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Improving depression outcomes among primary care patients: Protocol for a cluster randomised controlled trial

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Improving depression outcomes among primary care patients: Protocol for a cluster randomised controlled trial

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Abstract

Introduction Depression is a common and debilitating condition. In Australia, general practitioners (GPs) are key providers of depression care. However, available evidence suggests that case finding for depression in primary care is poor. This study will examine whether a systematic approach to screening for depression and assessing patient preferences for depression care improves depression outcomes among primary care patients.

Methods and analysis General practice clinics will be randomly assigned to either the intervention (n=12) or usual care group (n=12). Patients who are aged 18 and older, presenting for general practice care will be eligible to participate. Those who agree will be asked to complete a baseline survey administered on a touchscreen computer at their GP clinic, and then a follow-up survey at 3, 6 and 12 months. Those attending usual care practices will receive standard care. GPs at intervention practices will complete an online Clinical e-Audit, and will be provided with provider and patient-directed resources for depression care. Patients recruited at intervention practices who score 10 or above on the PHQ-9 will have feedback regarding their depression screening results and preferences for care provided to their GP. The primary analysis will compare the number of cases of depression between the intervention and control groups.

Ethics and dissemination The study has been approved by the University of Newcastle Human Research Ethics Committee, and registered with Human Research Ethics Committees of the University of Wollongong, Monash University and University of New South Wales. Results will be disseminated through peer reviewed journal publications and conference presentations.

Registration Australian New Zealand Clinical Trial Registration: ACTRN12618001139268, Approved 11th July 2018; UTN: U1111-1213-0171.

Key words: depression, randomized controlled trial, intervention study, primary health care

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Strengths and limitations of this study

- This study will use a cluster randomised controlled design
- Examining patient preferences for care as part of depression screening will facilitate a more patient-centred approach to care
- It is not feasible to use a gold standard clinical interview to diagnose depression, therefore a PHQ-9 score of 10 or more will be used to define 'cases' of depression at follow-up.
- PHQ-9 scores at 12 month follow-up will be the primary outcome, however, shorter-term impacts of the intervention will be examined via 3- and 6-month follow-up surveys.

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INTRODUCTION

Depression affects 350 million people worldwide.[1] It can have a profound impact on quality of life and is associated with unemployment and economic disadvantage.[2 3] Depression and anxiety are the second highest causes of disease burden in Australia, with mental disorders costing over $6.38 billion annually in direct and indirect costs.[4] In 2015-2016, depression was the fourth most common problem managed by general practitioners (GPs), accounting for 4.2 in every 100 encounters[5] and depression accounts for 12% of primary care initiated referrals to allied health providers.[5]

Available evidence suggests one barrier to improving depression outcomes is poor case finding in the primary care setting. Mitchell's meta-analysis of 41 studies indicated that there was agreement between GPs' unassisted diagnoses of depression among primary care patients and diagnoses from structured interviews in only 47% of cases.[6] Our study, conducted with 51 GPs and over 1500 primary care patients, also demonstrated that GP unassisted diagnosis was highly specific (87%), but poor in terms of sensitivity (51%) compared to a standardized instrument, the PHQ-9.[7]

Several reviews have addressed the question of whether providing GPs with feedback about patients' scores on a standardised assessment of depression is effective in improving outcomes in the primary care setting.[8-10] The most recent systematic review identified just five studies relevant to the general adult primary care population.[10] Of the five trials, three reported no intervention effect.[11-13] Notably, the two studies which reported a positive impact also included additional staff support to assist with managing depression. In the first study, 47% of those newly identified with depression achieved remission in the intervention group, compared to

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28% in the usual care group at 12 months.[14] In the second, 58% of people newly and previously identified as cases achieved remission in the intervention group, compared to 49% in the usual care group at 12 months.[15]

Despite the relative simplicity and potential benefits of providing feedback to GPs on patients' depression scores, there is a lack of methodologically adequate research to inform practice. Studies are characterised by a lack of power and high attrition.[10] Four out of five studies in O'Connor's review[10] were conducted in the United States, and no Australian trials have been conducted. Therefore, the applicability of available evidence to the Australian context is unknown.

Primary care patients who receive treatment that matches their preference recover more quickly than those who perceive a mismatch between their preferred and received treatment.[16] Therefore, information about patients' perceived needs and preferences for treatment are likely to be an important adjunct to information on severity of depressive symptoms. This study will examine the effectiveness of an intervention providing GPs with feedback about their patients' depressive symptoms, preferences, and perceived need for help.

Primary aim. To determine the effectiveness and cost-effectiveness of an intervention designed to facilitate delivery of patient-centred depression care in reducing the proportion of primary care patients identified as possible "cases" for depression at 12 months' follow up.

Secondary aims. To examine the impact of the intervention on GPs' patterns of referrals for mental health care and prescription of psychotropic medications over a 12 month follow up period.

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Primary hypotheses. 1) Compared to those attending practices allocated to the usual care group, the proportion of patients scoring 10 or more on the Patient Health Questionnaire (PHQ-9) will be 10% lower in the intervention group at 12-month follow-up. 2) The intervention will be cost-effective compared to usual care based on Quality-Adjusted Life Years and commonly employed willingness to pay thresholds.

Secondary hypotheses. Compared to those attending usual care practices, a 20% higher proportion of intervention patients identified with possible depression (PHQ9 ≥10) at baseline will receive mental health care and prescription medications that align with eTG recommendations for their level of depression (mild, moderate or severe depression) over the 12 month follow-up period.

METHODS AND ANALYSIS

Design: A two-arm cluster randomised controlled trial with general practices as the unit of allocation. Consenting practices will be randomly allocated to either: 1) usual care; or 2) intervention. Patient outcomes will be collected at baseline and at 3, 6, and 12-month follow-up. The primary endpoint will be the proportion of likely 'cases' of depression at 12 month follow-up, as measured by the PHQ-9. Cost-effectiveness and delivery of depression care will be assessed using data that reflects the resources used to deliver the intervention, including implementation costs, and health service utilisation, specifically the Pharmaceutical Benefits Scheme (PBS) and Medicare Benefits Schedule (MBS). Utilisation data will be obtained for the 12 months preceding patient recruitment and 12 months post-recruitment for consenting participants. Results will be reported in line with Consolidated Standards of Reporting Trials (CONSORT) recommendations.[17]

General practice sample.

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Practice eligibility: Eligible, practices must have at least one eligible GP who works at least 0.4 full time equivalent (or four sessions) a week who agrees to participate. Eligible GPs will have completed Royal Australian College of General Practitioners (RACGP) accredited GP Mental Health Skills Training. GPs who have previously completed the online Clinical e-Audit: Depression: Achieve remission, prevent relapse (92162) will not be eligible to participate. Sampling of practices will continue until 24 practices are recruited to the trial.

Recruitment*:* Practices will be sent an invitation letter from one of the academic GP investigators; then contacted by telephone after one week to discuss participation. Informed written consent will be sought from both the practice and individual GPs within the practices.

Randomization: Practices will be randomly allocated to the intervention (n=12) or usual care group (n=12). Randomisation will be stratified according to practice characteristics which influence the degree of co-location with mental health providers (community health centre, small private practice (1-3 GPs), large private practice (>3 GPs), and characteristics of the area in which the practice is located (metropolitan areas which are socioeconomically advantaged; metropolitan areas with lower socioeconomic advantage, and regional and remote areas). The latter has been shown to be associated with differences in patterns of depression care.[18] The Accessibility and Remoteness Index of Australia (ARIA+) will be used to define metropolitan (ARIA $\leq$ 2.4), and regional or remote (ARIA >2.4);[19] while a median split of post codes will define high versus lower socioeconomic advantage according to the Index of Relative Socioeconomic Advantage and Disadvantage.[20] The Clinical Research Design, IT and Statistical Support (CReDITSS) unit at the Hunter Medical Research Institute will oversee randomization.

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Patient Sample: ***Eligibility.*** Those attending a participating practice aged 18 years or older, and who have sufficient English to complete a survey independently. ***Exclusion criteria:*** Patients judged by staff to be physically or cognitively unable to complete the survey or provide independent informed consent.

Training of staff in recruitment processes: Recruitment will be conducted by trained practice staff (e.g. a practice nurse or receptionist). Nominated practice staff will receive videos demonstrating patient recruitment processes, a recruitment manual and one-to-one tutorials. These will be conducted by Skype and/or telephone. During the tutorials, staff will practice recruitment processes, including role-plays of simulated situations to assess competency, and receive feedback. A researcher will make site visits to practices to ensure that recruitment processes are being implemented in accordance with the protocol and assist with trouble shooting.

Recruitment of patients: Attending patients of participating GPs will be invited to participate in the study by practice staff upon presenting to reception for their appointment. Written informed consent will also be obtained from all participants for the study. This will include consent to access MBS and PBS data for the 12 months before and following recruitment.

<INSERT FIGURE 1>

Data collection: ***Baseline.*** Participants will complete a 5-10 minute survey using a web-connected touchscreen computer tablet while waiting for their GP consultation. The baseline survey will include screening questions to confirm eligibility, as well as questions about socio-demographic characteristics, history of depression, medical conditions, PHQ-9, Short Form Health Survey (SF-12v2), perceived need for GP help with behavioural risk factors (quitting smoking, improving diet, increasing exercise, reducing alcohol intake and losing weight),

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perceived need for GP help with emotional problems (assessed by the General Practice Users Perceived needs Inventory [GUPI][21]), and the name of the GP they are seeing. ***Follow-up.*** The same participants will complete a follow-up pen-and-paper survey at 3, 6 and 12 months follow-up. The survey will include questions about the patient's health, the PHQ-9, SF-12, questions about actions taken to improve health and quality of life, and questions regarding adherence to any prescribed treatments. The follow-up survey will be mailed to participants with a pre-addressed, reply paid envelope. A reminder package, including a second copy of the survey, will be sent to non-responders after two weeks. A second reminder package will be sent to non-responders after a further two weeks. Patients will be given the option to complete the survey online if they prefer, via a link provided in the package.

Ethical usual care: Patients attending practices allocated to this condition will complete the baseline screening questionnaire. In line with our duty of care, GPs will be provided with feedback for patients in the usual care condition who score 20 or more at baseline on the PHQ-9 (indicative of severe depression)[22] and/or who score >1 on item 9 of the PHQ-9 (indicative of potential self-harm).[23] At follow-up, patients who score 20 on the PHQ-9 or who score >1 on item 9 of the PHQ-9 will be sent a letter by the research team. The letter will include information about potential sources of help, including their GP and a mental health helpline LifeLine Australia.

Intervention. ***Step 1: GP education*****.** Consenting GPs will complete a RACGP-endorsed online active learning module prior to commencement of data collection. The module was developed by NPS MedicineWise and entitled "Depression: Achieving remission, preventing relapse" (92162). The module is in the form of a Clinical e-Audit whereby participants are asked to enter data and reflect on the management of 10 of their adult patients who have been prescribed antidepressant medication. It covers both pharmacological and non-pharmacological

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treatments for depression, and will guide GPs in the development of personalised management plans, reviewing patient responses to treatment and modifying plans accordingly. Each GP will also have access to a Quick Reference Guide with contact details of organisations available to support both clinicians and patients in managing depression.

***Step 2: Pre-GP consultation*.** Consenting patients will complete the baseline assessment via touchscreen computer prior to their consultation with the GP. Upon survey completion, the web-based software will automatically calculate the patient's PHQ-9 score. The patient will hand the computer tablet back to the practice staff member upon completion of the survey. The staff member will open a summary screen of the patient's responses to the PHQ-9 and GUPI. For those patients who score 10 or more on the PHQ-9, or greater than 0 on item 9, tailored feedback of the patient's PHQ-9 and GUPI results will be generated for provision to their GP. A copy of the feedback will be provided to the patient's GP.

***Step 3: GP consultation*.** The feedback sheet will provide GPs with summarised information about the patient's severity of depressive symptoms (i.e. PHQ-9 score) including information on the patient's response to the item 9 question about potential self-harm, and the patient's willingness to discuss help for depression with their GP and their preferred type of help (i.e. GUPI). Together with the GP's knowledge of the patient's personal and medical history, this information can be used by the GP to guide secondary screening to determine whether the patient has a diagnosis of depression, and if so, which treatment approach should be recommended.

***Step 4: Patient self-management strategies*.** GPs will also be provided with printed brochures on self-management strategies that can be offered to patients at GP discretion. For example, they may be offered to patients who indicate a preference for self-management strategies; or to those for whom self-management strategies are likely to be a useful adjunct to the agreed treatment approach. The brochures will comprise of the publicly available "beyondblue

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Connect toolkit." The toolkit consists of six worksheets with information and general advice for improving wellbeing through activities such as simple cognitive behavioural strategies. The toolkit also includes telephone and web contact details for beyondblue mental health support services.

Measures Participants will complete a survey at baseline, 3, 6 and 12 months' follow-up. ***Primary outcome.*** *Patient Health Questionnaire 9 (PHQ-9)*[22] (9-items) is a brief depression screening tool which has been widely used in primary care settings. Frequency of symptoms is rated from 0 (not at all) to 3 (nearly every day). Higher scores indicate more severe depression. A recent meta-analysis has shown that the tool has high specificity (0.8) and sensitivity (0.92) when used to screen and diagnose major depression.[24] The PHQ-9 will be administered at baseline and each follow-up.

Secondary outcomes: Quality of life will be measured using the *Short Form Health Survey (SF -12).* This instrument asks patients to self-rate their health and their ability to undertake normal activities. The SF-12 is a reliable measure of health related quality of life among people with mental health conditions[25] and has been validated for use within the Australian population.[26] Estimates for total health service utilisation and medication use for each participant will be sourced from the linked MBS and PBS data. *Delivery of mental health services* specifically will be assessed via the following MBS items: GP mental health treatment items (2700-2717); Provision of Focused Psychological Strategies (2721-2727); Provision of Psychological Therapy Services by a Clinical Psychologist (80000-80020); and Consultant Psychiatrist Referred Patient Assessment and Management Plan (296, 299, 361, 291, 293, 359). For each service, details such as the following will be provided: Date of service, Medicare item number; item description; provider charge; schedule fee; benefit paid;

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patient out of pocket; scrambled rendering provider number; date of referral; rendering provider postcode; ordering provider postcode.

Psychotropic medications. For each participant, the following details regarding prescription of psychotropic medications will be obtained: medication type; date of supply; date of prescription; PBS item code; item description; patient category; patient contribution; net benefit; scrambled prescriber number; pharmacy postcode.

Explanatory variables collected at baseline: *Patient socio-demographics and health variables.* Age, gender, marital status, education, Aboriginal and Torres Strait Islander status, postcode, number of family/household members, pregnancy, any diagnosed chronic diseases including depression, and name of GP patient is seeing will be collected at baseline.

General Practice Users' Perceived Need Inventory (GUPI)[21]. This instrument asks respondents to indicate their need for: (a) information about emotional problems and treatments; (b) medication to help manage emotional problems; (c) counselling for emotional problems; (d) help with practical issues such as housing or money; and (e) help with ability to work and care for oneself.

Explanatory variables collected at each follow-up: *Use of self-management strategies.* Participants will be asked if they undertook any self-management strategies or resources from their GP in the past three months; and to indicate the type and frequency of use of any self-management strategies or resources. *Adherence to medications for depression.* Patients will be asked if they have been prescribed any antidepressant medications in the past three months. Self-reported type of antidepressant medications will be crosschecked with PBS data. Participants who report having been prescribed antidepressants will be asked whether, in the past week, they have (a) missed any doses; (b) taken any doses late; and/or (c) taken more than the prescribed dose.

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Practice measures: Data on location, number full time equivalent GPs, and whether or not the practice employs a nurse will be obtained from each practice.

GP measures: GPs will answer a short survey at the time of consent to self-report characteristics including age; sex; number of years worked in general practice; employment status; and number of sessions worked per week. Details of training in mental health skills will be sought including type of course undertaken and year of course completion. Data about the number of full time equivalent GPs, and whether or not the practice employs a nurse will be obtained, as well as whether the practice bulk bills.

Acceptability data: *Acceptability of the intervention (intervention GPs only):* At the conclusion of recruitment, GPs at intervention sites will be invited to complete a telephone interview to provide feedback about intervention acceptability and feasibility.

Monitoring of intervention and protocol fidelity: A protocol implementation checklist will be used by the trial coordinator to monitor the implementation of trial procedures. GPs will be asked to self-report completion of the educational module, and the trial co-ordinator will record the date of provision of intervention materials to each intervention GP.

Data monitoring: Practices, GPs and patients will have access to a 1800 telephone number where any adverse events can be reported. Unintended effects will also be explored through analysis of trial outcome data on depressive symptoms and health service use.

The investigator team will take responsibility for monitoring adverse events, and determining, in consultation with relevant ethics committees, what steps need to be taken to minimise further adverse events.

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Data management: Data collected at baseline via an online survey will be automatically captured. Data collected at follow-up by paper and pencil will be entered into a SAS database. A number of quality assurance processes will be used to endure data entry is accurate. Firstly, programming of SAS will restrict the number of valid entries for a given question, thus alerting to a potential error if data outside these values is entered. A random sample of 20% will be double entered. Finally, data cleaning will take place to identify anomalies in the data that may require cross checking with original surveys. Survey data from baseline and each follow-up will be linked for each participant. These data will be linked to data obtained from the Department of Human Services on the use of MBS services and medications obtained via the PBS.

Statistical Analysis: ***Consenters versus non-consenters.*** *Practices*. Characteristics of consenting and non-consenting practices will be compared to identify any consent bias using the chi-square test for categorical variables and the t-test or a non-parametric equivalent for continuous variables. *Patients.* Examination of the demographic characteristics of consenting and non-consisting patients will also be tested. Data will be analysed using the intent to treat principal. Baseline data will be summarized as the number of observations, means, standard deviations, medians, minimums and maximums where the data are continuous and as number of observations and frequencies where the data are categorical. The data will be presented separately by treatment group. ***Aim 1.*** For the primary outcome, a PHQ-9 score of less than 10 at 12 months, we will test for group differences using a generalised linear mixed effects regression model, with a log link and a binomial distribution. The dichotomous outcome at each follow-up (baseline, 3 months, 6 months and 12 months) is the dependent variable. The model will include fixed effect for baseline history of depression, treatment group (intervention vs usual care), time, and treatment*time interaction. Treatment group comparisons at post-

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baseline each visit will be estimated by differences in LS means from the treatment*visit interaction and will be presented as risk ratios with accompanying p-values and 95% confidence intervals, with the primary comparison being that at 12 months. We will investigate various variance-covariance structures for the within-subject repeated measures (such as autoregressive, unstructured, and compound symmetric) and choose the model with the best fit according to the smallest Akaike Information Criteria. As a sensitivity analysis we will perform analyses under a variety of plausible assumptions regarding the missing data mechanism to investigate the impact of departures from the missing data assumptions. ***Aim 2.*** The proportion of newly identified cases at baseline who receive appropriate care at follow-up will be compared between groups using a generalised linear mixed model as described above, but the cohort will be restricted to the individuals that are identified as new cases at baseline, and the outcome will be whether or not they received appropriate care at each follow-up time point.

Sample Size: A sample of 720 patients per treatment arm (~60 per practice) at 12 months follow-up will give the study 80% power to detect a 10% decrease in the proportion of patients who score more than 10 on the PHQ-9 in the experimental group compared to usual care at a significance level of 5%. This calculation assumes, based on data from our prior study, an intra-class correlation coefficient of 0.04, and 20% of the patients in the usual care group will have PHQ-9 scores of more than 10. Allowing for 10% attrition at each follow-up, we will need to recruit 2000 eligible consenting patients (~83 per practice).

Cost-Effectiveness Analysis (CEA): The economic study will be based on a cost-effectiveness analysis using within-trial outcomes and will be undertaken from a healthcare provider perspective. The study will capture the costs and consequences from the intervention and compare them to usual care. Costs will be estimated based on the additional resources required for intervention delivery, as well as net costs associated with healthcare utilisation. Unit cost data for all resources associated with an intervention will be collated based on the

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Pharmaceutical Benefits Advisory Committee (PBAC) manual of resource items[27] and the Medicare Schedule, measured in real prices for the selected reference year. The measure of effect will be quality adjusted life years (QALYs). QALYs will be calculated from SF-6D, a multi-attribute utility instrument that can be derived from the responses to the SF-12. The costs and health outcomes will be used to determine the incremental cost-effectiveness ratio (ICER), reflecting the additional cost per QALY gained. Cost-effectiveness and acceptability will be assessed against commonly accepted willingness to pay estimates per QALY. The economic results will be considered in the context of decision-making criteria: strength of evidence; capacity of the intervention to reduce inequity; acceptability to stakeholders; feasibility; and sustainability. The analysis will conform to NHMRC protocols for economic evaluations.

RESEARCH ETHICS AND DISSEMINATION

Ethics approvals: The study has been approved by the University of Newcastle Human Research Ethics Committee (EC00144; Ref No. H-2017-0291), with this approval accepted and registered by Monash University Human Research Ethics Committee (EC00234; Project No. 14048); Joint University of Wollongong and Illawarra Shoalhaven Local Health District Health and Medical Human Research Ethics Committee (EC00150/EC00394; Ref No. 2018/143) and; University of New South Wales (UNSW) Sydney (H-2017-0291). Any changes to the protocol will be communicated to the study investigators and approved by each of the ethics committees. Approval to access PBS and MBS data was granted by the External Request Evaluation Committee (EREC), Department of Human Services (Ref No. MI9644).

Confidentiality and privacy of information: All participant data will be de-identified. The consent form which will link the participant name to their unique study identification number

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will be stored separately to survey data in a locked filing cabinet. Electronic files containing survey data will be stored on the University of Newcastle server in a password-protected file. Only the chief investigators and staff employed to work directly on the study will have access to data.

Dissemination: This will develop new knowledge that is applicable to the Australian health care system, and provide policy relevant information regarding the benefit of the intervention and its potential for broad adoption. Study findings will be disseminated through conference presentations and publications in peer reviewed journals.

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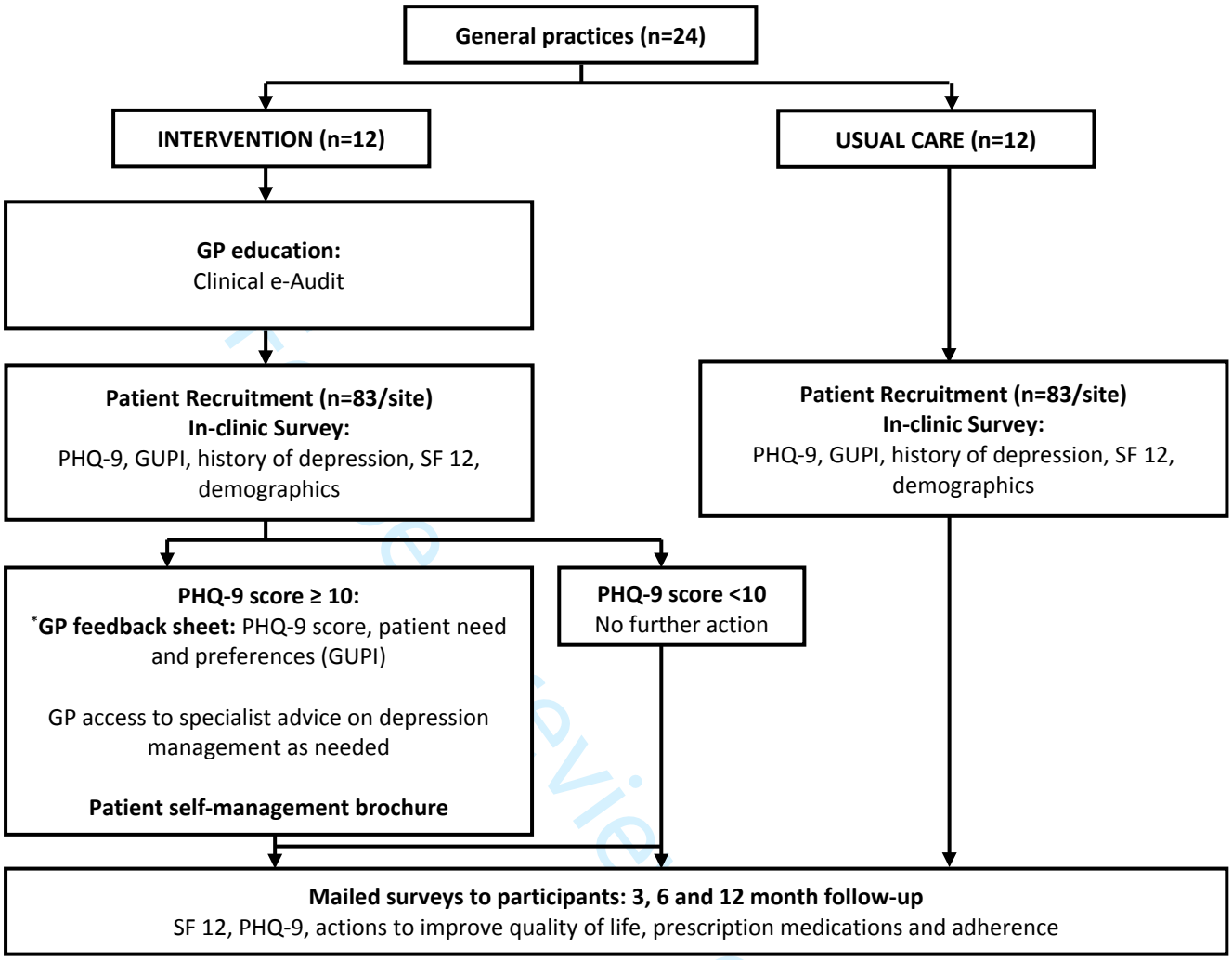
Figure 1: Flowchart of study process



*For duty of care purposes, GPs will also be provided with feedback for usual care participants at baseline who score 20 or more on PHQ-9 (indicative of severe depression) or any participant who scores >1 on item 9 of PHQ-9 (indicative of potential self-harm).

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Improving depression outcomes among Australian primary care patients: Protocol for a cluster randomised controlled trial

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Improving depression outcomes among Australian primary care patients: Protocol for a cluster randomised controlled trial

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Abstract

Introduction Depression is a common and debilitating condition. In Australia, general practitioners (GPs) are key providers of depression care. However, available evidence suggests that case finding for depression in primary care is poor. This study will examine whether a systematic approach to screening for depression and assessing patient preferences for depression care improves depression outcomes among primary care patients.

Methods and analysis A cluster randomized controlled design will be used with general practice clinics randomly assigned to either the intervention (n=12) or usual care group (n=12). Patients who are aged 18 and older, presenting for general practice care will be eligible to participate. Eighty-three participants will be recruited at each clinic. Participants will be asked to complete a baseline survey administered on a touchscreen computer at their GP clinic, and then a follow-up survey at 3, 6 and 12 months. Those attending usual care practices will receive standard care. GPs at intervention practices will complete an online Clinical e-Audit, and will be provided with provider and patient-directed resources for depression care. Patients recruited at intervention practices who score 10 or above on the PHQ-9 will have feedback regarding their depression screening results and preferences for care provided to their GP. The primary analysis will compare the number of cases of depression between the intervention and control groups.

Ethics and dissemination The study has been approved by the University of Newcastle Human Research Ethics Committee, and registered with Human Research Ethics Committees of the University of Wollongong, Monash University and University of New South Wales. Results will be disseminated through peer reviewed journal publications and conference presentations.

Registration Australian New Zealand Clinical Trial Registration: ACTRN12618001139268, Approved 11th July 2018; UTN: U1111-1213-0171. Protocol Version 1, 21st October 2019.

Key words: depression, randomized controlled trial, intervention study, primary health care

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Strengths and limitations of this study

- This study will use a cluster randomised controlled design
- Examining patient preferences for care as part of depression screening will facilitate a more patient-centred approach to care
- It is not feasible to use a gold standard clinical interview to diagnose depression, therefore a PHQ-9 score of 10 or more will be used to define 'cases' of depression at follow-up.
- PHQ-9 scores at 12 month follow-up will be the primary outcome, however, shorter-term impacts of the intervention will be examined via 3- and 6-month follow-up surveys.

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INTRODUCTION

Depression affects 350 million people worldwide.[1] It can have a profound impact on quality of life and is associated with unemployment and economic disadvantage.[2 3] Depression and anxiety are the second highest causes of disease burden in Australia, with mental disorders costing over $6.38 billion annually in direct and indirect costs.[4] In 2015-2016, depression was the fourth most common problem managed by general practitioners (GPs), accounting for 4.2 in every 100 encounters[5] and depression accounts for 12% of primary care initiated referrals to allied health providers.[5]

Available evidence suggests one barrier to improving depression outcomes is poor case finding in the primary care setting. Mitchell's meta-analysis of 41 studies indicated that there was agreement between GPs' unassisted diagnoses of depression among primary care patients and diagnoses from structured interviews in only 47% of cases.[6] Our study, conducted with 51 GPs and over 1500 primary care patients, also demonstrated that GP unassisted diagnosis was highly specific (87%), but poor in terms of sensitivity (51%) compared to a standardized instrument, the PHQ-9.[7]

Several reviews have addressed the question of whether providing GPs with feedback about patients' scores on a standardised assessment of depression is effective in improving outcomes in the primary care setting.[8-10] The most recent systematic review identified just five studies relevant to the general adult primary care population.[10] Of the five trials, three reported no intervention effect.[11-13] Notably, the two studies which reported a positive impact also included additional staff support to assist with managing depression. In the first study, 47% of those newly identified with depression achieved remission in the intervention group, compared to

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28% in the usual care group at 12 months.[14] In the second, 58% of people newly and previously identified as cases achieved remission in the intervention group, compared to 49% in the usual care group at 12 months.[15]

Despite the relative simplicity and potential benefits of providing feedback to GPs on patients' depression scores, there is a lack of methodologically adequate research to inform practice. Studies are characterised by a lack of power and high attrition.[10] Four out of five studies in O'Connor's review[10] were conducted in the United States, and no Australian trials have been conducted. Therefore, the applicability of available evidence to the Australian context is unknown.

Primary care patients who receive treatment that matches their preference recover more quickly[16] and are less likely to drop out of treatment[17] than those who perceive a mismatch between their preferred and received treatment. Therefore, information about patients' perceived needs and preferences for treatment are likely to be an important adjunct to information on severity of depressive symptoms. This study will examine the effectiveness of an intervention providing GPs with feedback about their patients' depressive symptoms, preferences, and perceived need for help.

Primary aim. To determine the effectiveness and cost-effectiveness of an intervention designed to facilitate delivery of patient-centred depression care in reducing the proportion of primary care patients identified as possible "cases" for depression at 12 months' follow up.

Secondary aims. To examine the impact of the intervention on GPs' patterns of referrals for mental health care and prescription of psychotropic medications over a 12 month follow up period.

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Primary hypotheses. 1) Compared to those attending practices allocated to the usual care group, the proportion of patients scoring 10 or more on the Patient Health Questionnaire (PHQ-9) will be 10% lower in the intervention group at 12-month follow-up. 2) The intervention will be cost-effective compared to usual care based on Quality-Adjusted Life Years and commonly employed willingness to pay thresholds.

METHODS AND ANALYSIS

Design: A two-arm cluster randomised controlled trial with general practices as the unit of allocation. (Please refer to Figure 1). Consenting practices will be randomly allocated to either: 1) usual care; or 2) intervention. Patient outcomes will be collected at baseline and at 3, 6, and 12-month follow-up. The primary endpoint will be the proportion of likely 'cases' of depression at 12 month follow-up, as measured by the PHQ-9. Cost-effectiveness and delivery of depression care will be assessed using data that reflects the resources used to deliver the intervention, including implementation costs, and health service utilisation, specifically the Pharmaceutical Benefits Scheme (PBS) and Medicare Benefits Schedule (MBS). Utilisation data will be obtained for the 12 months preceding patient recruitment and 12 months post-recruitment for consenting participants. Results will be reported in line with Consolidated Standards of Reporting Trials (CONSORT) recommendations.[18]

Setting: General practice clinics in Australia.

General practice sample.

Practice eligibility: Eligible, practices must have at least one eligible GP who works at least 0.4 full time equivalent (or four sessions) a week who agrees to participate. Eligible GPs will have completed Royal Australian College of General Practitioners (RACGP) accredited GP Mental Health Skills Training. GPs who have previously completed the online Clinical e-Audit:

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Depression: Achieve remission, prevent relapse (92162) will not be eligible to participate. Sampling of practices will continue until 24 practices are recruited to the trial.

***Recruitment**:* Practices will be sent an invitation letter from one of the academic GP investigators; then contacted by telephone after one week to discuss participation. Informed written consent will be sought from both the practice and individual GPs within the practices.

Randomisation: Practices will be randomly allocated to the intervention (n=12) or usual care group (n=12). Randomisation will be stratified according to practice characteristics which influence the degree of co-location with mental health providers (community health centre, small private practice (1-3 GPs), large private practice (>3 GPs), and characteristics of the area in which the practice is located (metropolitan areas which are socioeconomically advantaged; metropolitan areas with lower socioeconomic advantage, and regional and remote areas). The latter has been shown to be associated with differences in patterns of depression care.[19] The Accessibility and Remoteness Index of Australia (ARIA+) will be used to define metropolitan (ARIA $\leq$ 2.4), and regional or remote (ARIA >2.4);[20] while a median split of post codes will define high versus lower socioeconomic advantage according to the Index of Relative Socioeconomic Advantage and Disadvantage.[21] Randomisation will be conducted centrally by the Clinical Research Design, IT and Statistical Support (CReDITSS) unit at the Hunter Medical Research Institute. Due to the nature of the intervention, blinding of health care providers and patients will not be possible.

Patient Sample: ***Eligibility.*** Those attending a participating practice aged 18 years or older, and who have sufficient English to complete a survey independently. ***Exclusion criteria:*** Patients judged by staff to be physically or cognitively unable to complete the survey or provide independent informed consent.

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Training of staff in recruitment processes: Recruitment will be conducted by trained practice staff (e.g. a practice nurse or receptionist). Nominated practice staff will receive videos demonstrating patient recruitment processes, a recruitment manual and one-to-one tutorials. These will be conducted by Skype and/or telephone. During the tutorials, staff will practice recruitment processes, including role-plays of simulated situations to assess competency, and receive feedback. A researcher will make site visits to practices to ensure that recruitment processes are being implemented in accordance with the protocol and assist with trouble shooting. Practices will be reimbursed for staff time spent undergoing training. A fee of $100 per participant recruited will be provided to cover staff time spent on recruiting participants.

Recruitment of patients: Attending patients of participating GPs will be invited to participate in the study by practice staff upon presenting to reception for their appointment. Written informed consent will also be obtained from all participants for the study (see supplementary material). This will include consent for non-identifiable data to be shared with third parties to encourage scientific scrutiny or for the purpose of further research. Participants will also be asked to provide separate consent to access MBS and PBS data for the 12 months before and following recruitment.

<INSERT FIGURE 1>

Data collection: ***Baseline.*** Participants will complete a 5-10 minute survey using a web-connected touchscreen computer tablet while waiting for their GP consultation. The baseline survey will include screening questions to confirm eligibility, as well as questions about socio-demographic characteristics, history of depression, medical conditions, PHQ-9, Short Form Health Survey (SF-12v2), perceived need for GP help with behavioural risk factors (quitting smoking, improving diet, increasing exercise, reducing alcohol intake and losing weight),

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perceived need for GP help with emotional problems (assessed by the General Practice Users Perceived needs Inventory [GUPI][22]), and the name of the GP they are seeing. ***Follow-up.*** The same participants will complete a follow-up pen-and-paper survey at 3, 6 and 12 months follow-up. The survey will include questions about the patient's health, the PHQ-9, SF-12, questions about actions taken to improve health and quality of life, and questions regarding adherence to any prescribed treatments. The follow-up survey will be mailed to participants with a pre-addressed, reply paid envelope. A reminder package, including a second copy of the survey, will be sent to non-responders after two weeks. A second reminder package will be sent to non-responders after a further two weeks. Patients will be given the option to complete the survey online if they prefer, via a link provided in the package.

Ethical usual care: Patients attending practices allocated to this condition will complete the baseline screening questionnaire. In line with our duty of care, GPs will be provided with feedback for patients in the usual care condition who score 20 or more at baseline on the PHQ-9 (indicative of severe depression)[23] and/or who score >1 on item 9 of the PHQ-9 (indicative of potential self-harm).[24] At follow-up, patients who score 20 on the PHQ-9 or who score >1 on item 9 of the PHQ-9 will be sent a letter by the research team. The letter will include information about potential sources of help, including their GP and a mental health helpline Lifeline Australia.

Intervention. The intervention will comprise usual care in addition to the following steps. ***Step 1: GP education.*** Consenting GPs will complete a RACGP-endorsed online active learning module prior to commencement of data collection. The module was developed by NPS MedicineWise and entitled "Depression: Achieving remission, preventing relapse" (92162). The module is in the form of a Clinical e-Audit whereby participants are asked to enter data

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and reflect on the management of 10 of their adult patients who have been prescribed antidepressant medication. It covers both pharmacological and non-pharmacological treatments for depression, and will guide GPs in the development of personalised management plans, reviewing patient responses to treatment and modifying plans accordingly. Each GP will also have access to a Quick Reference Guide with contact details of organisations available to support both clinicians and patients in managing depression.

***Step 2: Pre-GP consultation*.** Consenting patients will complete the baseline assessment via touchscreen computer prior to their consultation with the GP. Upon survey completion, the web-based software will automatically calculate the patient's PHQ-9 score. The patient will hand the computer tablet back to the practice staff member upon completion of the survey. The staff member will open a summary screen of the patient's responses to the PHQ-9 and GUPI. For those patients who score 10 or more on the PHQ-9, or greater than 0 on item 9, tailored feedback of the patient's PHQ-9 and GUPI results will be generated for provision to their GP. A copy of the feedback will be provided to the patient's GP.

***Step 3: GP consultation*.** The feedback sheet will provide GPs with summarised information about the patient's severity of depressive symptoms (i.e. PHQ-9 score) including information on the patient's response to the item 9 question about potential self-harm, and the patient's willingness to discuss help for depression with their GP and their preferred type of help (i.e. GUPI). Together with the GP's knowledge of the patient's personal and medical history, this information can be used by the GP to guide secondary screening to determine whether the patient has a diagnosis of depression, and if so, which treatment approach should be recommended.

***Step 4: Patient self-management strategies*.** GPs will also be provided with printed brochures on self-management strategies that can be offered to patients at GP discretion. For example, they may be offered to patients who indicate a preference for self-management strategies; or to

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those for whom self-management strategies are likely to be a useful adjunct to the agreed treatment approach. The brochures will comprise of the publicly available "beyondblue Connect toolkit." The toolkit consists of six worksheets with information and general advice for improving wellbeing through activities such as simple cognitive behavioural strategies. The toolkit also includes telephone and web contact details for beyondblue mental health support services.

Measures Participants will complete a survey at baseline, 3, 6 and 12 months' follow-up. ***Primary outcome.*** *Patient Health Questionnaire 9 (PHQ-9)*[23] (9-items) is a brief depression screening tool which has been widely used in primary care settings. Frequency of symptoms is rated from 0 (not at all) to 3 (nearly every day). Higher scores indicate more severe depression. A recent meta-analysis has shown that the tool has high specificity (81%) and sensitivity (85%) when used to screen for major depression.[25] The pooled positive likelihood ratio was 5.37 and the negative likelihood ratio was 0.21. A high Cronbach's alpha of .89 has been reported in a primary care sample.[23] The PHQ-9 will be administered at baseline and each follow-up.

Secondary outcomes: Quality of life will be measured using the *Short Form Health Survey (SF -12).* This instrument asks patients to self-rate their health and their ability to undertake normal activities. The SF-12 is a reliable measure of health related quality of life among people with mental health conditions[26] and has been validated for use within the Australian population.[27] Estimates for total health service utilisation and medication use for each participant will be sourced from the linked MBS and PBS data. *Delivery of mental health services* specifically will be assessed via the following MBS items: GP mental health treatment items (2700-2717); Provision of Focused Psychological Strategies (2721-2727); Provision of Psychological Therapy Services by a Clinical Psychologist (80000-80020); and Consultant Psychiatrist Referred Patient Assessment and Management Plan (296, 299, 361, 291, 293, 359).

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For each service, details such as the following will be provided: Date of service, Medicare item number; item description; provider charge; schedule fee; benefit paid; patient out of pocket; scrambled rendering provider number; date of referral; rendering provider postcode; ordering provider postcode.

Psychotropic medications. For each participant, the following details regarding prescription of psychotropic medications will be obtained: medication type; date of supply; date of prescription; PBS item code; item description; patient category; patient contribution; net benefit; scrambled prescriber number; pharmacy postcode.

Explanatory variables collected at baseline: *Patient socio-demographics and health variables.* Age, gender, marital status, education, Aboriginal and Torres Strait Islander status, postcode, number of family/household members, pregnancy, any diagnosed chronic diseases including depression, and name of GP patient is seeing will be collected at baseline.

General Practice Users' Perceived Need Inventory (GUPI)[22]. This instrument asks respondents to indicate their need for: (a) information about emotional problems and treatments; (b) medication to help manage emotional problems; (c) counselling for emotional problems; (d) help with practical issues such as housing or money; and (e) help with ability to work and care for oneself.

Explanatory variables collected at each follow-up: *Use of self-management strategies.* Participants will be asked if they undertook any self-management strategies or resources from their GP in the past three months; and to indicate the type and frequency of use of any self-management strategies or resources. *Adherence to medications for depression.* Patients will be asked if they have been prescribed any antidepressant medications in the past three months. Self-reported type of antidepressant medications will be crosschecked with PBS data. Participants who report having been prescribed antidepressants will be asked whether, in the

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past week, they have (a) missed any doses; (b) taken any doses late; and/or (c) taken more than the prescribed dose.

Practice measures: Data on location, number full time equivalent GPs, and whether or not the practice employs a nurse will be obtained from each practice.

GP measures: GPs will answer a short survey at the time of consent to self-report characteristics including age; sex; number of years worked in general practice; employment status; and number of sessions worked per week. Details of training in mental health skills will be sought including type of course undertaken and year of course completion. Data about the number of full time equivalent GPs, and whether or not the practice employs a nurse will be obtained, as well as whether the practice bulk bills.

Acceptability data: *Acceptability of the intervention (intervention GPs only):* At the conclusion of recruitment, GPs at intervention sites will be invited to complete a telephone interview to provide feedback about intervention acceptability and feasibility.

Monitoring of intervention and protocol fidelity: A protocol implementation checklist will be used by the trial coordinator to monitor the implementation of trial procedures. GPs will be asked to self-report completion of the educational module, and the trial co-ordinator will record the date of provision of intervention materials to each intervention GP.

Data monitoring: Practices, GPs and patients will have access to a 1800 telephone number where any adverse events can be reported. Unintended effects will also be explored through analysis of trial outcome data on depressive symptoms and health service use.

The investigator team will take responsibility for monitoring adverse events, and determining, in consultation with relevant ethics committees, what steps need to be taken to minimise further adverse events.

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Data management: Data collected at baseline via an online survey will be automatically captured. Data collected at follow-up by paper and pencil will be entered into a SAS database. A number of quality assurance processes will be used to endure data entry is accurate. Firstly, programming of SAS will restrict the number of valid entries for a given question, thus alerting to a potential error if data outside these values is entered. A random sample of 20% will be double entered. Finally, data cleaning will take place to identify anomalies in the data that may require cross checking with original surveys. Survey data from baseline and each follow-up will be linked for each participant. These data will be linked to data obtained from the Department of Human Services on the use of MBS services and medications obtained via the PBS.

Statistical Analysis: ***Consenters versus non-consenters.*** *Practices*. Characteristics of consenting and non-consenting practices will be compared to identify any consent bias using the chi-square test for categorical variables and the t-test or a non-parametric equivalent for continuous variables. *Patients.* Examination of the demographic characteristics of consenting and non-consisting patients will also be tested. Data will be analysed using the intent to treat principal. Baseline data will be summarized as the number of observations, means, standard deviations, medians, minimums and maximums where the data are continuous and as number of observations and frequencies where the data are categorical. The data will be presented separately by treatment group. ***Aim 1.*** For the primary outcome, a PHQ-9 score of less than 10 at 12 months, we will test for group differences using a generalised linear mixed effects regression model, with a log link and a binomial distribution. The dichotomous outcome at each follow-up (baseline, 3 months, 6 months and 12 months) is the dependent variable. The model will include fixed effect for baseline history of depression, treatment group (intervention

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vs usual care), time, and treatment*time interaction, and a random intercept for each practice (assumed to be normally distributed) to account for the hierarchical structure in the data of patients nested within practices. Treatment group comparisons at post-baseline each visit will be estimated by differences in LS means from the treatment*visit interaction and will be presented as risk ratios with accompanying p-values and 95% confidence intervals, with the primary comparison being that at 12 months. We will investigate various variance-covariance structures for the within-subject repeated measures (such as autoregressive, unstructured, and compound symmetric) and choose the model with the best fit according to the smallest Akaike Information Criteria. As a sensitivity analysis we will perform analyses under a variety of plausible assumptions regarding the missing data mechanism to investigate the impact of departures from the missing data assumptions. ***Aim 2.*** The proportion of newly identified cases at baseline who receive appropriate care at follow-up will be compared between groups using a generalised linear mixed model as described above, but the cohort will be restricted to the individuals that are identified as new cases at baseline, and the outcome will be whether or not they received appropriate care at each follow-up time point. **Sample Size:** A sample of 720 patients per treatment arm (~60 per practice) at 12 months follow-up will give the study 80% power to detect a 10% decrease in the proportion of patients who score more than 10 on the PHQ-9 in the experimental group compared to usual care at a significance level of 5%. This calculation assumes, based on data from our prior study, an intra-class correlation coefficient of 0.04, and 20% of the patients in the usual care group will have PHQ-9 scores of more than 10. Allowing for 10% attrition at each follow-up, we will need to recruit 2000 eligible consenting patients (~83 per practice). Prior trials of depression screening interventions among general adult populations in primary care have demonstrated differences between study arms in depression outcomes of between 10% and 20%,[10] therefore an effect size of 10% was considered feasible for this study. The study outcome, a score of 10 or more on the PHQ-9,

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was selected because this threshold has been shown to identify clinically significant depressive symptoms with a high degree of accuracy.[25] Therefore a reduction of the proportion of people experiencing clinically relevant symptoms of depression of 10% may be considered clinically important, not only for the individuals affected but also on a population level.

Cost-Effectiveness Analysis (CEA): The economic study will be based on a cost-effectiveness analysis using within-trial outcomes and will be undertaken from a healthcare provider perspective. The study will capture the costs and consequences from the intervention and compare them to usual care. Costs will be estimated based on the additional resources required for intervention delivery, as well as net costs associated with healthcare utilisation. Unit cost data for all resources associated with an intervention will be collated based on the Pharmaceutical Benefits Advisory Committee (PBAC) manual of resource items[28] and the Medicare Schedule, measured in real prices for the selected reference year. The measure of effect will be quality adjusted life years (QALYs). QALYs will be calculated from SF-6D, a multi-attribute utility instrument that can be derived from the responses to the SF-12. The costs and health outcomes will be used to determine the incremental cost-effectiveness ratio (ICER), reflecting the additional cost per QALY gained. Cost-effectiveness and acceptability will be assessed against commonly accepted willingness to pay estimates per QALY. The economic results will be considered in the context of decision-making criteria: strength of evidence; capacity of the intervention to reduce inequity; acceptability to stakeholders; feasibility; and sustainability. The analysis will conform to NHMRC protocols for economic evaluations.

RESEARCH ETHICS AND DISSEMINATION

Ethics approvals: The study has been approved by the University of Newcastle Human Research Ethics Committee (EC00144; Ref No. H-2017-0291), with this approval accepted

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and registered by Monash University Human Research Ethics Committee (EC00234; Project No. 14048); Joint University of Wollongong and Illawarra Shoalhaven Local Health District Health and Medical Human Research Ethics Committee (EC00150/EC00394; Ref No. 2018/143) and; University of New South Wales (UNSW) Sydney (H-2017-0291). Any changes to the protocol will be communicated to the study investigators and approved by each of the ethics committees. Approval to access PBS and MBS data was granted by the External Request Evaluation Committee (EREC), Department of Human Services (Ref No. MI9644).

Confidentiality and privacy of information: All participant data will be de-identified. The consent form which will link the participant name to their unique study identification number will be stored separately to survey data in a locked filing cabinet. Electronic files containing survey data will be stored on the University of Newcastle server in a password-protected file. Only the chief investigators and staff employed to work directly on the study will have access to data.

Patient and public involvement: This research was informed by our prior work and the work of others on patient experiences and preferences for depression care. This includes our work that shows that many patients with elevated depression are not identified as depressed by their doctors.[7] Research by others has shown that patients have varied preferences for the management of psychological concerns.[29] As a consequence, unlike other screening trials, our screening assessment covers both patient depressive symptoms and preferences for management. Patients have not been directly involved in the design of the study. Patients will be asked to participate in the study via the procedures outlined previously. Upon consenting the study, participants will be asked if they would like to receive a summary of the study findings at the completion of the study. Objective data obtained through Medicare will allow

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us to quantify differences in health care contacts attributable to the intervention, thus providing an indication of participant burden. GPs will be asked to self-report their views about the impact of the intervention on practice functioning. Processes measures including consent rates, and dropout rates will be used to monitor acceptability.

Dissemination: This will develop new knowledge that is applicable to the Australian health care system, and provide policy relevant information regarding the benefit of the intervention and its potential for broad adoption. Study findings will be disseminated through conference presentations and publications in peer reviewed journals.

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Author contributions: MC, AW and JW contributed to study conception and design, undertook the first draft of the manuscript and approved the final version for publication. NZ, DM, GM, LP, RSF, FH, BK, SD, AS and CO contributed to conception and design, re-drafting the manuscript, and approved the final version for publication. No patients were involved in the design of the study or production of this manuscript.

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Conflicts of interest*:* The authors have no conflicts of interest to declare.

Figure legend:

Figure 1: Flowchart of study process

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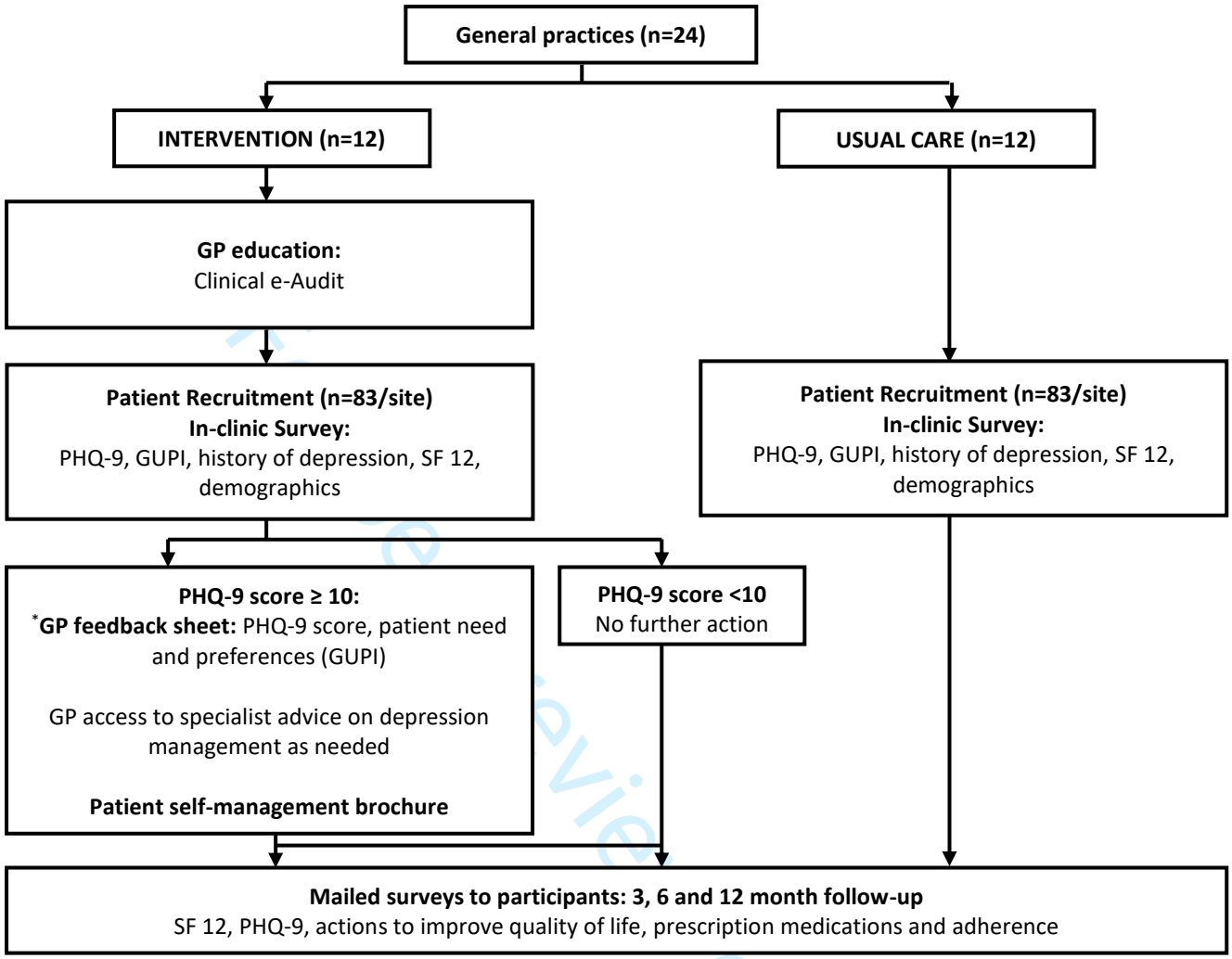

*For duty of care purposes, GPs will also be provided with feedback for usual care participants at baseline who score 20 or more on PHQ-9 (indicative of severe depression) or any participant who scores >1 on item 9 of PHQ-9 (indicative of potential self-harm).

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☐☐☐☐☐☐

THE UNIVERSITY OF NEWCASTLE AUSTRALIA

Patient Consent Form

Improving wellbeing among primary care patients

The Research Team:
University of Newcastle: Dr Mariko Carey, L/Prof Rob Sanson-Fisher, Dr Amy Waller, A/Prof Frans Henskens, Prof Brian Kelly, Mr Sam Lawson, Mr Justin Walsh, Dr Christopher Oldmeadow, A/Prof Andrew Searles
University of Wollongong: Prof Nicholas Zwar
Monash University: Prof Danielle Mazza, Prof Graham Meadows, Prof Leon Piterman

Please tick (✓) the following box to indicate if you would like to take part in the study.

☐ **Yes, I agree to participate in the below research project and give my consent freely**

- I understand that the project will be conducted as described in the Information Statement, a copy of which I have retained.
- I understand I can withdraw from the project at any time and do not have to give any reason for withdrawing.
- I consent to completing a short touchscreen survey and also taking part in a follow-up pen-and-paper surveys in 3, 6 and 12 months' time
- I consent to my general practitioner being provided with printed feedback about my health care needs. I understand that this will only occur for some participants who are attending practices allocated trial the new strategy.
- I understand that my personal information will remain confidential to the researchers. Data reported as a result of this research will not identify me in any way.
- I have had the opportunity to have questions answered to my satisfaction.
- I would like to receive a summary of the project results (please tick a box) ☐ Yes ☐ No

Please complete the section below with your name and contact details.

Title *(please circle one):* Mr / Mrs / Miss / Ms / Dr / Other _____			
Name:			
Postal Address:			
Suburb:		State:	Postcode:
Mobile no.	Home phone:		
Signature:			Date:

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If you are willing to, please include the contact details of secondary contact (who does not live with you). We will only use this if we are unable to get in contact with you using the information provided above. (For example, if you move to a new address).

Title *(please circle one):* Mr / Mrs / Miss / Ms / Dr / Other _____			
Name:	Relation to you:		
Postal Address:			
Suburb:	State:	Postcode:	
Mobile no.	Home phone:		

☐ I do not wish to provide a secondary contact

If you wish to participate, please complete this consent form and return it to the Research Assistant on duty

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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	2,21
	5b	Name and contact information for the trial sponsor	21
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21

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	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8, 14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	10
Objectives	7	Specific objectives or hypotheses	6-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7,8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10

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Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-13, 16
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	1, Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8,9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			

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Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9, 12-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	14-15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15-16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			

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Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17-18
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9, 18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18,19
	31b	Authorship eligibility guidelines and any intended use of professional writers	9
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary online files

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Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____N/A_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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