Contemporary Clinical Trials Communications 6 (2017) 131–139

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc

Intervention development for the indicated prevention of depression in later life: The "DIL" protocol in Goa, India

Amit Dias, MD[a], Fredric Azariah, MSc Public Health[b], Alex Cohen, PhD[c], Stewart Anderson, PhD[d], Jennifer Morse, PhD[e], Pim Cuijpers, PhD[f], Miriam Sequeira, MA Psychology[b], Vithoba Gaude, MBA[b], Salvino Soares, MCom[b], Vikram Patel, MD, PhD[c,g,1], Charles F. Reynolds III, MD[h,*,1]

[a] SANGATH and Goa Medical College, India
[b] SANGATH, Goa, India
[c] London School of Hygiene and Tropical Medicine, United Kingdom
[d] University of Pittsburgh Graduate School of Public Health, USA
[e] Chatham College, Pittsburgh, PA, USA
[f] Free University, Amsterdam, The Netherlands
[g] Harvard Medical School, USA
[h] University of Pittsburgh School of Medicine and Graduate School of Public Health, USA

ARTICLE INFO

Keywords:
Indicated depression prevention
Lay health counsellor
Low- and middle-income countries (LMICs)

ABSTRACT

Because depression is a major source of the global burden of illness-related disability, developing effective strategies for reducing its incidence is an important public health priority, especially in low-income countries, where resources for treating depression are scarce. We describe in this report an intervention development project, funded by the US National Institute of Mental Health, to address "indicated" prevention of depression in older adults attending rural and urban primary care clinics in Goa, India. Specifically, participants in the "DIL" ("Depression in Later Life") trial were older adults living with mild, subsyndromal symptoms of depression and anxiety and thus at substantial risk for transitioning to fully syndromal major depression and anxiety disorders. Building upon the MANAS treatment trial ("Promoting Mental Health") led by Patel et al. in the same locale, we present here lessons learned in the development and implementation of a protocol utilizing lay health counsellors (LHCs) who deliver a multi-component depression prevention intervention organized conceptually around Problem Solving Therapy for Primary Care (PST), with additional components addressing brief behavioural treatment of sleep disturbances such as insomnia, meeting basic social casework needs, and education in self-management of prevalent comorbid chronic diseases, such as diabetes mellitus. To our knowledge, DIL is the first randomized clinical trial addressing the prevention of depressive disorders ever conducted in a low- or middle-income country.

1. Introduction

Depression in older adults is a growing public health problem in Low and Middle Income Countries (LMICs), as a result of demographic transitions [13]. Studies have shown that, in the absence of treatment options, prevention of depression could prove to be an important strategy [3,13,14]. In developing such an intervention, previous research [3,19] indicates that acceptability, feasibility and cost reduction have to be factored into depression prevention models. Evidence [8,11,14]shows that older adults are known to suffer from substantial depressive symptomatology without meeting diagnostic criteria for syndromal major depression. There are several studies [4] [22,23] on prevention of depression in later life conducted in developed countries but none from Low and Middle Income countries (LMICs). Hence, there is a need to develop a scalable intervention that targets older adults with subthreshold depression, with an aim to prevent the onset of depressive disorders in later life [10,14,20].

Progress in research [8,14,23] among older adults has yielded an accumulation of knowledge on how to identify those individuals with the highest risk of developing a mental disorder, together with several

* Corresponding author. 758 Bellefield Towers, 3811 O'Hara Street, Pittsburgh, PA, 15213, USA.
E-mail address: reynoldscf@upmc.edu (C.F. Reynolds).
[1] Indicates conjoint last authors.

http://dx.doi.org/10.1016/j.conctc.2017.04.006
Received 31 December 2016; Received in revised form 23 March 2017; Accepted 8 April 2017
Available online 28 April 2017

preventive interventions in randomized controlled trials [4,11] showing that (indicated) prevention may be possible and effective in older adults. One such study was the MANAS ("Promoting Mental Health") cluster-randomized trial by Patel et al. [11], which showed a relative risk reduction at 6 months of 50% in the incidence of ICD-10 confirmed depression and anxiety disorders in a mixed-age sample of those receiving a collaborative stepped care (12.7%) versus those receiving enhance usual care (25%). We hypothesised that the MANAS intervention, modified to add other evidence-based components [1,11]and delivered by lay health counsellors (LHCs), is not just a treatment intervention but a preventive intervention as well.

Indicated prevention [1,3,13,20,23]is aimed at individuals who have sub-threshold depression (i.e. some symptoms of a depressive disorder) but do not meet diagnostic criteria for a depressive disorder. Indicated prevention has two objectives; one to reduce the symptoms of emotional distress that place persons at risk for common mental disorders like depression and anxiety, thereby increasing the quality of life; and secondly, to strengthen protective factors in order to prevent the onset of major depression disorder and other common mental disorders, such as anxiety disorders.

In this study, we aimed to extend the incidental prevention results of the MANAS study [11] into a specific hypothesis-driven study. The MANAS study documented a trend worthy reduction in the incidence of depressive and anxiety disorders at six months, incidental to the primary treatment results for prevalent cases. The specific focus on older adults in Goa reflects both their growing numbers in Goa and the high exposure to risk factors for late-life depression. This was the first trial aimed at prevention of depression in older people living in a low or middle income country, using lay health counsellors (LHCs) and exploring a combination of approaches. The primary approach applied in this study is problem-solving therapy as developed for use in primary care settings (PST).

PST is a brief, focused, and scalable psychological intervention [7,14] that has been used with a variety of patients in primary care settings, including people with depression, chronic illness, and suicidal thoughts and behaviours. In essence, PST is a learning-based psychotherapy that has elements of behavioural activation, aims to improve active coping, and enhances a sense of self-efficacy. While other structured, depression-specific psychotherapies (e.g., cognitive behavioural therapy and interpersonal psychotherapy) have been shown to prevent major depression in indicated prevention trials, PST is briefer and simpler than CBT or IPT and can be delivered by personnel without extensive training in mental health.

1.1. Objectives

The Depression in Late life ("DIL") trial was funded by the US National Institute of Mental Health through an intervention development grant (R34 MH96997) and a center grant (P30 MH90333). ("DIL" also means "heart" in the local Konkani language.) The trial was registered with the ClinicalTrials.gov (NCT02145429). The objectives of the study were twofold: 1) to develop a scalable intervention (DIL, "Depression in Later Life"), using risk reduction strategies aimed at prevention of depression and frequently co-occurring anxiety disorders by targeting persons with sub-threshold depression; and, 2) to test the feasibility and acceptability of delivering the intervention with LHCs, who had been used to deliver treatment for people with dementia, schizophrenia, and common mental disorders (depression and anxiety) in this region in various other studies [11,12,17]. The DIL intervention as developed in the formative work described here integrated evidence-based components: (1) Problem Solving Therapy (PST) and Brief Behavioural Therapy for Insomnia (BBTI) as reported in a previous review [1,13] (2) locally relevant social casework, such as facilitating access to senior citizen programs from the Government of Goa and (3) education in self-management of medical comorbidities frequent in depression, including diabetes mellitus, hypertension, arthritis and other chronic ailments, based on the formative work by Cohen et al. [2].

We used a pilot randomized controlled trial design to: 1) gather data on the feasibility and acceptability of identifying, enrolling, randomizing and retaining participants; 2) implement the experimental intervention and, as a comparator condition, enhanced usual care; 3) identify barriers to study conduct and develop strategies for addressing them; and 4) assess the fidelity of the DIL implementation. We collected measures of feasibility, acceptability, tolerability, and safety and gathered information to estimate an effect size in the reduction of symptoms of emotional distress and in the incidence of common mental disorders (depression and anxiety).

2. Material and methods

2.1. Setting

The study was conducted in Goa, the smallest state in India, with a population of 1.3 million [2,11]. Goa has a greater proportion of older adults, and age-related medical and social conditions have become more relevant in this region. Thirty eight percent of the population live in rural areas, and 66% are Hindus. Agriculture and tourism are the main sources of income. We conducted the study at two health centres under the jurisdiction of the Department of Preventive and Social Medicine at the Goa Medical College, the Urban Health Center, St Cruz and Rural Health Center, Mandur and the surrounding communities served by these centers. The urban health center serves a population of around 12,000 while the Rural Health Center caters to a population of 42,000. The participants were recruited by screening those visiting the health centers, as well as from the community in both the rural and urban regions.

2.2. Study design

We conducted a randomized controlled trial with parallel arms and with equal allocation of participants in each arm. The study was a trial of "indicated" prevention, enrolling persons with sub-threshold depression/anxiety symptoms and thus at high risk for transitioning into fully syndromal common mental disorders, such as major depression and frequently co-occurring anxiety disorders, e.g., generalized anxiety disorder.

2.3. Randomization

Randomization was carried out after baseline assessment and consent to participate. The project statistician (SJA) randomly assigned participants to either Enhanced Usual Care [EUC] (Treatment A) or DIL Problem-Solving Treatment [DIL-PST] (Treatment B), using a randomized block scheme. The sample was stratified for urban/rural status, sex, and the site of recruitment (community/health facility). The criteria for stratification were selected by the Trial Steering Committee based upon the possible impact of each stratification variable on the final outcome. Random blocks of size 8 were used to ensure equal distribution in the two arms at shorter intervals. All study personnel were masked to random assignment.

2.4. Instruments

The instruments (see Table 1) used for the study were chosen to measure sub-threshold depression and disability and to rule out prevalent cases of cognitive impairment (dementia), depression and anxiety. These instruments had been used in the region in previous studies. Data collection was done using hand-held tablet devises programmed with the Sangath digital Tool for Advanced Research (STAR) [15] software. Electronic data capturing improved efficiency and minimised missing data.

Table 1
DIL assessment instruments.

Instrument	Description	Outcome	Contextual validity
GHQ	12-item questionnaire screening tool for identifying non-psychotic and minor psychiatric disorders. Designed to capture depression and anxiety.	Prevalence of moderate to severe non-psychotic disorders; mean total score	Validated for international use and used in previous trials[6,18] in Goa
MINI 6.0[19]	Brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10 and is divided into **modules.** Major depressive episode, panic disorder, alcohol abuse/dependence, substance abuse/dependence and generalized anxiety disorder are the modules used in this study	Presence of Axis I psychiatric disorders	Validated for international use and used in previous trials in Goa
WHODAS[20]	12-item questionnaire for measuring functional impairment over the previous 30 days. In addition, two items assess number of days the person was unable to work in the previous 30 days	Total disability score; quality adjusted life years; number of days out of work	Validated for international use and used in previous trials in Goa
HMMSE	22 items questionnaire which test different components of intellectual capability. The items cover several areas of cognitive functioning such as orientation to time and place, memory, attention and concentration, recognition of objects, language function, both comprehension and expressive speech, motor functioning and praxis	Total cognitive score	Adapted Hindi version validated for use in illiterate Hindi speaking population. Hindi adapted version has been translated to Konkani.
PHQ-9 (item-9)	Nine-item questionnaire assessment of depressive symptoms on scale of 0–3. (Only item 9 pertaining to suicidal behaviour is used in this study) since the GHQ did not have this item.	Prevalence of suicide risk	Validated in primary care and Konkani version validated in Goa [6,9,11]

3. Participants and procedures

3.1. Inclusion criteria

To be eligible for the study, a potential participant had to be aged 60 or older. S/he needed to score 4 or more on the General Health Questionnaire, considered to be an indication of increased depressive and anxiety symptomatology. We arrived at the cutoff based on our formative work and in consultation with experts in the Trial Steering Committee. Participants had to speak Konkani, Hindi or English and were expected to reside in the same area for the next 12 months (the duration of follow up in the study).

3.2. Exclusion criteria

We excluded those with a current depressive or anxiety disorder, as determined by the MINI 6.0, moderate/high suicide risk, i.e., intent or plan to attempt suicide in the near future, history of psychiatric disorders other than non-psychotic unipolar major depression or anxiety disorder, those with low cognitive scores (HMMSE score below 24), patients taking antidepressants, or those with acute or severe medical illness. Our intention was to enroll participants at high risk for a common mental disorder but without a history of current mental illness that would indicate treatment. Approximately 20–25% of older adults with subthreshold symptoms are expected to transition to an episode of frank clinical depression [8,13,14]or anxiety disorder within 1–2 years, while another third will continue to live with chronic mild symptoms which can be disabling in their own right.

3.3. Sample size and power calculations

We initially set out to recruit a sample of 120 participants (60 per arm), but as the trial progressed with a faster rate of enrollment than originally anticipated, we increased the sample size to 180 (90 per arm) after consultation with NIMH program staff and with the members of our Data Safety Monitoring Board. Assuming that α is set to 0.05, with two-sided tests, then with sample sizes of 60 per group, we could detect, with 81% power, a standardized (pre-post) mean difference of depression measures (GHQ 12 score) between intervention groups to 0.52 sd, which is typically considered to be a medium to large effect size. Increasing to 90 patients per group allows detection of a more modest mean difference of 0.42 sd, – a more likely effect. If the N's were kept the same (60/group), the power to detect the same 0.42 sd mean difference would be less than 63%.

Therefore, we revised our sample "n" upward to 180 people aged 60 or older. Recruitment took 12 months (an average intake of about 15 participants monthly or 3–4 per week). As a pilot study, the randomized prevention trial focused primarily on feasibility, retention, and acceptability, and preliminary estimates of efficacy. We defined recruitment feasibility as meeting 100% of targeted randomization (n = 180), with 20% or less of eligible subjects refusing randomization. We were able to demonstrate feasibility of enrollment and retention. Our proposed approaches to inferential data analysis are specified below.

3.4. Screening: identification and recruitment procedure

Trained research assistants interviewed all those aged 60 and older attending the rural and urban health centres. Recruitment was extended to the sub-centers under the rural health center and directly from the community in order to achieve the targeted enrollment. Research staff visited every house in a given locality to identify participants eligible for the trial during community screening. The researchers used the standardised General Health Questionnaire (GHQ) to evaluate depressive and anxiety symptoms of respondents. Those who scored 4 or more in the GHQ scale were deemed to have symptoms of depression and anxiety placing them at risk for episodes of mental illness. However, potential participants were further screened using a diagnostic tool, the Mini International Neuropsychiatric Interview (MINI) 6.0, to rule out active cases of depression or anxiety disorders. Hence only those participants who were negative on the MINI 6.0 and scored 4 or more on the GHQ were eligible. To assess the cognitive ability of the participants, we administered the standardised Hindi Mini Mental State Examination (HMMSE). Those who scored 24 or more were included in the study. As a secondary outcome, we assessed the participant's disability rating using the WHO Disability Assessment Schedule. Informed consent was sought from those participants deemed eligible for the study. The informed consent process was audio recorded to assess fidelity.

3.5. Baseline assessment

The assessment included collection of demographic data, e.g., age, gender, marital status, educational qualification, and occupation. In addition, we collected data on the number of persons in the household, including children and/or grandchildren, and on self-reported chronic diseases for which participants were currently receiving care, including

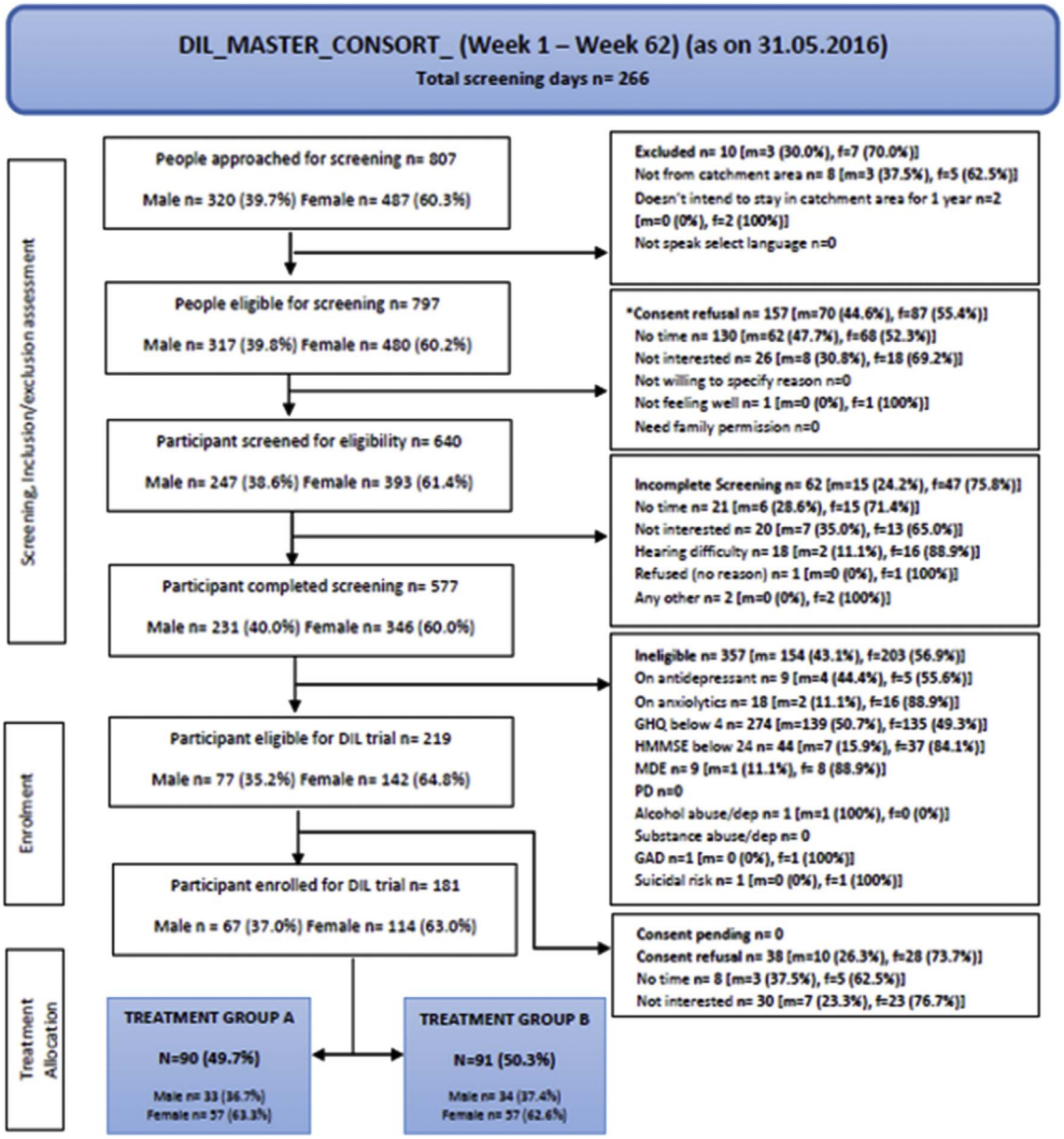

Fig. 1. DIL Master Consort Chart Denise, please DROP this figure.

diabetes mellitus and hypertension. Current medication history was sought before administering the GHQ scale. Medication use, with a particular focus on psychotropic drug use, was ascertained via examination of hospital records and prescriptions, and not merely by self-report of respondents. We also collected the cognitive scores of the participants using the Hindi Mini Mental State Examination (HMMSE) tool and the disability rating using the WHO Disability Assessment Schedule.

3.6. Summary of trial accrual

We approached 807 persons at the recruitment centres (primary healthcare clinics and the community) (DIL consort diagram shown in Fig. 1). Of these, 797 were eligible for the screening; after consent refusal, a total of 640 persons were screened for trial eligibility. 577 persons completed the screening, of whom 219 were eligible for the study. The primary reason for non-eligibility was failure to meet the criterion for sub threshold depression (i.e. a GHQ score below 4). This was seen in 274 persons and accounted for 76.8% of persons deemed ineligible. The other notable reason for ineligibility was low cognitive ability, as assessed using HMMSE. Cognitive impairment accounted for 44 (12.3%) of the exclusions.

Of the 219 eligible persons, 38 (17.4%) did not consent to the study, leaving 181 (82.6%) participants enrolled in the study. Of the 181 participants 67 (37.0%) were male and 114 (63.0%) were female. Gender was equally distributed in the two study arms.

In summary, of the 640 persons screened for DIL trial eligibility, we enrolled 181 (28.3%), representing a substantial proportion of primary-care and community-resident older adults endorsing subthreshold symptoms of emotional distress, depression and/or anxiety.

Baseline socio-demographic and clinical data are presented in Table 1. The mean age of participants at baseline was 69.6 (SD 7.2), and the mean GHQ was 6.3 (SD 1.9).

3.7. DIL intervention

3.7.1. DIL problem solving therapy

As we developed the DIL intervention in our formative work, it evolved into three components. First, the main theoretical framework of the DIL intervention was provided by Problem-Solving Therapy

(PST). Thus, trial participants randomized to the experimental arm were taught the original seven steps of PST, abbreviated into the acronym INSPIRE. We developed an acronym to simplify the steps of PST for use by the lay health counsellors who delivered the intervention:

Identify the problem
Note down a realistic achievable goal
Search for possible solutions
Probe through the pros and cons of each solution
Identify a preferred solution(s)
Run with it (action plan)
Evaluate the outcome

However, during the initial formative phase of DIL, we learned that the participants were unable to remember these seven steps, and thus we further simplified PST to a three stage process called Problem-Solution-Action. We developed a local acronym for these three steps, called "SAUD," which means 'health' in Konkani. Within these three components, all seven steps of INSPIRE were taught and practiced during the session and reinforced during subsequent booster sessions. Altogether, face to face time with the lay health counsellor totalled 6–7 h over the course of one year, thus constituting a relatively brief and focused behavioural intervention.

The second component of intervention was social casework. DIL counsellors were provided with all the relevant information and forms for the latest revision of the social resources made available for senior citizens by the Government of Goa. The focus on social case work originated during the formative phase, in which we learned that people in this region are often worried about issues of security, including finances, food and personal care. Thus the majority of participants needed help in navigating to available resources.

The third component of the DIL intervention addressed education and self-management of common medical illnesses. The most common source of anxiety and worry ("tension" in the local Konkani language) for the elderly population related to the burden of chronic disease, such as diabetes, hypertension, and painful osteoarthritis. As part of this component, lay health counsellors were trained in basic information regarding common medical disorders among older adults. They were trained to educate participants about the nature of these disorders and basic non pharmacological self-management. For chronic pain, counsellors demonstrated suitable, gentle exercises during the session.

The formative phase of the DIL intervention also taught us that participants were finding it difficult to follow an intervention which primarily involved verbal counselling. We therefore developed pictorial flip charts to aid the counsellor in engaging participants, especially those with no or very limited literacy. DIL flip charts contained large images for elders to relate to and understand, while the counsellors had images and text to ensure fidelity to the theory of the intervention.

Because poor sleep is a risk factor for developing depressive and anxiety disorders, we believe that improving sleep quality represents an opportunity for prevention [1,13]. A special strategy to overcome sleep problems such as insomnia was taught to participants. Based upon our previous work in older adults attending primary care in the U.S., we used strategies from Brief Behavioural Therapy for Insomnia (BBTI), shown to reduce depressive and anxiety symptoms and to improve the quality of sleep [1]. DIL lay health counsellors provided participants with basic sleep hygiene information and taught them to monitor their sleep and wake patterns. A simple sleep monitoring chart was used for this purpose, requiring the elders to put a tick mark on the chart. A similar chart was used to monitor their action plan and to motivate the elders to be proactive. Clinically, we have observed a useful synergy between improved sleep and more efficient cognitive functioning required by PST strategies.

3.8. Intervention delivery

The DIL intervention was delivered by lay health counsellors (LHCs) who are members of the local community, above 30 years of age, and bachelor's level graduates from any non-health related field (including counselling). We determined desirable characteristics of the LHC based on the findings from our initial qualitative study with the older participants, who defined characteristics of the LHC, with whom they would be comfortable to interact. The use of LHC's addresses the shortage of specialty mental health workers and, hence, the need to task-share and task-shift simple behavioural intervention delivery to less highly skilled persons. The effectiveness of LHCs in treating prevalent cases of common mental disorders has been demonstrated by Patel et al. [11]. The DIL study now represents an extension of LHC-based intervention models into the realm of prevention. LHC's lacked any prior training in professional mental health but had some experience either living with or working with the elderly. LHCs were recruited by placing advertisements in local newspapers and through word of mouth. Candidates were screened using a structured interview with the site principal investigator, project coordinator, and intervention supervisors, during which they were asked to role play one basic aspect of the DIL intervention which was sent to them 24 h before the interview via email. The selected candidates underwent a one-week training which covered all the aspects of the DIL intervention, including practice caseloads on non-eligible participants. On completion of the training, LHC's underwent competency assessments comprised of highly structured role plays. The counsellors who met the minimum requirement of 80% on the competency assessment progressed to the pilot study. To assess competency, we used the Therapy Quality Assessment Scale (TQS). This tool has been utilised in other studies [17,18]in the region. Counsellors who failed to attain the minimum requirement received additional training and practise caseload of non-eligible participants until they achieved required standards of intervention delivery.

3.9. Supervision

Supervision, an important component of LHC-led interventions, was carried out on a weekly basis with one or both local supervisors present at every group meeting. The local psychological intervention specialists were trained by international experts (Jennifer Morse, Ph.D., Assistant Professor, Counselling Psychology (MSCP), Chatham University and, Charles F Reynolds III, UPMC Endowed Professor in Geriatric Psychiatry at the University of Pittsburgh) in PST and BBTI, and they continued to be supervised by one international specialist via Skype every fortnight. Supervision included assessment of the quality of the sessions, using the Therapy Quality Assessment Scale (TQS), based on selected audio-recordings of the sessions followed by a round of peer-led feedback. The LHCs discussed their difficult cases with their peers and local supervisors during group supervision meetings. If intervention-related issues were not addressed by the peer group and local supervisors, then they discussed the same cases with the international experts via fortnightly Skype meetings.

3.10. Enhanced usual care

The control group received Enhanced Usual Care (EUC). The results of repeated assessments of mood and anxiety among participants randomly assigned to EUC were made known to participants. If the participant was found to have developed a depressive disorder or an anxiety disorder, then we notified their physicians. In addition, we shared a copy of the DIL manual with physicians caring for participants randomly assigned to care as usual. In this sense, care as usual was enhanced by the forwarding of assessments to physicians and patients, to allow them to act as they deemed appropriate. While enhancing care as usual in this fashion may make it more challenging to demonstrate meaningful differences between the intervention and control arms of

DIL, we believed it to be ethically necessary to share such clinically actionable information—a view shared by NIH reviewers and by our Data Safety Monitoring Board (DSMB).

3.11. Minimizing contamination

Contamination of the Enhanced Usual Care arm was reduced by masking the clinic doctor to the allocation status. Moreover, the clinic staffs were not conversant with the DIL intervention.

3.12. Outcome evaluation

Outcome evaluation was done at 3, 6 and 12 months after enrolment. We used the same set of measures as during the baseline assessment. The primary outcome of the study was to evaluate changes in symptom burden as reflected in GHQ scores. This focus is consistent with a model of "indicated" depression/anxiety prevention, which addresses the reduction of symptoms that constitute risk for transition to clinical episodes of depression and anxiety disorders. We also collected data on the incidence of episodes of depressive and anxiety disorders, WHODAS scores and the HMMSE scores as secondary outcomes. The schedule of assessments and interventions is depicted in Table 2.

3.13. Fidelity assessments

The fidelity of the DIL intervention was assessed with the following indicators:

Number and duration of sessions delivered, using Information was collated from the Counsellor's Session Record which recorded basic information about the session – the date, time, and duration of the session along with problems discussed during the session using the PST outline.
Number of participants who completed the intervention
Number of participants who did not complete the intervention due to unplanned discharge or who were referred to specialists
A team of external independent raters expert in the field of delivering Problem-Solving Therapy rated about 10% of the DIL intervention sessions in order to rate the quality of the sessions delivered: Quality was assessed through ratings of audio-recordings and transcripts of audio-recordings, by both peers as well as psychological treatment experts (supervisors). Sessions were selected by the data manager purposively to ensure that beginning, middle, and end phases of the intervention were covered. The Therapy Quality Assessment Form was used to rate the quality of the session, with feedback provided to the counsellors by both peers and supervisors. Group supervision meetings took place once weekly. In Supplementary Table 2, we describe challenges commonly encountered in the delivery of DIL, together with steps taken to meet these challenges.

3.14. Nested qualitative study (exit qualitative study)

We plan to conduct in-depth exit interviews with 20 participants but may increase the number if thematic saturation is not attained. The sample will be purposively selected and will include representatives from both the intervention and control arm. We will also select participants who have benefitted from the study and those who have experienced an episode of clinical depression or anxiety. A proportion of participants who have dropped out of the study will also be included for the interviews. The objective of the interview will be to obtain feedback on the acceptability and helpfulness of the intervention.

3.15. Data collection and management

Quantitative data were collected for the baseline assessment, the intervention process and the outcome evaluations (at 3, 6 and 12 months post enrolment). Data were collected electronically using Tablet computers at the participating sites for the baseline and outcome evaluations. We used the STAR software designed by Sangath, previously used in other studies [12,15,17] conducted at Sangath and found to be extremely feasible and effective. Elderly patients visiting the primary health centre were approached by members of the research team and assessed for eligibility. If the patient was eligible, informed consent was sought for enrolment in the study. Data were then uploaded to the Sangath server, from which the data manager downloaded and stored it in a password -protected computer. Data from the intervention sessions were recorded on paper and subsequently entered into the electronic system by the data manager on a weekly basis. Back up of all the data was maintained in hard disks on a daily basis.

No member of the trial had access to the data except the data manager. Hard copies of the data were locked in a cupboard, with access only to the data manager.

3.16. Analysis (descriptive, outcome & qualitative)

Data will be analyzed at the University of Pittsburgh Graduate School of Public Health, under the supervision of Stewart Anderson, Ph.D., Professor of Biostatistics. We will examine data descriptively using cross-tabulation, histograms and tests for normality (with corrective actions, data transformation or nonparametric alternatives as needed for subsequent analyses).

Primary analyses of the data from this study will be performed using the principle of intention to treat, that is, all patients randomized will be included over all of their observed time and will be analyzed according to the group to which they were randomized regardless of their eligibility or compliance status. Secondary investigations to explore the potential effect of interventions in compliant individuals will employ "per protocol" analyses that may include only fully compliant individuals. The proportion of individuals who are lost to follow-up or otherwise have missing endpoints will be assessed over time using a Kaplan-Meier approach.

The analyses for the outcomes measured longitudinally at several

Table 2
Primary and Secondary outcomes of the DIL trial could add social anxiety disorder as well.

Outcome	Data Source	End-point
Severity of symptoms	GHQ	3, 6, 12 months
Disability levels	WHODAS	12 months
Suicidal behaviour	PHQ-9 (item-9) and additional questions on suicide thoughts/attempts	3, 6, 12 months
Major depressive episode	MINI 6.0	3, 6, 12 months
Panic disorder	MINI 6.0	3, 6, 12 months
Generalized anxiety disorder	MINI 6.0	3, 6, 12 months
Alcohol abuse/dependence	MINI 6.0	3, 6, 12 months
Substance abuse/dependence	MINI 6.0	3, 6, 12 months
Cognitive performance	HMMSE	12 months

Table 3
Trial management committees.

Committee	Role	Members	Meeting frequency
Trial Steering Committee (TSC)	To monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself	Principal Investigator Co-investigators Project Coordinator Intervention Facilitator Research Coordinator Data Manager	Twice a month
Data Safety Monitoring Board (DSMB)	To review serious adverse event reports in order to assess whether there are any safety issues that should be brought to participants' attention or any reasons for the trial not to continue. It is the only body that makes recommendations to unblind data and makes further recommendations to the Trial Steering Committee	K S Shaji (Psychiatrist), Ladson Hinton (Geriatric Psychiatrist), Sunita Bandewar (Anthropologist with expertise in research ethics), Girish Rao (Psychiatrist)	Six-monthly

time points (GHQ, MINI 6.0, modified PHQ-9) [5,6,16] will seek to compare trajectories of the outcomes between interventions over the complete time period of the study. Analyses of other outcomes that are measured only at the time of entry and at 12 months (HMMSE, WHODAS [21]) will seek to compare the change of those outcomes from baseline between intervention groups.

To characterize and compare the trajectories between interventions, we will employ a mixed model approach using intervention and time, and adjusting primarily for the stratification variables (urban/rural status, sex and the site of recruitment). Tests of time by intervention and stratification variable by intervention interactions will be employed. If such interaction terms are significant then they will be appropriately included in the final mixed effect models for the comparison of interventions. Other covariates such as age, gender, education, history of previous anxiety and depression will also be explored for potential relationships with outcomes of interest. Tests of the normality of the outcome variables will be employed and if such tests indicate lack of normality, then log or square root transformations will be employed when appropriate. The best fitting models will be determined by examining individual coefficients for significance within multivariate models and also comparing BIC values between models. Time variables in the analysis will be derived by subtracting the date of randomization from the actual date of assessment at each time point.

Because of the growth curve analysis approach that we will use, missing outcome information, when the proportion of missing data is small, is not problematic. This is also true if the missingness is completely at random (MCAR) or at random (MAR) as long as the missing data mechanism is properly accounted for. Accordingly, we will employ tests for determining whether or not the missingness is at random. If appropriate, imputation methods will be considered for missing data and appropriate sensitivity analyses will be performed.

Marginal significance levels of formal tests will be set at $\alpha = 0.05$. While we acknowledge that multiple endpoints are being tested, this trial is a pilot study and hence, we will relax the strict experiment-wise error rates associated with multiple testing procedures. However, tests with p-values less than 0.01 will be noted as particularly strong evidence of differences between the two arms.

3.17. Ethical considerations

The trial protocol was approved by the Institutional Review Boards at Goa Medical College, Sangath (an NGO in Goa and the major public mental health research institute in India), the London School of Hygiene and Tropical Medicine, and the University of Pittsburgh. In addition, we obtained approval from the Indian Council for Medical Research. Written informed consent is mandatory for all enrolments, and the process of consent was audio-recorded for quality assessments. In the case of illiterate participants, a significant other (SO), ideally a family member, was involved. In such cases, a witness signature was obtained from the SO. Care was taken to protect confidentiality and anonymity of the participant by assigning a unique trial ID to each participant. The records of all participants were specified only by the trial ID. Hard copies of all the data collected were stored in a locked cabinet with access only to the data manager. Similarly, soft data were password protected with access rights given only to the data manager.

Whenever a participant developed a depressive or anxiety disorder during the trial, s/he was referred to attending physicians for further evaluation and treatment. We developed a suicide risk assessment protocol (approved by the IRB) specifying steps to be taken in the event a participant became suicidal during the trial. To date this event has not occurred (see Fig. 1).

3.18. Trial management

In order to monitor the conduct and progress of the trial, a trial management committee was formed and held teleconferences every two weeks. In addition, we formed a Data Safety Monitoring Board (DSMB) to review the progress of the trial and to review serious adverse events. The DSMB could make recommendations to view un-blinded data prior to the completion of the study. The DSMB has met twice annually through teleconference meetings to review the progress of the trial, data integrity, and participant safety. Following all five meetings of the DSMB, a recommendation to continue the DIL trial without modification of design was made (see Table 3).

4. Discussion

“DIL” is the first randomized clinical trial addressing the prevention of common mental disorders (depression and anxiety) in a low or middle income country. By implementing a model which uses lay health counsellors, DIL circumvents the challenge of scarce mental health resources and allows more rational and efficient use of these resources, to the potential benefit of a large population of older adults in primary care settings. DIL builds upon the MANAS trial (“Promoting Mental Health”), extending the deployment of lay health counsellors from treating to preventing common mental disorders (depression and anxiety) in rural and urban primary care clinics. DIL's focus on preventing common mental disorders in older adults is based upon a recognition of India's growing population of persons aged 60 and older. In addition, since the treatment of disorders like depression is only partially successful in averting years lived with disability, prevention of depression becomes an important public health priority. Not only is depression a major contributor to the global burden of illness-related disability, it also is now recognized as an important risk factor for the subsequent onset of dementing illnesses and for shortening life expectancy. Thus, it is plausible to suggest that preventing depression in older adults may also repay downstream benefits in terms of both quality and quantity of life. Depression is an important contributor to care-giver burden; thus its prevention may be a benefit to the wellbeing of family members, as well as to at-risk older adults.

Randomized clinical trials of indicated depression prevention conducted in high-income countries have generally shown an incidence rate reduction on the order of 20–25% over varying follow-up intervals of 1–2 years, in persons living with subsyndromal symptoms. DIL now lays the groundwork for the extension of prevention science into low and middle income countries, via a potentially scalable model using lay health counsellors to reduce the burden of symptoms, improve well-being and health-related quality of life, and delay or prevent the onset of major depression, generalized anxiety disorder, and other common mental illnesses. Further down-stream benefits may also accrue, including better adherence with co-prescribed medical treatments.

DIL shares several important features with randomized mental illness prevention trials conducted in high-income countries. Primary among these shared features is the use of a brief behavioural intervention based in learning theory, namely, Problem Solving Therapy (PST). PST is effective in the treatment of prevalent mental disorders like depression; its use in the service of prevention is based upon two considerations: (1) its behaviourally activating effects, and (2) its teaching of problem solving strategies that restore active coping and support a sense of self-efficacy to counteract the “learned helplessness” at the core of depression. Like preventive interventions conducted in high-income countries, PST as adapted for use in India is a brief intervention that entails relatively little face-to-face time with the lay health counsellor, on the order of 6 h, during the initial 5–7 sessions and in quarterly booster sessions during the follow up interval.

The adaptation of PST for use in the DIL RCT was based upon lessons learned during the initial qualitative work and open-case series. In particular, these lessons addressed three needs: (1) to simplify the seven steps of traditional PST (“INSPIRE”) into a more easily managed “package” of three steps (“SAUD”) that could be easily taught via the use of pictorial flip charts to elders of limited literacy; (2) to incorporate basic social casework to help elders access needed services; and (3) to impart basic information about commonly occurring medical comorbidities, especially useful and straightforward techniques of self-care. It is our impression that the modification and enrichment of PST contributed to the high retention rates observed among trial participants, with less than a 20% dropout rate (comparable to trials conducted in high-income countries).

In summary, our intervention development research has now achieved its primary goal of adapting the use of simple behavioural interventions to prevent common mental disorders in a low- or middle-income country, for implementation by lay health counsellors, to older adults with subsyndromal symptoms attending rural and urban primary care clinics. The adaptation has necessitated the integration of simple social casework interventions and basic health education in commonly comorbid medical disorders such as hypertension and diabetes. These adaptations have been well received by patients and family caregivers and are seen as responsive to the particular social and medical contexts in which indicated prevention of common mental disorders can unfold in a low- or middle-income country having large proportions of older patients with limited health literacy. Our intervention development work has demonstrated the feasibility of both enrolling and retaining at-risk participants (with dropout rates of less than 20%), together with the safety and acceptability of “indicated” depression prevention. Finally, it is our contention that DIL should be viewed within the larger framework of successful, active aging. Thus, DIL is not only about preventing depression. It also focuses on restoration of a sense of well-being in elders burdened with emotional distress, and it teaches and reinforces skills of active coping with the common challenges of old age.

Trial status

Conflict of interest: the authors report no conflict of interest in the conduct of this study. The sole source of support is the U.S. National Institute of Mental Health and the University of Pittsburgh Medical Center endowment in geriatric psychiatry.

Acknowledgments

The authors acknowledge the dedicated collaboration of research staff at SANGATH, India's major research institute in public mental health. Also, the Data Safety & Monitoring Board: Dr K S Shaji, MD (Chair), Dr Girish Rao MD, Dr Sunita Bandewar PhD, Dr Ladson Hinton MD. The Department of Preventive & Social Medicine, Goa Medical College, and Seema Sambari, BA, Sabina Rodrigues HSSC, Rajnarayan Bind BA, Caetano Sousa HSSC, Dr Diptesh Amonkar BHMS, Allen Mascarenhas MA.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.conctc.2017.04.006.

References

[1] D.J. Buysse, A. Germain, D.E. Moul, P.L. Franzen, L.K. Brar, M.E. Fletcher, A. Begley, P.R. Houck, S. Mazumdar, C.F. Reynolds 3rd, T.H. Monk, Efficacy of brief behavioral treatment for chronic insomnia in older adults, Arch. Intern Med. 171 (2011) 887–895.
[2] A. Cohen, A. Dias, F. Azariah, R.N. Krishna, M. Sequeira, S. Abraham, P. Cuijpers, J.Q. Morse, C.F. Reynolds, V. Patel, Aging and well-being in Goa, India: a qualitative study, Aging Ment. Health (2016) 1–7.
[3] P. Cuijpers, A.T. Beekman, C.F. Reynolds 3rd, Preventing depression: a global priority, JAMA 307 (2012) 1033–1034.
[4] P. Cuijpers, M. Sijbrandij, S. Koole, M. Huibers, M. Berking, G. Andersson, Psychological treatment of generalized anxiety disorder: a meta-analysis, Clin. Psychol. Rev. 34 (2014) 130–140.
[5] D. Goldberg, General Health Questionnaire (GHQ-12), Nfer-Nelson, Windsor, UK, 1992.
[6] K. Kroenke, R.L. Spitzer, The PHQ-9: a new depression diagnostic and severity measure, Psychiatr. Ann. 32 (2002) 509–515.
[7] O.I. Okereke, Prevention of Late-life Depression, (2015).
[8] O.I. Okereke, J.M. Lyness, F.E. Lotrich, C.F. Reynolds 3rd, Depression in late-life: a focus on prevention, Focus Am. Psychiatr. Publ. 11 (2013) 22–31.
[9] V. Patel, R. Araya, N. Chowdhary, M. King, B. Kirkwood, S. Nayak, G. Simon, H.A. Weiss, Detecting common mental disorders in primary care in India: a comparison of five screening questionnaires, Psychol. Med. 38 (2008) 221–228.
[10] V. Patel, M. Prince, Ageing and mental health in a developing country: who cares? Qualitative studies from Goa, India, Psychol. Med. 31 (2001) 29–38.
[11] V. Patel, H.A. Weiss, N. Chowdhary, S. Naik, S. Pednekar, S. Chatterjee, M.J. De Silva, B. Bhat, R. Araya, M. King, G. Simon, H. Verdeli, B.R. Kirkwood, Effectiveness of an intervention led by lay health counsellors for depressive and anxiety disorders in primary care in Goa, India (MANAS): a cluster randomised controlled trial, Lancet 376 (2010) 2086–2095.
[12] V. Patel, B. Weobong, A. Nadkarni, H.A. Weiss, A. Anand, S. Naik, B. Bhat, J. Pereira, R. Araya, S. Dimidjian, S.D. Hollon, M. King, J. Mccambridge, D. Mcdaid, P. Murthy, R. Velleman, C.G. Fairburn, B. Kirkwood, The effectiveness and cost-effectiveness of lay counsellor-delivered psychological treatments for harmful and dependent drinking and moderate to severe depression in primary care in India: PREMIUM study protocol for randomized controlled trials, Trials 15 (2014) 101.
[13] C.F. Reynolds 3rd, P. Cuijpers, V. Patel, A. Cohen, A. Dias, N. Chowdhary, O.I. Okereke, M.A. Dew, S.J. Anderson, S. Mazumdar, F. Lotrich, S.M. Albert, Early intervention to reduce the global health and economic burden of major depression in older adults, Annu. Rev. Public Health 33 (2012) 123–135.
[14] C.F. Reynolds, S.B. Thomas, J.Q. Morse, S.J. Anderson, S. Albert, M.A. Dew, A. Begley, J.F. Karp, A. Gildengers, M.A. Butters, J.A. Stack, J. Kasckow, M.D. Miller, S.C. Quinn, Early intervention to preempt major depression among older black and white adults, Psychiatr. Serv. 65 (2014) 765–773.
[15] Sangath, OPSPL: STAR: Sangath Digital Tool for Advanced Research, (2013).
[16] D.V. Sheehan, Y. Lecrubier, K.H. Sheehan, P. Amorim, J. Janavs, E. Weiller, T. Hergueta, R. Baker, G.C. Dunbar, The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10, J. Clin. Psychiatry (1998).
[17] S. Sikander, A. Lazarus, O. Bangash, D.C. Fuhr, B. Weobong, R.N. Krishna, I. Ahmad, H.A. Weiss, L. Price, A. Rahman, V. Patel, The effectiveness and cost-effectiveness of the peer-delivered Thinking Healthy Programme for perinatal depression in Pakistan and India: the SHARE study protocol for randomised controlled trials, Trials 16 (2015) 534.
[18] D.R. Singla, B. Weobong, A. Nadkarni, N. Chowdhary, S. Shinde, A. Anand, C.G. Fairburn, S. Dimijdan, R. Velleman, H. Weiss, V. Patel, Improving the scalability of psychological treatments in developing countries: an evaluation of peer-led therapy quality assessment in Goa, India, Behav. Res. Ther. 60 (2014) 53–59.
[19] F. Smit, A. Ederveen, P. Cuijpers, D. Deeg, A. Beekman, Opportunities for cost-effective prevention of late-life depression: an epidemiological approach, Arch.

Gen. Psychiatry 63 (2006) 290–296.
[20] R. Sriwattanakomen, A.F. Ford, S.B. Thomas, M.D. Miller, J.A. Stack, J.Q. Morse, J. Kasckow, C. Brown, C.F. Reynolds 3rd, Preventing depression in later life: translation from concept to experimental design and implementation, Am. J. Geriatr. Psychiatry 16 (2008) 460–468.
[21] T.B. Üstün, S. Chatterji, N. Kostanjsek, J. Rehm, C. Kennedy, J. Epping-Jordan, S. Saxena, M.V. Korff, C. Pull, Developing the World Health Organization disability assessment schedule 2.0, Bull. World Health Organ. 88 (2010) 815–823.
[22] P.J. Van't Veer-Tazelaar, H.W. Van Marwijk, P. Van Oppen, H.P. Van Hout, H.E. Van der Horst, P. Cuijpers, F. Smit, A.T. Beekman, Stepped-care prevention of anxiety and depression in late life: a randomized controlled trial, Arch. Gen. Psychiatry 66 (2009) 297–304.
[23] G.R. Willemse, F. Smit, P. Cuijpers, B.G. Tiemens, Minimal-contact psychotherapy for sub-threshold depression in primary care, Br. J. Psychiatry 185 (2004) 416–421.