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Integrated Moving on After Breast Cancer and Culturally Adapted Cognitive Behavior Therapy intervention for depression and anxiety among Pakistani women with breast cancer: Protocol of a randomized controlled trial

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Abstract

Objective: The diagnosis and treatment of breast cancer is associated with significant distress that has huge impact on survivors' quality of life. The objective of this study is to assess the effectiveness of an integrated intervention "Moving on After Breast Cancer (ABC) Plus culturally adapted Cognitive Behavior Therapy" (Moving on ABC Plus).

Method: This is a randomized controlled trial that aims to recruit 354 breast cancer survivors from the inpatient and outpatient oncology departments in public and private hospitals in Karachi, Hyderabad, Lahore, Multan, and Rawalpindi in Pakistan. Patients scoring 10 or above on either the Patient Health Questionnaire—9 and/or the Generalized Anxiety Disorder scale (GAD-7) will be recruited. Baseline assessments will include Functional Assessment of Cancer Therapy—Breast; EuroQol-5D; Multidimensional Scale for Perceived Social Support; Intrusive Thoughts Scale; and Rosenberg Self-Esteem Scale. Participants randomized into intervention arm, Moving on ABC Plus, will receive 12 individual therapy sessions over 4 months. Follow-up will be completed at 4- and 6-month post-randomization, using all baseline instruments along with the Client Satisfaction Questionnaire (CSQ-8). We will also explore the participants', their family members', and the therapists' experiences of the trial and intervention.

Results: We will be assessing the effectiveness of intervention in reducing depression and anxiety in breast cancer survivors as a primary outcome of the trial. The secondary outcomes will include effectiveness of intervention in terms of reduction in intrusive thoughts and improvement in health-related quality of life, self-esteem, and perceived social support.

Conclusion: The results of the study will inform the design of a future larger randomized control trial with long-term follow-up.

Keywords

Depression, anxiety, breast cancer, randomized control trial, moving on ABC, Pakistan, cognitive behavior therapy

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Introduction

Globally, breast cancer impacts 2.3 million women annually.[1] Breast cancer is the greatest contributor of cancer-related deaths in women. It has been estimated that 685,000 women died from breast cancer in 2020.[1] Though the prevalence of breast cancer is higher in high-income countries, rates are gradually increasing in all regions across the world.[1] According to a report published by GLOBOCAN in 2018, breast cancer incidence will increase from 2 million patients in 2018 to approximately 3 million in 2046, indicating a 46% increase.[2,3] Moreover, welfare lost to breast cancer also increased from 0.05% to 0.08% of gross domestic product.[4] The treatment expenditure of cancer is a burden not only for the people diagnosed with cancer but also for their families and society as a whole.[5]

Comorbidity of mental health problems such as depression with other medical illnesses such as diabetes, heart failure, and hepatitis is well established.[6–9] Similarly, findings from systematic reviews show that the prevalence of depressive symptoms is higher among breast cancer survivors as compared to the general population,[10] and these symptoms may persist up to 5 years after the diagnosis.[11] This mental health comorbidity during survivorship is determined by several factors such as impaired physical, mental, and cognitive functioning[12] as well as fear of recurrence that impacts survivors' quality of life.[13] Global prevalence of depression in breast cancer was reported to be 32.2% in a recent systematic review of 72 studies conducted in 30 countries.[14] In addition, morbidity associated with breast cancer and its subsequent treatment can cause functional deficits such as limitations in carrying out daily life activities and social interactions.[15]

Evidence on mental health challenges experienced by long-term breast cancer survivors is limited compared to findings with regard to the diagnosis and acute treatment phases.[16,17] It is important to identify strategies to manage mental health problems in breast cancer survivors as depression and anxiety may predict recurrence of cancer and survival.[18]

Pakistan has the highest age-standardized incidence rates of breast cancer in Asia[19]; 20-year data from Shaukat Khanum Memorial Cancer Hospital and Research Center has reported breast cancer to be the most frequently diagnosed cancer (45.4%) among Pakistani women, particularly among younger Pakistani women.[20] A cross-sectional study exploring the pattern of anxiety and level of depression among Pakistani breast cancer patients has reported that most of the patients were suffering from moderate to severe depression and anxiety, while few were experiencing mild symptoms.[21] A recent study has also reported high rates of depression (69.4%), anxiety (59.7%), and suicidal ideation (47.5%) in breast cancer survivors.[22]

The Institute of Medicine has recommended psychosocial interventions as standard clinical care in breast cancer patients across all phases of the treatment.[23] A Cochrane review of 28 RCTs with 3940 breast cancer patients reported that Cognitive Behavior Therapy (CBT) resulted in greater reduction in depression and anxiety as compared to the control group.[24] A recent meta-analysis assessing the effect of CBT on psychological well-being and quality of life of breast cancer patients concluded that the effect sizes for anxiety and depression were large.[25]

The current proposal is based on our extensive experience of research with the South Asian population in Pakistan and the UK. Our previous studies show that Pakistani women experience higher rates of depression, self-harm, and low level of perceived social support.[26–29] Furthermore, our previously tested CBT group-based intervention[28] has been tailored to Pakistani women, taking cultural needs into account. We found that the culturally adapted group CBT intervention was acceptable to Pakistani women and has led to improvement in mood and self-esteem.[28] Cultural adaptation of existing evidence-based interventions for a specific group of population is important considering community-specific cultural context of risk and resilience factors and existing evidence is in favor of higher effect size for the culturally adapted interventions.[30] Moreover, considering the existing evidence on limited awareness about breast cancer (including risk and protective factors, screening and detection, early intervention, etc.) in LMICs,[31,32] particularly in Asia,[33] as part of a PhD feasibility study, CBT intervention was further adapted for breast cancer survivors to be delivered as one-on-one intervention and integrated with the Moving on After Breast Cancer (Moving on ABC), which is an educational intervention described in detail below[34] to meet the psychosocial needs of Pakistani breast cancer survivors. A patient and public involvement and engagement (PPIE) group comprising six breast cancer survivors with history of mental health experiences played an instrumental role during cultural adaptation and integration of intervention. A total of 50 breast cancer patients were randomized in this trial with 100% retention rate and a large proportion of participants (92%) attended all 12 sessions. The current study aims to evaluate the effectiveness of Moving on ABC Plus intervention for breast cancer survivors experiencing mental health difficulties (depression and anxiety) in Pakistan.

Study goals and objectives

The primary objective of this study is to assess the effectiveness of an integrated culturally adapted intervention called Moving on ABC Plus CBT (Moving on ABC Plus) for Pakistani breast cancer survivors with depression and/or anxiety, attending primary care and oncology services in Karachi, Hyderabad, Lahore, Multan, and Rawalpindi. Secondary objectives include assessing the effectiveness of Moving on ABC Plus in improving health-related quality of life, level of perceived social support, level of self-esteem and reducing svereity of intrusive thoughts among breast cancer survivors, as well as improvement in level of

satisfaction with treatment. Services received by the participants during the last 3 months will also be recorded.

Method

Study design

A two-arm multicenter, pragmatic rater-blind randomized controlled trial design. Trial registration number: NCT03571984.

Duration

Total duration of the trial will be 2 years.

Randomization and masking

This trial will follow parallel arms (1:1) randomization. Eligible participants with written (thumb impression or a verbal audio-recorded consent in the presence of a Legally authorized representative identified by the participant if she is unable to read/write) informed consent will be randomized to either of the two trial arms—Moving on ABC Plus added to the Treatment as Usual (TAU) or the TAU alone. The randomization will be carried out by an independent statistician using a computer-generated algorithm through a web software (http://www.randomisation.com). Outcome assessments will be completed by assessors masked to treatment allocation. Considering the nature of the intervention, participants themselves cannot be masked to treatment allocation. Before follow-up assessments, all participants will be requested not to share any information about intervention to researchers doing assessments. Moreover, outcome assessors will be located separately from trial interventionists to avoid unmasking, and in cases of unintentional unmasking, new outcome assessors will be assigned by the trial manager. Statistical analysis will be partially masked (knowing treatment arms, but not what each trial arm is). Registration on Clinicaltrials.gov and publication of results regardless of the outcome will both minimize reporting bias.

Study setting. Participants will be recruited from primary care, inpatient, and outpatient oncology and medical units from both public and private hospitals in Karachi, Hyderabad, Lahore, Multan, and Rawalpindi.

Sample size calculation. The sample size estimation is based on a reduction in the proportion of participants being classified with depression (Patient Health Questionnaire; PHQ-9) at end of intervention. It is expected that 50% of the participants in the TAU group will have depression (the estimates are based on published evidence indicating approximately 40% breast cancer patients with persistent depression even at 1-year follow-up,[35] our calculation is based on comparatively higher proportion considering high prevalence of depression, that is, 60% in this population[36] and poor availability of psychological support as routine care), and in the intervention group, this will reduce to 30% (higher scores on the PHQ-9 ($\geqslant$10) scale indicating greater risk). A standard significance level of 5%, and to provide a power of 90%, will require 124 patients per group, 248 in total. Allowing for an anticipated dropout rate of 30% at 4 months' follow-up, we will need to recruit 177 patients in each arm and hence a total sample size of 354 to achieve 90% power at 4th month follow-up (end of intervention).

Inclusion criteria

- Women aged 18 years and above.
- Stages I to IV breast cancer.
- Patients have received and completed primary treatment for breast cancer.
- Score 10 or more on the PHQ-9[37] and/or Generalized Anxiety Disorder Scale (GAD-7).[38]

Exclusion criteria

- Women diagnosed with severe learning disabilities, psychosis, and substance misuse or who are acutely suicidal thus preventing participation in psychological intervention.
- Women too unwell to engage with the intervention (in the opinion of the treating clinician).
- Although there are men who have breast cancer, the current group intervention focuses on women.

Participant recruitment procedure. Trained researchers will approach breast cancer patients in primary care, oncology, and medical departments in public and private hospitals in Karachi, Hyderabad, Lahore, Multan, and Rawalpindi. Study information will be provided to potential participants through a detailed participant information sheet (PIS) written in the local language. Potential participants will be screened using the PHQ-9, GAD-7, and an eligibility-screening checklist. Profile of each eligible and potential participant will be discussed with the treating consultant, making sure that patient is not experiencing any other chronic illness that would prevent them from participation in the trial. Written (thumb impression or a verbal audio-recorded consent in the presence of a Legally authorized representative identified by the participant if she is unable to read/write) informed consent will be obtained from eligible participants and they will be assured that confidentiality will be maintained and information will only be used for research purposes. A baseline assessment will be completed using standard questionnaires (detailed below), already translated into Urdu. After baseline assessment study, identification numbers (IDs) will be assigned to all the participants and these IDs will be shared with off-site, independent statistician for randomization into the treatment arms (individually delivered Moving on ABC Plus intervention in addition to TAU) or TAU alone. Those in the intervention arm will receive 12 individual sessions over

a 4-month period: eight weekly and four fortnightly sessions. Intervention sessions will be delivered at a place and time convenient to the participants. Follow-up assessment will be completed at 4- and 6-month post-randomization.

Defining the intervention

Moving on ABC Plus intervention. The moving on ABC Plus is an integrated intervention using two treatment manuals:

- Moving on ABC manual
- Culturally adapted CBT manual

The Moving on After Breast Cancer (ABC) was developed by service user collaborator, Dr Anneela Saleem who suffered from breast cancer.[34] The manual offers practical support and advice on life after breast cancer. It includes managing difficulties through self-management such as "Mindfulness" techniques and addressing fatigue. The intervention focuses on understanding the participant's model of illness and physical symptoms and reattribution with explanations of physical symptoms of anxiety and depression, improving personal effectiveness and social relationships. It also includes relaxation techniques to reduce stress, fatigue, modification of illness behavior, and cognitive restructuring to address dysfunctional cognitions (Table 1).

The culturally adapted CBT manual was developed in the USA for low-income Spanish and English-speaking people.[39,40] The sessions include psychoeducation about symptoms of common mental disorders (depression and anxiety); causes of anxiety, stress, and depression; treatment options for common mental disorders and their likely outcomes; exploring pleasant activities that can engage participants; problem-solving techniques; working on negative thinking patterns; and improving interpersonal relationships. The group CBT manual has been adapted for use for individual therapy sessions.

The intervention will be delivered face to face or over a telephone call/zoom keeping the COVID-19 SOPs in consideration by a trained master-level psychologist. Each session will last for 45–60 minutes.

Training and supervision. The intervention will be delivered by the master-level psychologists who will receive training in delivering the manual-based Moving on ABC Plus intervention. The training will involve presentation of each intervention session followed by a role-play, feedback, discussion, and a question/answer session. They will receive regular supervision from a Clinical Psychologist in order to increase the likelihood of maintaining fidelity. During supervision sessions, all trial therapists will do mock sessions, and the supervisor will rate each role-play against intervention-specific checklists that contain the content of each session. This will help ensuring that therapists adhere to the intervention manual.

Treatment as usual: This will consist of routine assessment and management offered by oncology clinics and general practice. The patients' General Practitioners will be informed about the psychiatric diagnosis.

Assessments. *Sociodemographic questionnaire*: A study specific sociodemographic questionnaire will be administered on all participants at baseline to collect information about variables such as age, marital status, education, occupation, socioeconomic status, information about breast cancer (time since onset, history of illness in family, history of any psychiatric illness in patient and family, etc.).

Primary outcome measure. *Patient Health Questionnaire-9*[37]: PHQ-9 will be used both to screen and to assess severity of depression. Each item is rated on four response categories: not at all, several days, more than half the days, and nearly every day. Minimum score of PHQ-9 is 0 and maximum score is 27. This scale categorizes depression in five different categories: minimal depression (score range 1–4), mild depression (5–9), moderate depression (10–14), moderately severe depression (15–19), and severe depression (20–27). PHQ-9 scores $>$ 10 had sensitivity of 88% and specificity of 88% for major depression.[37] The Urdu version of scale has already been used in Pakistan.[41,42] The Cronbach alpha for Urdu translated version is reported to be 0.91.[43]
Generalized Anxiety Disorder-7[44]: This is a short self-report measure to assess the presence and severity of generalized anxiety. With a threshold of 10, the GAD-7 demonstrates an excellent sensitivity of 89% and a specificity of 82%.[38] The Urdu version of scale has already been used in Pakistan.[41,42] Cronbach's alpha for the Urdu translated version of the scale was reported to be 0.92 and split-half reliability was 0.82.[45]

Secondary outcome measure. *Functional Assessment of Cancer Therapy—Breast (FACT-B)*[46]: This scale measures health-related quality of life in breast cancer patients in five domains: physical, social, emotional, functional well-being as well as a breast-cancer subscale (BCS). The internal consistency for (FACT-B) total score was reported to be 0.90 and for subscales ranging from 0.63 to 0.86.[46] There is also evidence on the convergent validity of the FACT-B as it correlates significantly ($r = .87$; $P < .001$) with another measure of quality of life, Functional Living Index Cancer-FLIC.[46]
EuroQol-5D[47]: The EuroQol-5D (EQ-5D), a 5-item scale, will be used to assess the quality of life. The scale was developed by EuroQol group in 1990. There are total five items regarding five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problems, some problems, and extreme problems. The Urdu version of scale has already been used in Pakistan.[48]
Multidimensional Scale for Perceived Social Support[49]: Multidimensional Scale for Perceived Social Support (MSPSS) will be used to assess the level of social support. It

Table 1. Content of Moving on ABC Plus sessions.

Session #	Content
1	Introduction and welcome • Purpose of the intervention, duration, and frequency • Participants' expectations about the intervention • Agenda settings process for each session
2	Psychoeducation • CBT model of comorbidity, anxiety, and depression • Vicious circle of negative thoughts
3	Psychoeducation • Risk and protective factors of breast cancer • Role of stress • Helping participants to identify harmful and helpful thoughts
4	Understanding and managing self-esteem: Looking good and feeling good • Practical steps (e.g., reduce exposure to chemicals, use of body creams, etc.) • Healthy eating • Feeling good by examining the evidence for negative thoughts • Three C's for harmful thoughts—*C*atch, *C*heck, and *C*hange
5	Technical aspects of breast cancer and ABC cycle of CBT • Encouraging self-physical examination • Monitoring for the lymphedema signs • Antecedents, beliefs, and consequences model of CBT • Using "yes and but" statements to challenge unhelpful thoughts
6	Healthy lifestyle • Connection between the activities and mood • Developing list of pleasant activities
7	Dealing with emotions • Chain activity to understand link between thought, feeling, and activity • Understanding how anxiety and depression sneak in with healthy activities
8	Mindfulness • Deep breathing • Relaxation exercise • Body scan meditation
9	Breaking social isolation and building social networks • Perceived benefits of maintaining social support • Protective factors related to socialization • Role of cancer-related fatigue • Learning problem-solving steps to overcome impact of fatigue on socialization and other areas of functioning
10	Strengthening motivation • Role of physical exercise • Maintaining healthy relationships and strengthening support network • Healthy lifestyle
11	Using new skills for improvement in interpersonal relationships • Identifying obstacles that create hurdle in improving relationships • Assertiveness
12	Feedback and certificate distribution

consists of 12 items with 7-point Likert-type scales ranging from "very strongly disagree" to "very strongly agree." MSPSS measures the adequacy of support from three sources: family, friends, and significant others. Coefficient alphas for the subscales and scale as a whole range from 0.85 to 0.91 and test-retest values ranged from 0.72 to 0.85. The Urdu version of scale has already been used in Pakistan.[50]

Intrusive Thoughts Subscale[51]: We will measure breast cancer distress with the 7-item subscale of the revised Impact of Event Scale (IES) which is reported to be sensitive to change in breast cancer survivors who are receiving CBT intervention. The internal consistency of Intrusive Thoughts Subscale is reported to be 0.86. Mean correlation between two subscales of IES (intrusion and avoidance) was reported to be 0.63 which suggests that they are independent of each other (content validity).[52]

Rosenberg Self-Esteem Scale (RSE)[53]: This is a 10-item Likert scale to measure self-esteem.[53] The internal consistency of the scale was reported to be 0.92 and it correlates significantly with other measures of self-esteem, including the

Coopersmith Self-Esteem Inventory.[53] The scale was used previously in Pakistan.[28]

Client Service Receipt Inventory[54]: Client Service Receipt Inventory (CSRI) is a resource use inventory commonly used in mental health economic evaluations, which will be adapted for Pakistan's health service. In addition to separately collecting information about resources associated with the intervention, the CSRI will be used to collect information about the use of other health services (including the informal sector faith healers/Imams). We will use (and further adapt) a CSRI version used in our previous work in Pakistan.[55]

Client Satisfaction Questionnaire-8 (CSQ-8)[56]: This is a well-validated self-report measure of client–patient satisfaction with health services. The Cronbach's alpha coefficients for the scale range from 0.83 to 0.93. The Client Satisfaction Questionnaire (CSQ-8) total raw score correlated 0.70 with the Service Satisfaction Scale (SSS-30) total raw score, lending empirical support for the construct validity.[57] The scale was used previously in Pakistan.[58]

Participant session attendance log: The research team will maintain session attendance log for each participant in intervention arm to record compliance to the intervention.

Follow-up: Assessment will be completed at baseline, and then all participants will be followed up at 3- and 6-month post-randomization.

Safety considerations: Distress policy both for participants and researchers is in place. Moreover, lone worker policy is also in place.

Theory of Change

Theory of Change (ToC) is an approach that has been widely used for a range of different programmatic contexts in order to develop, implement, monitor, and evaluate the proposed program or intervention.[59] The benefits of using ToC approach has been demonstrated to complement the framework for complex interventions proposed by the Medical Research Council (MRC).[60] Using the ToC approach offers ways to better understanding why and how and to what extent change happens as a result of the implementation of proposed complex intervention.[60]

This study will be underpinned by the ToC causal model to ensure that the voices of stakeholders are included in developing the vision of the project. The stakeholders will include the following:

- Breast cancer survivors
- Carers
- Health professionals
- Representative from non-profit organizations
- Researchers

Following activities will be done as part of developing a causal pathway with key stakeholders for the proposed trial.

- Identification of perceived barriers and challenges, possible consequences, and suggestions about mitigation strategies. This will help us to identify any social and or cultural factors that are present in the context.
- Identification of direct and indirect contributors of change (stakeholders) and their role.
- Identification of short, intermediate, and long-term goals to brainstorm.
- Identification of specific tasks that will lead toward the goals.
- This will also include articulating assumptions that will help identify the contextual conditions that are essential in order to achieve certain outcomes. Together with our stakeholders, we will retrofit our model by testing our assumptions when the context changes.
- Developing a model for assessing impact that will include establishing areas of change, lines of enquiry, and measuring impact.
- Implementing the causal pathway that will be agreed with and owned by the stakeholders.

Process evaluation

Process evaluation will be guided by the UK Medical Research Council Framework of Process evaluation.[61] According to this framework, a purely quantitative approach (experimental design) with no element of process evaluation is rarely adequate for complex intervention research, and hence mixed methods designs are necessary to answer questions beyond effectiveness. Effect estimates are context bound, and average effects are not a useful guide to decision makers working in different contexts. Contextualized understandings of how a complex intervention produces change; details on the important enablers; and barriers on intervention delivery might be more useful.[61] We will conduct individual in-depth interviews with participants ($n = 15–20$) and family members ($n = 15–20$) and a focus group with health service providers. These interviews will consist of open-ended questions, with prompts and guidance on exploratory questions. The purpose of the qualitative phase is to understand perception of breast cancer survivors and family members about perceived effectiveness of Moving on ABC Plus intervention, as well as facilitators and barriers of the intervention. A focus group ($n = 8–10$) will be conducted with health professionals to explore their experience and barriers they face while helping these breast cancer survivors. All interviews and the focus group will be digitally recorded and transcribed. We will use a framework analysis to analyze the qualitative data.[62]

Statistical analysis

Data will be analyzed by using the Statistical Package for Social Sciances (SPSS) software version 23.0, and the intention-to-treat analysis principles will be used to analyze

participants according to their allocated group. A two-sided significance level of 0.05 will be used to determine the significance of the primary outcomes. A significance level of 0.05 (two-sided) will also be used to determine the significance of differences in the secondary and other outcome variables. The demographic and other baseline variables will be compared between study arms using descriptive statistics of means, standard deviations, and proportions. For the primary analyses, a two-sample two-sided test of proportions will be operated to compare the difference in the depression and anxiety at 6-month post-randomization between the intervention and TAU groups. For the secondary analyses, we will use analysis of covariance (ANCOVA) to compare groups, considering the outcome values at baseline as a covariate to control the confounding variables. Moreover, repeated measure ANOVA will be used to compare baseline and follow-up scores on PHQ-9; GAD-7; Quality of life; FACT-B; MSPSS; Intrusive Thoughts Scale; RSE; and CSQ-8. Based on the distribution of the values, a transformation of the outcomes will be performed, if required.

Health economics

We will review health care resource use data (from trial records for information related to the intervention and the CSRI for other health care use) to calculate health care costs falling to public services and to participants/their families. Unit costs will be collected from national data where possible, or calculated from relevant national/local sources. By applying unit costs to individual-level resource use data, we will estimate participant level costs for: (1) hospital services, (2) other health services and (3) the full costs of delivering the intervention (including staff time for delivery/training/supervision, relevant overheads and equipment/materials). We will then undertake a preliminary cost-consequences analysis which presents mean differences in costs between the two trial arms, alongside mean differences in all effectiveness measures including quality-adjusted life years derived from the EQ-5D. The potential impact of any key estimation uncertainties/assumptions will be explored using sensitivity analyses.

Data management

The management, storage, and curation of the data will adhere to the Pakistan Institute of Living and Learning (PILL) data security and confidentiality standards. Data will be collected by the trained researchers at each of the participating centers. Predefined tools will be used for data collection as outlined above while data will be recorded on Case Report Forms. Data will be entered by designated researchers and double entry will be done by Site Leads to ensure quality. A Signed Delegation of Duty Log will be maintained. Principles and Guidelines of Data Protection Act 1998, GDPR 2018 and the NIHR's policy on research data sharing will be followed and practiced in this study.

All paper documents to be digitalized as soon as possible and they will be stored in password protected folders which will only be known by the designated study research team. Hard copies of consent forms will be stored in a locked cabinet in a secure location only available to the designated researchers. The office will be locked when it is not occupied. The PILL office building is securely locked in out-of-office hours. In accordance with the PILL's Information Governance Office Records Retention Schedule, all the data (paper and electronic) will be kept for 10 years.

Data will be available to the broader scientific community in a timely manner and certainly within 2 years of the completion of the study. Data will be completely anonymized, ensuring appropriate documentation, and research team will seek to deposit the data on a suitable data archive. Following measures will be taken for data sharing;

Any publications will indicate contact details of the Principal Investigator (PI). Any application to gain permission to access the data will be made through the PI.

The PI shall ensure that a data-sharing agreement is issued and signed by appropriate authorities before data are released or analyses are performed on behalf of the requester. The data-sharing agreement will set out details such as to whom the data is released, the analyses to be undertaken, the handling of publication, authorship and acknowledgment, requirements in relation to preventing onward transfer of the data to a third party, requirements in relation to notification of all publication based on the use of the data, and arrangements for ongoing support from the study to facilitate data use.

Ethics

Full ethics approval has been sought as well as obtained from both the National Bioethics Committee (NBC), Pakistan (Ref No.4-87/NBC-365/19/1403) and Institute of Professional Psychology Bahria University, Karachi (IPP/BU/OM103/1676) and any changes to the protocol will be duly submitted and approved by the NBC and the trial registration will be updated accordingly.

The trial will be conducted in compliance with the Consolidated Standards of Reporting Trials (CONSORT) statement.[63] The trial protocol was written in accordance with the Standard Protocol Items for Randomised Trials statement.[64] For the SPIRIT flow chart, please see the SPIRIT Flow Diagram in Figure 1.

Quality assurance

Research staff will be trained in good clinical practice (). Detailed participant information sheets (PIS) in local language explaining the purpose of study, potential risks and benefits of the participation, details of therapy sessions and their right to withdraw from the study any time during the trial will be given to all participants before taking written (thumb impression or a verbal audio-recorded consent in the

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
TIMEPOINT	$-t_1$	0	*Moving on ABC Plus intervention*	*TAU*	*3-month FU*	*6-month FU*	
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Baseline assessment	X						
Allocation		X					
INTERVENTIONS:							
[Moving on ABC Plus added to TAU]			X	X			
[TAU Alone]				X			
ASSESSMENTS:							
[PHQ-9 Kroenke et al., 2001***]***	X				X	X	
[GAD-7 *Spitzer et al., 2006]*	X				X	X	
[FACT-B Brady et al., 1997***]***	X				X	X	
[EQ-5D EuroQol Group, 1990***]***	X				X	X	
[MSPSS Zimet et al., 1988***]***	X				X	X	
[Intrusive Though Scale Weiss, 2007***]***	X				X	X	
[Rosenberg Self-esteem Scale Rosenberg, 1965***]***	X				X	X	
[CSRI Beecham & Knapp, 2001***]***	X				X		
[CSQ Attkisson & Greenfield, 1995***]***					X		
Qualitative Interviews					X		
Analysis							X
Report writing							X

Figure 1. SPIRIT flow diagram.

presence of a Legally authorized representative identified by the participant if she is unable to read/write) informed consent. Written (thumb impression or a verbal audio-recorded consent in the presence of a Legally authorized representative identified by the participant if she is unable to read/write) informed consent will be obtained from all the study participants. Those participants who cannot read or write will be explained PIS by the researcher in the presence of a community representative, family member, or carer who can read or write and whom the participant trusts. In such cases, participants will give thumb impression or give verbal consent that will be audio recorded in the presence of a legally

authorized representative identified by the participant and this person will sign the informed consent. Adverse events will be recorded and reported to the Principal Investigator within 48 hours of incidence. For any serious physical adverse event, the participant will be referred to clinicians at recruiting health facilities, and for psychological adverse consequences, referrals will be made to mental health professionals at recruiting sites (TK, IBC, SS, SD, AN, ZZ, NC). If any participant displays signs of distress or is identified as needing more intensive care, the participant will be provided immediate support or if needed\referred to relevant services. Best practice confidentiality and privacy processes of data encryption, protection, storage, and sharing will be followed. Regular supervision and training will be provided to research staff and therapists to ensure clinical and research integrity. The trial Data Monitoring Committee will review the anonymized data on regular basis to ensure the safety of the participants.

Discussion

This trial will address an issue of great public health importance. If Moving on ABC plus is found to be effective, it will provide an evidence-based intervention to reduce psychological morbidity in cancer survivors and potentially reduce overall healthcare costs in this patient population.[65] The development of a culturally appropriate, innovative, feasible, acceptable, effective, and sustainable intervention that is endorsed by the service users may result in advancement in knowledge in the field of multi-morbidity. RCTs are instrumental in providing the evidence for subsequent implementation trials for breast cancer in LMICs where there are limited resources.

Evidence for effectiveness of Moving on ABC plus may lead to health gains that may be considered meaningful for potential changes in clinical practice. Community 'buy in' is hugely important for any intervention and this trial is the product of more than 20 years of patient and community involvement and engagement in mental health research in Pakistan.

The proposed study has some limitations that future research project may consider while developing proposals. This study has only two follow-up time points (end of intervention and 6-month post-randomization). Long-term follow-up assessment may confirm maintenance of impact of the intervention on primary and secondary outcomes. Additionally, this study will only recruit breast cancer survivors, and results may not be generalizable to patients at other stages such as post-diagnosis, during treatment, etc. This study will assess the integrated intervention (selection of interventions was based on —PPIE work in Pakistan) using a two-arm design. It will not be possible to identify whether integrated intervention (Moving on ABC Plus CBT) is more useful compared to CBT alone, though perceived usefulness of components of intervention will be explored during process evaluation.

Conclusion

This trial will be the first randomized controlled trial to assess the effectiveness of an integrated Moving on ABC Plus intervention for breast cancer survivors, which uses cultural knowledge to adapt existing evidence-based therapy (CBT). This will contain information about breast cancer (Moving on ABC) and core components of CBT, incorporating cultural elements and the concepts of psychological well-being.

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Author's contribution and project management

NH, TK, IBC, and FL conceived the idea of this project. NC, NH, IBC, MH, and TK were involved in developing the protocol. AN, SS, ZU, and SD will be responsible for the training and supervision of research team in recruitment and retention of the trial participants. ZZ is responsible for the training and supervision of the trial therapists. LS and AQ will be lead on the qualitative process evaluation. RM is leading on Theory of Change and impact assessment. SS has developed statistical analysis plan of the study. MHA has worked on plan for the health economics section of the trial.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: NH is a former trustee of the Pakistan Institute of Living and Learning (PILL), Abaseen Foundation UK and Lancashire Mind UK. NH is the chair of board of trustees of Manchester Global Foundation (MGF) a Charitable Incorporated Organisation registered in England and Wales. He is a board member of the executive committee for the Faculty of Academic Psychiatry, at the Royal College of Psychiatrists, London. NH has received honorarium and travel grants from various pharmaceutical industries. NH is a NIHR Senior Investigator. IBC has given lectures or advice to Eli Lilly, Bristol Myers Squibb, Lundbeck, Astra Zeneca, and Janssen pharmaceuticals for which he or his employing institution has been reimbursed, outside the submitted work; Prof. Chaudhry was previously trustee of the Pakistan Institute of Living and Learning (PILL). RM is a former trustee of Pakistan Institute of Living and Learning (PILL), UK Association for Medical Aid to Pakistan (UKMAP). The authors declare no conflicts of interest associated with this trial. NC is the CEO of the Pakistan Institute of Living and Learning. She is Associate Director of the Global Mental Health and Cultural Psychiatry Research Group, Head of Psychological Medicine at the Remedial Centre Hospital, Consultant Psychiatrist at South City Hospital, Consultant for Manchester Global Foundation and Professor of Psychiatry, Dow University of Health Sciences. NC has received travel grants from Lundbeck and Pfizer

pharmaceutical companies to attend one national and one international academic meeting and conference in the last three years. She is a chief investigator and co-investigator for a number of research projects funded by various grant bodies such as the Medical Research Council, Welcome Trust, NIH-R, and Global Challenges Research Fund.

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Ethics approval and consent to participate

Full ethics approval has been sought as well as received from the National Bioethics Committee (NBC), Pakistan (Ref No.4-87/NBC-365/19/1403). Written (thumb impression or a verbal audio-recorded consent in the presence of a Legally authorized representative identified by the participant if she is unable to read/write) informed consent will be obtained from all participants. All methods will be carried out in accordance with relevant guidelines and regulations (the Declaration of Helsinki).

Consent for publication

Written (thumb impression or a verbal audio-recorded consent in the presence of a Legally authorized representative identified by the participant if she is unable to read/write) informed consent will be obtained from all participants for publication of findings.

Informed consent

Written (thumb impression or a verbal audio-recorded consent in the presence of a Legally authorized representative identified by the participant if she is unable to read/write) informed consent will be obtained from all participants.

Trial registration

The trial was registered on clinicaltrials.gov on 28/06/2018 (Trial registration number NCT03571984).

Availability of data and material

The datasets generated and/or analyzed during the current study will not be publicly available due to sensitive nature of the information provided by the participants on mental health but are available from the corresponding author on reasonable request.

Supplemental material

Supplemental material for this article is available online.

References

1. WHO. *Breast cancer statistics*. 2021. https://www.who.int/news-room/fact-sheets/detail/breast-cancer
2. Siegel RL, Miller KD and Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; 69(1): 7–34.
3. TGC, TGCO and GLOBOCAN. *Breast cancer 2019*. 2018. Geneva, Switzerland: WHO: International Agency for Research on Cancer.
4. Ranganathan K, Singh P, Wilkins EG, et al. The global macroeconomic burden of breast cancer: implications for oncologic and reconstructive surgery. *Plast Reconstr Surg Glob Open* 2018; 6(4 Suppl): 2–3.
5. Sun L, Legood R, dos-Santos-Silva I, et al. Global treatment costs of breast cancer by stage: a systematic review. *PLoS One* 2018; 13(11): e0207993.
6. Nouwen A, Adriaanse M, van Dam K, et al. Longitudinal associations between depression and diabetes complications: a systematic review and meta-analysis. *Diabet Med* 2019; 36(12): 1562–1572.
7. Husain MI, Chaudhry IB, Husain MO, et al. Depression and congestive heart failure: a large prospective cohort study from Pakistan. *J Psychosom Res* 2019; 120: 46–52.
8. Fatima K, Ghani MU, Ali M, et al. Frequency and severity of depression in patients with Hepatitis C. *Rawal Medical J* 2019; 44(2): 255–258.
9. Pitman A, Suleman S, Hyde N, et al. Depression and anxiety in patients with cancer. *BMJ* 2018; 361: k1415.
10. Carreira H, Williams R, Müller M, et al. Associations between breast cancer survivorship and adverse mental health outcomes: a systematic review. *J Natl Cancer Inst* 2018; 110(12): 1311–1327.
11. Maass SW, Roorda C, Berendsen AJ, et al. The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: a systematic review. *Maturitas* 2015; 82(1): 100–108.
12. Firkins J, Hansen L, Driessnack M, et al. Quality of life in "chronic" cancer survivors: a meta-analysis. *J Cancer Surviv* 2020; 14(4): 504–517.
13. Heidkamp P, Breidenbach C, Hiltrop K, et al. Individual courses and determinants of fear of cancer recurrence in long-term breast cancer survivors with and without recurrence. *Support Care Cancer* 2021; 29(12): 7647–7657.
14. Pilevarzadeh M, Amirshahi M, Afsargharehbagh R, et al. Global prevalence of depression among breast cancer patients: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2019; 176(3): 519–533.
15. de Oliveira NPD, Guedes TSR, Holanda AM, et al. Functional disability in women submitted to breast cancer treatment. *Asian Pac J Cancer Prev* 2017; 18(5): 1207.
16. Niedzwiedz CL, Knifton L, Robb KA, et al. Depression and anxiety among people living with and beyond cancer: a growing clinical and research priority. *BMC Cancer* 2019; 19(1): 943.
17. Syrowatka A, Motulsky A, Kurteva S, et al. Predictors of distress in female breast cancer survivors: a systematic review. *Breast Cancer Res Treat* 2017; 165(2): 229–245.
18. Wang Y-H, Li J-Q, Shi J-F, et al. Depression and anxiety in relation to cancer incidence and mortality: a systematic review and meta-analysis of cohort studies. *Mol Psychiatry* 2020; 25(7): 1487–1499.
19. Yasmeen F and Zaheer S. Functional time series models to estimate future age-specific breast cancer incidence rates for women in Karachi, Pakistan. *J Health Sci* 2014; 2(5): 213–221.
20. Basra M, Saher M, Athar MM, et al. Breast cancer in Pakistan a critical appraisal of the situation regarding female health and where the nation stands. *Asian Pac J Cancer Prev* 2016; 17: 3035–3041.

21. Khan S, Khan NA, Rehman AU, et al. Levels of depression and anxiety post-mastectomy in breast cancer patients at a public sector hospital in Karachi. *Asian Pac J Cancer Prev* 2016; 17(3): 1337–1340.
22. Kiran T and Malik AA. Psychological comorbidity of breast cancer: a cross-sectional study from Pakistan. *Pak J Int Aff* 2021; 4(2): 292–302.
23. Nekhlyudov L and Wenger N. Institute of medicine recommendations for improving the quality of cancer care: what do they mean for the general internist? *J Gen Intern Med* 2014; 29(10): 1404–1409.
24. Jassim GA, Doherty S, Whitford DL, et al. Psychological interventions for women with non-metastatic breast cancer. *Cochrane Database Syst Rev* 2023; 1(1): CD008729.
25. Ye M, Du K, Zhou J, et al. A meta-analysis of the efficacy of cognitive behavior therapy on quality of life and psychological health of breast cancer survivors and patients. *Psychooncology* 2018; 27(7): 1695–1703.
26. Husain N, Parveen A, Husain M, et al. Prevalence and psychosocial correlates of perinatal depression: a cohort study from urban Pakistan. *Arch Women's Ment Health* 2011; 14(5): 395.
27. Husain N, Gater R, Tomenson B, et al. Social factors associated with chronic depression among a population-based sample of women in rural Pakistan. *Soc Psychiatry Psychiatr Epidemiol* 2004; 39(8): 618–624.
28. Husain N, Chaudhry N, Fatima B, et al. Antidepressant and group psychosocial treatment for depression: a rater blind exploratory RCT from a low income country. *Behav Cogn Psychother* 2014; 42(6): 693–705.
29. Husain MO, Umer M, Taylor P, et al. Demographic and psychosocial characteristics of self-harm: the Pakistan perspective. *Psychiatry Res* 2019; 279: 201–206.
30. Hall GCN, Ibaraki AY, Huang ER, et al. A meta-analysis of cultural adaptations of psychological interventions. *Behav Ther* 2016; 47(6): 993–1014.
31. Akram M, Iqbal M, Daniyal M, et al. Awareness and current knowledge of breast cancer. *Biol Res* 2017; 50(1): 33.
32. Kisiangani J, Baliddawa J, Marinda P, et al. Determinants of breast cancer early detection for cues to expanded control and care: the lived experiences among women from Western Kenya. *BMC Women's Health* 2018; 18(1): 81.
33. Tazhibi M and Feizi A. Awareness levels about breast cancer risk factors, early warning signs, and screening and therapeutic approaches among Iranian adult women: a large population based study using latent class analysis. *Biomed Res Int* 2014; 2014: 306352.
34. Saleem A. Moving on ABC after breast cancer: a complete approach, http://www.afterbreastcancer.com (2016).(accessed 12 July 2019).
35. Lopes C, Lopes-Conceição L, Fontes F, et al. Prevalence and persistence of anxiety and depression over five years since breast cancer diagnosis—the NEON-BC prospective study. *Curr Oncol* 2022; 29(3): 2141–2153.
36. Rahman R, Nisar A, Hussain N, et al. P02-82-depressive disorder among the breast cancer patients in outpatient department of a tertiary care hospital in Pakistan. *Eur Psychiatry* 2011; 26: 677.
37. Kroenke K, Spitzer RL and Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; 16(9): 606–613.
38. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006; 166(10): 1092–1097.
39. Miranda J, Woo S, Lagomasino I, et al. *Group cognitive behaviour therapy for depression: thoughts and your mood*. San Francisco: San Francisco General Hospital Depression Clinic, 2006.
40. Munoz RF and Miranda J. *Group therapy for cognitive behavioural treatment of depression*. San Francisco: San Francisco General Hospital Depression Clinic, 1986.
41. Husain N, Kiran T, Shah S, et al. Efficacy of learning through play plus intervention to reduce maternal depression in women with malnourished children: a randomized controlled trial from Pakistan. *J Affect Disord* 2021; 278: 78–84.
42. Husain N, Zulqernain F, Carter L-A, et al. Treatment of maternal depression in urban slums of Karachi, Pakistan: a randomized controlled trial (RCT) of an integrated maternal psychological and early child development intervention. *Asian J Psychiatr* 2017; 29: 63–70.
43. Ahmad S, Hussain S, Akhtar F, et al. Urdu translation and validation of PHQ-9, a reliable identification, severity and treatment outcome tool for depression. *J Pak Med Assoc* 2018; 68(8): 1166–1170.
44. Spitzer R, Kroenke K and Williams J. Generalized anxiety disorder 7-item (GAD-7) scale. *Arch Intern Med* 2006; 166: 1092–1097.
45. Ahmad S, Hussain S, Shah FS, et al. Urdu translation and validation of GAD-7: a screening and rating tool for anxiety symptoms in primary health care. *J Pak Med Assoc* 2017; 67(10): 1536–1540.
46. Brady MJ, Cella DF, Mo F, et al. Reliability and validity of the functional assessment of cancer therapy-breast quality-of-life instrument. *J Clin Oncol* 1997; 15(3): 974–986.
47. EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy* 1990; 16(3): 199–208.
48. Husain MI, Chaudhry IB, Husain N, et al. Minocycline as an adjunct for treatment-resistant depressive symptoms: a pilot randomised placebo-controlled trial. *J Psychopharmacol* 2017; 31(9): 1166–1175.
49. Zimet GD, Dahlem NW, Zimet SG, et al. The multidimensional scale of perceived social support. *J Pers Assess* 1988; 52(1): 30–41.
50. Akhtar A, Rahman A, Husain M, et al. Multidimensional scale of perceived social support: psychometric properties in a South Asian population. *J Obstet Gynaecol Res* 2010; 36(4): 845–851.
51. Weiss DS. The impact of event scale: revised. In:Wilson JP and Tang CS (eds) *Cross-cultural assessment of psychological trauma and PTSD*. Boston: Springer, 2007, pp. 219–238.
52. Sundin EC and Horowitz MJ. Impact of event scale: psychometric properties. *Br J Psychiatry* 2002; 180(3): 205–209.
53. Rosenberg M. *Rosenberg self-esteem scale (RSE). Acceptance Commitment Ther* 1965; 61(52): 18.
54. Beecham J and Knapp M. Costing psychiatric interventions. In:Thornicroft G, Brewin CR and Wing J (eds) *Measuring mental health needs*. London, UK: Gaskell, 2001, pp. 200–224.

55. Alvi MH, Shiri T, Iqbal N, et al. Cost-effectiveness of a culturally adapted manual-assisted brief psychological intervention for self-harm in Pakistan: a secondary analysis of the culturally adapted manual-assisted problem-solving training randomized controlled trial. *Value Health Reg Issues* 2021; 25: 150–156.
56. Attkisson C and Greenfield T. The client satisfaction questionnaire (CSQ) scales. *Outcome assessment in clinical practice*. Baltimore: Williams & Wilkins, 1995.
57. Attkisson CC and Greenfield TK. The client satisfaction questionnaire (CSQ) scales and the service satisfaction scale-30 (SSS-30). *Outcomes Assess Clin Pract* 1996; 120(7): 120–127.
58. Husain MO, Khoso AB, Renwick L, et al. Culturally adapted family intervention for schizophrenia in Pakistan: a feasibility study. *Int J Psychiatry Clin Pract* 2021; 25(3): 258–267.
59. Vogel I. *Review of the use of 'Theory of Change' in international development*. London: DFID, 2012.
60. De Silva MJ, Breuer E, Lee L, et al. Theory of change: a theory-driven approach to enhance the Medical Research Council's framework for complex interventions. *Trials* 2014; 15(1): 267.
61. Skivington K, Matthews L, Simpson SA, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. *BMJ* 2021; 374: n2061.
62. Ritchie J, Lewis J, Nicholls CM, et al. *Qualitative research practice: a guide for social science students and researchers*. Thousand Oaks, CA: Sage, 2013.
63. Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMC Med* 2010; 8(1): 18.
64. Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013; 346: e7586.
65. Butow PN, Bell ML, Smith AB, et al. Conquer fear: protocol of a randomised controlled trial of a psychological intervention to reduce fear of cancer recurrence. *BMC Cancer* 2013; 13(1): 201.