypertension in the intervention and control groups respectively. A third (33%) of

Table 1
Demographic and Clinical Enrolment characteristics of participants.

Characteristic	Intervention n (%), N=504	Control n (%), N=539
Proportion women	430 (85)	424 (79)
Age in years: mean (SD); median (IQR)	54 (11); 54 (47, 60)	55 (11); 55 (48, 62)
PHQ-9 score: mean (SD); median (IQR)	13 (4); 13 (11, 15)	14 (4); 13 (11, 16)
PHQ-score=9	47 (9)	48 (9)
PHQ-9 score category:		
9-14: mild/moderate	356 (71)	338 (63)
15-27: moderately severe or severe	168 (29)	201 (37)
Blood pressure		
Systolic blood pressure: mean (SD); median (IQR)	136 (23); 133 (120, 149)	138 (24); 137 (120, 152)
BP ≥180/110 mmHg	59 (12)	81 (15)
BP ≥140/90-179/109 mmHg	237 (47)	248 (46)
BP <140/90	208 (41)	210 (39)
Medical history		
Previous heart attack	98 (19)	97 (18)
Previous stroke	50 (10)	45 (8)
Previous heart attack or stroke	132 (26)	124 (23)
History of diabetes	69 (14)	97 (18)
History of depression	100 (20)	130 (24)
On antiretroviral treatment	167 (33)	131 (24)
Previous tuberculosis	98 (19)	97 (18)
On antiretroviral treatment or previous tuberculosis	204 (40)	186 (35)
Smoking history		
Current smokers	44 (9)	94 (17)
Pack year history: mean (SD); median (IQR)	9 (10); 6 (4, 9)	12 (16); 7 (4, 14)
BMI (kg/m^2): mean (SD); median (IQR)	30 (9); 29 (24, 36)	30 (9); 29 (23, 35)
BMI category	N=497	N=536
BMI >30: Obese	241 (48)	241 (45)
BMI ≤30: Not obese	256 (52)	295 (55)
CVD risk percent >20%	139 (28)	201 (37)
Reported a hospitalisation in the last 3 months	12 (2)	22 (4)
World Health Organization disability assessment schedule 2 score[1]: mean (SD); median (IQR)	10 (7); 9 (4; 13)	11 (8); 10 (4; 16)
Highest level of education achieved		
Never attended school	125 (25)	133 (25)
Some primary school education	235 (47)	261 (48)
Some secondary school or tertiary education	144 (29)	145 (27)
Employed or self employed	117 (23)	117 (22)
Receiving a government social grant	264 (52)	336 (62)

BMI=body mass index; BP =blood pressure; CVD=cardiovascular disease; IQR=interquartile range; PHQ-9= the 9-item patient health questionnaire; SD=standard deviation.

[1] Score out of 37, with a score of 0-1 considered no disability, and 2-37 considerable disability (37 is the lowest level of functioning (Hanass-Hancock et al., 2015).

participants in the intervention group and a quarter (24%) in the control group were on antiretroviral treatment for HIV. More than half of participants did not meet blood pressure targets at the time of the trial (<140/90 mmHg) in both the intervention (59%) and control groups (61%). There was minimal difference in mean PHQ-9 scores between groups at baseline, with the majority of participants in both groups having PHQ-9 scores falling in the moderate range (9-14) (71% and 63% in the intervention and control groups, respectively). A higher number of participants scored in the moderate-severe to severe symptoms range (15-27) in the control group (37%) compared to the intervention group (29%). High levels of disability were reflected by the WHODAS 2.0 scores, with mean scores of 10 and 11 in the intervention and control groups respectively with a score >2 being indicative of disability (Hanass-Hancock et al., 2015).

We present secondary treatment exposure results at 6 and 12 months first to elucidate the primary outcome findings. In relation to treatment exposure (see Table 2), only 11% of the intervention trial participants reported a referral to the clinic lay-counselling service over the trial period; and even fewer participants reported receipt of the service (7%). Receipt of lay-counselling was not associated with baseline PHQ-9 score, age, sex or any other variable recorded at baseline. While roughly equal numbers of participants received specialist services before the trial, this was not the case at 6 and 12 months follow-up, with a significantly greater number of control participants in receipt of such services at 12 months. Receipt of antidepressant medication was minimal in both groups (see Table 2).

In relation to the primary outcome, a small proportion of the intervention group had ≥ 50% improvement in PHQ-9 scores at 6 months compared with enrolment (55.9% vs 50.9%). This was not significantly different in the primary analysis (risk difference = -0.04 ([95% CI = -0.19; 0.11], p = 0.6) (See Table 3) or when additional enrolment measurements were included in the full model (See online Supplementary File S2). Sub-group analysis of intervention participants who received lay counselling revealed a similar reduction in PHQ-9 scores to the overall sample at 6 months follow-up compared with enrolment.

The results of the non-inferiority analysis indicate that absolute PHQ-9 scores at 6 months follow-up were no worse in the intervention group compared to the control group (Intervention: mean 7.3 [SD 5.4], Control: 7.59 [SD 5.5], with an estimated adjusted mean difference of -0.10 PHQ-9 points [90% CI -1.51 to 1.31], p = 0.900). The same pattern was observed at 12 months (Intervention: mean 6.3 [SD 4.5], Control: 7.04 [SD 4.8], with an estimated adjusted mean difference of -0.46 PHQ-9 points [90% CI -1.88 to 0.96], p = 0.583). The estimated 90% confidence interval for the mean difference in the 6 and 12 months PHQ-9 scores falls within the *a priori* defined non-inferiority limit of -1.9 to 1.9, favouring the intervention group (Fig. 2).

There were no differences between the intervention and control groups for any of the other secondary PHQ-9 outcomes at 6 and 12 months (Table 2), except for new diagnosis of depressive symptoms at 12 months (online Supplementary Table S6). Sub-group analysis of the effect of the intervention on depressive symptoms in participants with moderate symptoms (9-14) at baseline (online Supplementary files S3-S5) indicates a 75% chance of being in remission or having mild depressive symptoms at 6 months follow-up, with further improvement at 12 months follow-up. This contrasts with participants having a history of depression or who had moderately severe to severe depressive symptoms (15-27) at baseline; with roughly a third in this group still displaying moderately severe to severe symptoms at both 6 and 12 months follow-up.

Regarding secondary cardiovascular risk outcomes, there was a reduction in uncontrolled blood pressure in both groups at both 6 and 12 months compared to baseline. However, the proportions of patients who failed to meet blood pressure targets was still high in both groups at both follow-up time points (Table 4). There were no significant differences in WHODAS 2.0 disability scores at 12-month follow-up.

Other secondary outcomes are reported in Supplementary File S6. Significantly more participants in the control group were diagnosed with both depression and tuberculosis during the trial period compared to the intervention group. There were no differences in hospitalisations, mortality and adverse events at follow-up between the groups (See Table 5).

Discussion

In relation to the primary outcome, the collaborative care model incorporating lay counselling services did not result in a significant reduction in depressive symptoms in the intervention group compared to the control group. However, neither was it inferior. Being a pragmatic trial, participants were enrolled independently of exposure to the intervention. This enrolment process was unlike similar trials in South Africa, such as Project Mind, where enrolled patients were referred directly into the intervention being tested by study-employed research

Table 2
Receipt of the components of collaborative care for depression by trial participants.

Receipt of depression treatment	Treatment prior to the trial				Treatment at 6 months				Treatment at 12 months			
	Intervention	Control	Effect estimate (RD; 95% CI)	p value	Intervention	Control	Effect estimate (RD; 95% CI)	p value	Intervention	Control	Effect estimate (RD; 95% CI)	p value
PRIME Project employed counsellors	4/504 (0.8)	0/539 (0)			23/504 (4.6)	0/539 (0)			14/504 (2.8)	2/539 (0.4)		
State employed specialist mental health workers	70/504 (13.4)	81/539 (15.0)	RD=0.01 (-0.12; 0.14)	0.877	16/456 (3.5)	40/492 (8.1)	RD=-0.04 (-0.08; 0.01)	0.089	8/441 (1.8)	20/484 (4.1)	RD=-0.03 (-0.04; -.002)	0.038
On antidepressants at a therapeutic dose at any point									4/504 (0.8)	14/539 (2.6)	RD=-0.02 (-0.04; 0.001)	0.069
Initiated or intensified antidepressants									5/504 (1.0)	7/539 (1.3)	RD=-0.003 (-0.02; 0.01)	0.641
Referred to PRIME counsellor over 12 months period									57/504 (11.3)	0/539		

RD=risk difference.

Table 3
Effect of the intervention on depressive symptoms as measured with the PHQ-9 questionnaire.

Outcome	Intervention n (%)	Control n (%)	Effect estimate[1] (95% CI)	p-value
Primary outcome	N=456	N=492		
PHQ-9 response: 50% improvement in PHQ-9 score at 6 months from baseline[5]	275 (56)	232 (51)	-0.04 (-0.19; 0.11)	0.595
Secondary outcomes at 6 months	N=456	N=492		
PHQ-9 score at 6m: mean (SD); median (IQR)[2]	7 (5); 6 (3, 10)	7 (5); 7 (4, 10)	-0.10 (-1.81; 1.60)	0.900
Severity of depressive symptoms at 6 months[4]				
PHQ-9 score 0-4: no depressive symptoms	145 (32)	160 (33)	1.06 (0.54; 2.08)	0.866
PHQ-9 score 5-9: mild depressive symptoms	182 (40)	192 (39)		
PHQ-9 score 10-14: moderate depressive symptoms	93 (20)	93 (20)		
PHQ-9 score 15-27: moderately severe depressive symptoms	36 (8)	44 (6)		
Secondary outcomes at 12 months	N=441	N484		
PHQ-9 score at 12m: mean (SD); median (IQR)[2]	6 (5); 6 (3, 9)	7 (5); 7 (3, 10)	-0.46 (-2.18; 1.26)	0.583
PHQ-9 response at 12 months: 50% improvement in PHQ-9 score at 12 months from baseline[5]	249 (56)	271 (56)	0.02 (-0.17; 0.20)	0.866
Remission of depression symptoms: PHQ-9 score of ≤5 at 12 months[3]	196 (44)	197 (41)	1.05 (0.65; 1.69)	0.854
PHQ9 recovery: PHQ-9 score of ≤5 at both 6 and 12 months[3]	103 (23) N=448	118 (24) N=495	0.92 (0.41; 2.07)	0.847
Severity of depressive symptoms at 12 months[4]				
PHQ-9 score 0-4: no depressive symptoms	162 (37)	170 (35)	0.89 (0.43; 1.86)	0.764
PHQ-9 score 5-9: mild depressive symptoms	198 (45)	192 (40)		
PHQ-9 score 10-14: moderate depressive symptoms	58 (13)	98 (18)		
PHQ-9 score 15-27: moderately severe depressive symptoms	23 (5)	24 (7)		

IQR=interquartile range; PHQ-9= the 9-item patient health questionnaire; SD=standard deviation.
[1] Adjusted for trial design and baseline characteristics.
[2] Effect estimate coefficient;
[3] Effect estimate risk ratio.
[4] Effect estimate odds ratio;
[5] Risk Difference

assistants (Myers et al., 2018). This pragmatic approach, however, reduced the power of the trial to show a significant difference in the primary outcome. Independently of the trial data, referrals to the lay counsellors were recorded as part of the intervention. This process data reveals close to 1400 referrals to the lay counsellors in the intervention clinics during the trial period. However, only 11.3% and 5% of trial participants in the intervention group reported receiving referrals to either the clinic lay counsellors or mental health specialists respectively, suggesting a relatively low referral rate relative to patients presenting with depressive symptoms. Following Moore et al. (2015), an extensive process evaluation was conducted alongside the trial. This involved quantitative process variables to assess quality and fidelity of the implementation of the intervention that could have impacted on referral rates, as well as qualitative interviews with facility managers, providers and patients to understand causal mechanisms and identify contextual factors associated with variation between the outcomes of the clusters in the trial, including referral rates. These data are currently being analysed and reported in separate papers. Within this real-world context, there are, however, several possible explanations for these low referral rates. Organizationally, process data collected alongside the trial revealed that the nurse training in the PC101/APC mental health module provided by the facility-based trainers under real-world conditions, was uneven across the clinics. This could be attributed to mental health not being a priority at the time of the trial - with the focus being on improving services to achieve priority targets, especially those linked with reducing the HIV burden. Provider factors, in particular nurse confidence in diagnosing depressive symptoms, in the absence of uniform exposure to the PC101/APC mental health module could have consequently played a role. Previous research suggests the importance of training to improve nurse confidence in diagnosing depression (McCabe et al., 2012). Regarding patient factors, low mental health literacy rates, associated with low educational levels (a quarter of participants reported no schooling at baseline), could have impacted negatively on demand for mental health services (Saraceno et al., 2007).

The null findings could also be a product of an observed co-intervention during the trial. As shown in Table 2, participants in the control clinics had greater exposure than participants in intervention clinics to district specialist mental health services during the trial. Participants in the intervention clinics had, on the other hand, greater exposure to the task-shared lay counselling service. District specialist providers were observed to have focused their limited mental health specialist resources on servicing the control clinics during the trial, ostensibly to improve coverage of mental health services in PHC clinics overall in the district in line with the district mental health care plan; and made possible by the presence of project-employed lay counsellors in the intervention clinics. It has been argued previously that pragmatic trials have the potential for contamination despite cluster randomisation through unplanned co-interventions and other factors (Fairall et al., 2017).

This co-intervention did, however, render the trial suitable for conducting a non-inferiority analysis. The results of this analysis indicate that the collaborative care model incorporating clinic lay counsellors did not introduce harm and produced outcomes as good as those of CAU where referrals were restricted to PHC doctors and mental health specialists.

In contexts where global mental health trials of task-sharing have mostly been explanatory and focused on testing proof of concept (Singla et al., 2017); the findings of this pragmatic trial highlight the need to understand how to improve the adoption of task-sharing within routine services at PHC level. To this end, since the completion of the trial, investigators have engaged in implementation science research through the Southern African Mental health INTegration (SMhINT) project. More information can be found on www.crh.ukzn.ac.za.

There were several noteworthy results concerning secondary outcomes. Three-quarters of participants with moderate symptoms at baseline had minimal to mild symptoms (PHQ-9 score of < 9) at 6 months, sustained at 12 months. However, roughly one-third of participants with a history of depression, or moderately severe to severe symptoms at baseline, showed no improvement at 6 and 12 months. In the face of low treatment exposure, these findings are not surprising given a higher probability of spontaneous remission in people with milder depressive symptoms compared to those with severe symptoms (Whiteford et al., 2013). This calls for a targeted approach to depression treatment in PHC, prioritizing patients with more severe symptoms. In particular, the very low rates of reported antidepressant treatment at 12 months for both intervention and control participants (see Table 2) need to be addressed. At the time of the study, PHC nurses could identify and

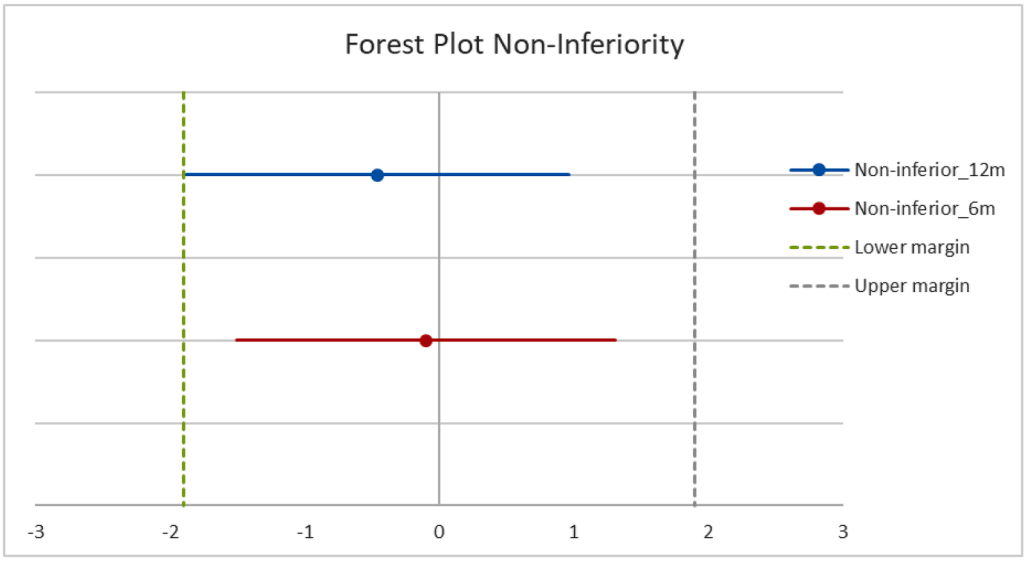

Fig. 2. Non-inferiority margins for PHQ-9 scores at 6 and 12 months.

Table 4
Effect of the intervention on blood pressure, risks for cardiovascular disease and disability.

Outcome	Intervention n (%)	Control n (%)	Effect estimate: Risk difference (95% CI)	p-value
Outcomes at 6 months	N=456	N=492		
Systolic blood pressure at 6m: mean (SD); median (IQR)	130 (21); 130 (117; 141)	129 (24); 127 (112; 145)	1.85 (-0.94; 4.65)	0.181
Blood pressure <140/90	233 (51)	281 (57)	-0.08 (-0.15; 0.002)	0.057
Blood pressure ≥140/90	223 (49)	211 (43)		
Outcomes at 12 months	N=441	N=484		
Systolic blood pressure at 12m: mean (SD); median (IQR)	132 (20); 130 (119; 144)	135 (23); 131 (120; 146)	-1.24 (-6.21; 3.72)	0.606
Blood pressure <140/90	222 (50)	242 (50)	-0.01 (-0.12; 0.10)	0.850
Blood pressure ≥140	219 (50)	242 (50)		
Cardiovascular disease risk percent >20%[1]	111 (25)	157 (32)	-0.07 (-0.17; 0.03)	0.170
World Health Organization disability assessment schedule 2 score[2]: mean (SD); median (IQR)	7.8 (6.4); 7.6 (2.2; 12.0)	9.2 (7.6); 7.6 (3.3; 14.1)	-1.12 (-3.67; 1.44)	0.376

IQR=interquartile range; SD=standard deviation.
[1] effect estimate=coefficient;
[2] Score out of 37, with a score of 0-1 considered no disability, and 2-37 considerable disability (37 is the lowest level of functioning)

Table 5
Adverse events/outcomes at follow-up.

Outcome	Intervention n/N (%), N=504	Control n/N (%), N=539)	Effect estimate[1] Risk Difference (95% CI)	p-value
Mortality	13 (2.6)	10 (1.9)	0.01 (-0.01; 0.03)	0.462
Death by suicide	0 (0)	1 (0.2)		
Number with a hospitalization	20 (4.0)	34 (6.3)	-0.02 (-0.05; 0.01)	0.136
End of study referrals				
PHQ-9 score ≥20 at 12 m	6 (1.2)	13 (2.4)	-0.01 (-0.02; 0.01)	0.489
Uncontrolled hypertension[2]	33 (6.6)	59 (11.0)	-0.04 (-0.11; 0.02)	0.187

[1] Adjusted for trial design and baseline characteristics.
[2] Uncontrolled hypertension= blood pressure≥160/100 at all measured time points or blood pressure≥180/110 at 12 months while on hypertension medication

refer patients for depression treatment, but were not authorized to initiate antidepressant medication. They had to refer patients to PHC doctors for antidepressant medication initiation. Besides the need to strengthen the capacity of PHC doctors to initiate antidepressant medication, they are a scarce resource, particularly outside of the main metropoles of South Africa. This highlights the need for professional PHC nurses to be authorized and capacitated to initiate antidepressant medication for moderate-severe and severe depressive symptoms as a matter of urgency.

In relation to multimorbidity and cardiovascular risk, the study participants had substantial levels of multimorbidity and displayed poor blood pressure control, with a quarter already having had a cardiovascular event. These findings are concordant with other South African studies (Berry et al., 2017; National Department of Health & South African Medical Research Council, 2019), and highlight the need to improve blood pressure control to reduce stroke and ischaemic heart disease mortality - the second and fourth leading causes of mortality respectively in the country in 2012 (Pillay-van Wyk et al., 2016). Concerted efforts are required to improve treatment adherence to hypertension medication. Targeted screening for moderate-severe to severe depressive symptoms in patients with uncontrolled blood pressure (Folb et al., 2015) is recommended given a growing body of evidence of the role of comorbid depression in increasing risk for cardiovascular events (Cohen et al., 2015).

Limitations

Low exposure to the strengthened collaborative care model substantially reduced power to show a significant difference on the primary outcomes between the groups. The observed co-intervention of concentrating referral specialist mental health services in the control clinics to improve service coverage in the district also introduced bias into the study.

Conclusion

Collaborative care for comorbid depressive symptoms in patients on hypertension treatment that includes referral to clinic lay counsellors is neither superior nor inferior to referral to mental health specialists. The use of lay counsellors within a collaborative care approach to increase access to psychological treatments for depressive symptoms in contexts where specialist resources are scarce, is supported. A targeted approach to screening for moderate-severe to severe depressive symptoms in patients with uncontrolled hypertension is recommended. The low exposure to any intervention in both groups of the trial highlights the need for implementation science research to enhance our understanding of how to improve identification and referral of comorbid depression in primary health care clinics – this being the first step in the treatment cascade.

Consent for publication

Not applicable

Availability of data and materials

The anonymised participant-level data will be made publicly available one year after publication of the main trial outcome paper, in accordance with PRIME publication and data management policies through a formal Expression of Interest request available at http://www.prime.uct.ac.za/contact-prime

Credit Authorship Contribution statement

IP and LF led the conceptualisation and designing the study, funding application, development, piloting and implementation of the intervention, planning and monitoring data collection, data analysis, and wrote the first draft. BZ participated in designing the study, planning the data collection, and analysis of data. AB participated in conceptualising and designing the study, applying for funding, developing, piloting and implementing the intervention, and planning the data collection. CLom participated in designing the study and analysed the data. NF participated in designing the study, developing, piloting and implementing the intervention, and planning and monitoring data collection, and data management. GT participated in conceptualising and designing the study, developing, piloting and implementing the intervention, and planning the data collection. OS participated in developing, piloting and implementing the intervention, and planning the data collection. RP participated in developing, piloting and implementing the intervention. NM participated in developing, piloting and implementing the intervention. DGP participated in developing, piloting and implementing the intervention, and planning the data collection. TK participated in applying for funding, and developing, piloting and implementing the intervention. MB participated in designing the study. NL participated in designing the study. CLu participated in conceptualising and designing the study and applying for funding. All authors reviewed the manuscript and approved the final version.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of Competing Interest

All authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.12.123.

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