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Proactive Identification and Digital Mental Health Intervention for the Treatment of Depression Among Individuals With Likely Incurable Cancer: A Pilot Randomized Clinical Trial

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ABSTRACT

Background: Although depression is prevalent and has significant consequences among individuals living with likely incurable cancer (ILLIC), optimal methods of identifying and treating depression in this population remain unknown.

Aims: To evaluate a paradigm of (1) proactive identification (ID) (i.e., remotely and asynchronously from clinical encounters) of depression among ILLIC and (2) digital mental health intervention (DMHI) for depression treatment.

Methods: In this decentralized randomized clinical trial, ILLIC with elevated depressive symptoms were proactively identified using electronic health record data and randomized 2:1 to a DMHI-based Behavioral Activation treatment or usual care (UC) depression treatment. Measures of feasibility (accrual, retention) and acceptability (engagement) were described; depression severity (change in PHQ-9 scores through 4 weeks post-randomization) was modeled with a generalized estimating equation.

Results: Among 88 ILLIC who completed screening, 30 were eligible and randomized to the trial. No patients were lost to follow-up or withdrew; 80% of patients randomized to proactive ID + DMHI used the app through 4 weeks. Proactive ID + DMHI improved depression from baseline to 4 weeks relative to proactive ID + UC (mean difference in change from baseline to week 4 = -2.7 ; 90% CI: -4.9 to -0.4). At 4 weeks, the odds of a clinical response (PHQ-9 decrease of ≥ 5 points) was 9.0-fold higher for patients in proactive ID + DMHI relative to proactive ID + UC (OR 9.0; 90% CI: 1.1–74.2).

Conclusions: A proactive ID + DMHI approach to identifying and treating depression among ILLIC is feasible, acceptable, and potentially efficacious. These promising data support conducting a large efficacy trial evaluating this approach.

Trial Registration: ClinicalTrials.gov identifier: NCT05932810

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1 | Introduction

With improvements in treatment and supportive care, there are a growing number of individuals living longer with advanced or metastatic cancer that is likely incurable [1, 2]. This understudied survivor subpopulation is highly heterogeneous and has unique survivorship care needs [1, 3]. Individuals living with likely incurable cancer (ILLIC) may transition on and off therapy, have considerable prognostic uncertainty, and experience a unique symptom profile due to cumulative effects of multiple cancer-directed therapies and novel agents. Living longer with likely incurable cancer often comes with burdensome psychosocial symptoms and up to 50% of people living with advanced or metastatic cancer report depressive symptoms [4–6]. Depression in this patient population is highly significant as it is associated with worse quality of life (QOL), reduced adherence to anti-cancer therapies, suicidal ideation, and desire for hastened death [7, 8].

Although numerous trials [9, 10] and meta-analyses [5, 11] have documented that evidence-based psychosocial treatment improves depression outcomes for people living with advanced or metastatic cancer, multilevel barriers limit access. Patients lack treatment information, experience stigma, do not receive treatment referrals, and are faced with geographic barriers to care [12, 13]. Providers lack treatment knowledge and have limited time and resources [14]. Organizational barriers, such as unclear referral pathways, further limit uptake [14]. Novel care delivery approaches that address these multilevel barriers and extend psychosocial treatment access for ILLIC are clearly needed.

One promising approach to improve access to depression treatment is to proactively link patients with evidence-based treatment outside the context of (i.e., asynchronous from) a medical encounter [15, 16]. As a pre-requisite to this care delivery approach, it is necessary to first identify patients with (1) elevated depressive symptoms and (2) likely incurable advanced and metastatic cancer. Currently, information available in the electronic health record (EHR) can be leveraged to accomplish both goals. For example, short depression screening tools (e.g., PHQ-2 [17]) are routinely administered in oncology care settings to systematically identify people with cancer at risk for experiencing elevated depressive symptoms [18, 19]. In addition, patients with advanced or metastatic cancer that is likely incurable can be identified using both structured and unstructured data from the EHR [20].

Digital mental health interventions (DMHIs), which offer adaptations of evidence-based mental health interventions, are another component of a promising strategy to improve access to mental health treatment in this population. DMHIs overcome many of the barriers to depression treatment among cancer survivors including stigma, a shortage of trained mental health professionals, and geographic barriers. DMHIs have comparable effects to standard psychosocial interventions [21, 22]. Although trials have demonstrated that DMHIs are feasible, acceptable, and may improve depressive symptoms among cancer survivors [23–26], they have not been evaluated specifically among ILLIC. Self-guided DMHIs, which allow on-demand access with each survivor selecting their optimal frequency and duration, are particularly well suited to the unique needs of ILLIC. Unlike

traditional psychotherapies and guided DMHIs which present content in a “sessionized” fashion, the on-demand scheduling and flexible, self-directed pace of the self-guided DMHI can accommodate the fluctuating and unpredictable physical and mental health symptoms in this population related to unpredictable cancer progression, accumulating treatment toxicity, and cycling on and off of cancer-directed therapy. Among DMHIs that could be deployed to treat depression among ILLIC, those featuring Behavioral Activation (BA) treatment are particularly appealing because BA specifically targets decreased activity level, a key mechanism purported to underlie depression in this population [27, 28].

To address the lack of adequate mental health care delivery for people living with likely incurable advanced or metastatic cancer and depressive symptoms, we conducted a pilot randomized clinical trial (RCT) to evaluate the feasibility, acceptability, and preliminary efficacy of proactive identification (ID) + DMHI versus proactive ID + Usual Care (UC) for treating depression in this population.

2 | Methods

This decentralized 2-arm parallel-group RCT was conducted among patients receiving care from the Medical University of South Carolina (MUSC) Hollings Cancer Center. The study was approved by the MUSC institutional review board (Pro00126828) and registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT05932810). Trial information is presented according to the CONSORT extensions for randomized pilot [29], psychological intervention trials [30], and e-health trials [31].

2.1 | Participants

Eligible patients were ≥ 18 years of age, had any type of advanced or metastatic cancer that was likely incurable, reported current elevated depressive symptoms (defined per ASCO Guidelines [8] as a PHQ-9 [32] score ≥ 8), owned an iOS- or Android-compatible smartphone, and had English fluency. Patients were excluded if they had severe cognitive impairment precluding informed consent (self-report or diagnosis of dementia or neurocognitive disorder) or if they had current suicidal ideation (≥ 2 on PHQ-9 item 9). If a participant screened positive for suicidal ideation during the eligibility assessment (or during post-randomization follow-up), they were contacted for completion of a risk assessment and provided with follow-up care as appropriate. Potentially eligible patients were sent a study invitation via the EHR patient portal (MyChart), text message, email, and/or phone (based on preferences in the EHR) and underwent remote final eligibility assessment, including completion of the PHQ-9 [32] to ensure current depression at accrual.

2.2 | Procedures

Following remote informed e-consent and completion of baseline assessments, patients were randomized 2:1 to proactive ID + DMHI or proactive ID + UC using a mixed block design

with block sizes of 3, 6, and 9. The 2:1 randomization allocation was selected to maximize information about the acceptability of proactive ID + DMHI. The randomization sequence was generated by the biostatistician using a computer-generated algorithm and implemented in REDCap. Patients were compensated \$40 for completion of baseline assessments, \$40 for completion of each post-baseline assessment, and \$100 if all study assessments were completed (total potential compensation = \$300).

2.3 | Proactive ID + DMHI (Intervention)

Proactive ID refers to the use of structured and unstructured EHR data asynchronous from clinical encounters to proactively identify patients who are (1) living with advanced or metastatic cancer that is likely incurable and (2) who likely have elevated depressive symptoms. This paradigm is contrasted with the standard of care approach of screening patients for depression during a routine clinical encounter and linking them in real time to mental health treatment. To date, the gold standard method of identifying ILLIC is through manual review of the EHR. To proactively identify ILLIC for this trial, we performed an automated EHR search of all patients with a cancer diagnosis who had undergone or were undergoing treatment and had a clinical encounter at the MUSC Hollings Cancer Center on Jan 1, 2023 or later. We then manually reviewed charts to identify those with likely incurable advanced or metastatic cancer. To proactively identify the subset of survivors likely to have elevated depressive symptoms, we performed an automated EHR search to identify patients with a PHQ-2 score of ≥ 3 (i.e., positive screening [33]), depression on their problem list, or a depression-related billing code associated with their last visit.

The DMHI deployed within this trial was “Moodivate,” a DMHI-based approach to deliver Behavioral Activation (BA) Treatment for Depression [16, 34, 35]. BA is an evidence-based first-line depression treatment for cancer survivors [8, 27, 28, 36] which aims to help patients identify, schedule and reengage in positive activities. BA is ideal for people living with advanced or metastatic cancer that is likely incurable because it specifically targets decreased activity level, a key mechanism purported to underly depression in this population [27, 28]. As illness progresses among ILLIC, daily tasks may be abandoned, leading to decreased activity levels, an environment that perpetuates depressed mood, and subsequent exacerbation of depressive symptoms. BA works by helping ILLIC re-engage in meaningful activities, thereby improving mood.

Moodivate has been described previously [16, 34, 35]. For this study, psychoeducational content was tailored within the app specifically for survivors living with advanced or metastatic cancer that is likely incurable. Moodivate is available on both iOS and Android and is free for initial download. Following successful app download, study staff provide a brief, scripted overview regarding app utilization and provide the patient with 10 min to use the app and ask questions. Moodivate users can track daily mood to monitor progress and are prompted to complete a clinical assessment of depressive symptoms once every 2 weeks. Users can view a graph of mood and depressive symptoms overlaid upon a graph of the number of completed

activities, illustrating the connection between activity and mood. Gamification elements (e.g., badges) promote continued engagement with Moodivate over time [34]. Patients are encouraged to use the app regularly at least once per day, throughout the study and have access to the app through the entire study period and beyond. As a self-guided DMHI, there is no prescribed minimum “dose” of Moodivate; the app may be used for shorter or longer duration than the 8–12 weeks suggested in the original BA manual [37] depending on user preference.

2.4 | Proactive ID + UC (Control)

Proactive ID of ILLIC and elevated depressive symptoms was performed in an identical fashion for those randomized to UC. UC mimics existing depression treatment for people living with advanced or metastatic cancer that is likely incurable. Participants in either arm could receive treatment (e.g., pharmacotherapy) or a referral for evidence-based psychotherapy (e.g., cognitive behavioral therapy) either within our integrated behavioral medicine clinic or to an outside mental health provider from their oncology team as part of their usual clinical care (i.e., unrelated to trial participation).

2.5 | Study Measures and Outcomes

Demographic data were collected via self-report. Clinical characteristics were extracted from the EHR. All patient-reported study assessments were collected via a REDCap link which was sent to the participant via text message and/or email. Concomitant mental health treatment was measured at baseline and all post-randomization visits by self-report. Rurality was defined based on rural-urban commuting area (RUCA) codes with RUCA codes of 1–3 classified as non-rural and 4–10 as rural. Digital literacy was assessed at baseline via the Mobile Device Proficiency Questionnaire (MDPQ-16) [38]. The MDPQ-16 is a validated, 16-item self-report measure of mobile device proficiency. Scores range from 0 to 40 with higher scores indicating greater mobile device proficiency.

For the primary objective of evaluating the feasibility of conducting a fully decentralized RCT comparing proactive ID + DMHI with proactive ID + UC, we selected feasibility endpoints of accrual and trial retention. For the secondary objective of determining the acceptability of proactive ID + DMHI among depressed ILLIC, we selected a battery of passively collected app analytics data (collected continuously post-randomization), a quantitative program evaluation with open-ended feedback, and the System Usability Scale (SUS) [39] as measured at week 4. The SUS is a validated 10-item self-report measure of acceptability. The SUS score ranges from 0 to 100; higher scores indicate better usability.

Depressive symptoms were measured using the PHQ-9 [32] at baseline and weekly for 4 weeks post-randomization for participants in both arms. The PHQ-9 score ranges from 0 to 27; higher scores represent more severe depressive symptoms and severity of depressive symptoms is categorized as moderate (8–14), moderately severe (15–19), and severe (20–27). An

additional depression-related endpoint was a clinically important reduction in depressive symptoms, defined as a decrease in PHQ-9 score ≥ 5 points from baseline to week 4. Anxiety and health-related quality of life (HRQOL) were measured with the Hospital Anxiety and Depression Scale, Anxiety subscale (HADS-A) [40] and Functional Assessment of Cancer Therapy-7 item version (FACT-G7) [41], respectively, at baseline and weekly for 4 weeks post-randomization for participants in both arms. Lower scores on the HADS-A indicate lesser anxiety while higher scores on the FACT-G7 indicate better HRQOL. Per protocol, assessments were to be completed within a 72-h window of their assignment; all assessments were completed within the protocol-specified window except one end of study assessment at week 4 for one participant.

2.6 | Statistical Analysis

Feasibility and acceptability endpoints were summarized by mean (SD) or median (IQR) descriptive statistics. A generalized estimating equation (GEE) with identity link was used to model expected PHQ-9 scores at weeks 1–4 as a function of treatment group, time (continuous), and treatment group-by-time interaction, with adjustment for baseline PHQ-9 score and gender. A compound symmetric correlation structure was used, and the variance of the fitted model parameters was estimated using the robust sandwich estimator. The functional form of time was evaluated and no significant departure from linearity was detected. The fitted model was used to estimate average change from baseline for the proactive ID + DMHI and proactive ID + UC arms. To estimate average group scores based on the fitted linear predictor, coefficients for baseline PHQ-9 and gender were weighted using the average overall baseline PHQ-9 score and the proportion of male study participants, respectively. Linear contrasts were constructed to estimate the difference between arms in change from baseline at week 4. A similar GEE modeling approach was utilized to analyze the HADS-A and FACT-G7 scores. The probability of a ≥ 5 -point change in PHQ-9 score from baseline to week 4 was modeled using a binary regression generalized linear model with logit link and treatment arm, baseline PHQ-9 score and gender as independent variables. An odds ratio (OR) and corresponding 90% confidence interval (CI) were reported to evaluate the association between treatment arm and the incidence of a > 5 -point change in PHQ-9 score from baseline to week 4.

All participants randomized to proactive ID + DMHI ($n = 20$) or proactive ID + UC ($n = 10$) were included in the regression analyses of PHQ-9, HADS-A, and FACT-G7 scores. However, one participant did not have week 4 measurements due to mortality. A change from baseline to week 4 could not be estimated for this participant and they were not included in the analysis of a ≥ 5 point change in PHQ-9 score.

Aligned with the pilot stage of the research and the intention to identify promising findings for follow-up evaluation in a fully powered RCT, model-based differences between treatment arms were used to assess the direction and strength of the efficacy signal for changes in score from baseline to week 4 on the PHQ-9, FACT-G7, and HADS-A. We constructed 90% confidence intervals to convey uncertainty around these point estimates.

3 | Results

The CONSORT diagram is shown in Figure 1. Patients who did not complete the screening eligibility assessment ($n = 261$) were similar to those who completed the assessment ($n = 88$) in terms of demographic characteristics except that Black patients were less likely to complete the assessment than White patients (Supporting Information S1: Table 1). Baseline characteristics for patients randomized to proactive ID + DMHI ($n = 20$) and proactive ID + UC ($n = 10$) are summarized in Table 1. The median (IQR) age was 57.5 (47.0, 65.5) years; 40% of patients identified as male; 23% self-reported being from a racial or ethnic minority population, and 13% lived in rural areas. Overall, 73% of patients had metastatic cancer that was likely incurable and 27% had locoregionally advanced cancer that was likely incurable. At randomization, 30% of participants were receiving psychotherapy for their depression and 80% were on pharmacotherapy for their depression. Post-randomization usage of concomitant mental health therapies through the end of the study was similar to baseline (Proactive ID + DMHI: 35% psychotherapy, 70% pharmacotherapy; Proactive ID + UC: 20% psychotherapy; 90% pharmacotherapy).

3.1 | Feasibility and Acceptability

For the primary feasibility endpoint of accrual to the RCT, among 349 ILLIC with likely depression identified in the EHR, 88 (25%) completed screening, and 30 met trial eligibility criteria. Among the 30 eligible potential participants, 100% were enrolled and randomized to the trial. For the feasibility endpoint of retention, one participant in proactive ID + UC died between weeks 3 and 4; no patients were lost to follow-up or withdrew from the study.

In terms of acceptability among patients randomized to the Proactive ID + DMHI arm, the Moodivate app was rated as having good usability (mean [SD] System Usability Scale score = 73.0 [18.9] at week 4). Table 2 shows engagement metrics for participants randomized to proactive ID + DMHI. Engagement was high, as 80% of patients randomized to proactive ID + DMHI continued to use the app through 4 weeks. Participants completed a mean (SD) of 35.9 (26.6) Moodivate app sessions and scheduled a mean (SD) of 66.8 (114.7) activities within the app. The quantitative program evaluation and open-ended questions regarding the acceptability of the proactive ID + DMHI approach are shown in Supporting Information S1: Table 2.

3.2 | Depression

The estimated average change in PHQ-9 score from baseline over time is shown in Figure 2. For participants in the proactive ID + DMHI arm, PHQ-9 scores decreased by a mean of 3.2 points (90% CI: -4.5 to -1.9) from baseline to week 4. Proactive ID + DMHI improved depression severity as measured by PHQ-9 scores relative to proactive ID + UC (mean difference in change in PHQ-9 score from baseline to week 4 = -2.7 ; 90% CI: -4.9 to -0.4). At 4-week post-randomization, 45% (9/20; exact 90% CI:

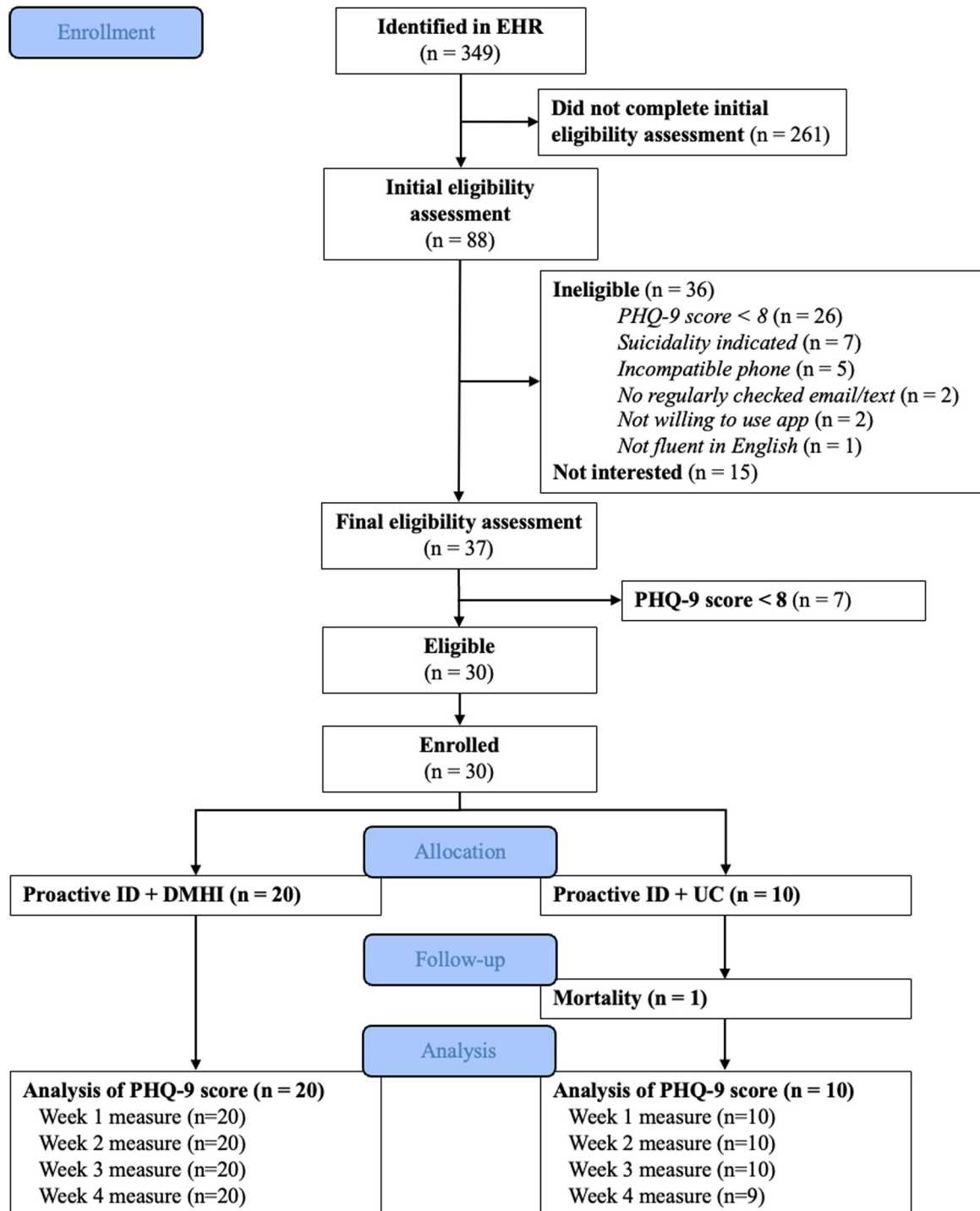


FIGURE 1 | CONSORT diagram. Total of ineligible patients by reason sums to > n = 36 because patients may be ineligible for > 1 concurrent reason.

26%–65%) of patients in proactive ID + DMHI experienced a clinically important decrease in depression severity (i.e., decrease in PHQ-9 of ≥ 5 points). The odds of experiencing a clinically important decrease in depression was 9 times higher for patients randomized to proactive ID + DMHI relative to those randomized to proactive ID + UC (OR = 9.0; 90% CI 1.1–74.2).

3.3 | Anxiety and HRQOL

Proactive ID + DMHI decreased anxiety over time (change in HADS-A score from baseline to week 4 = -1.7 ; 90% CI: -2.8 to -0.6), although this result did not differ relative to proactive ID + UC (mean difference in change in HADS-A score from

TABLE 1 | Baseline demographic and clinical characteristics.

Variable	No. (%)		Overall (N = 30)
	Proactive ID + DMHI (N = 20)	Proactive ID + UC (N = 10)	
Age, median (IQR), years	60.0 (50.0, 66.2)	56.5 (43.2, 62.8)	57.5 (47.0, 65.5)
Sex			
Male	10 (50%)	2 (20%)	12 (40%)
Female	10 (50%)	8 (80%)	18 (60%)
Gender			
Male	10 (50%)	2 (20%)	12 (40%)
Female	10 (50%)	8 (80%)	18 (60%)
Race and ethnicity			
Non-Hispanic White	15 (75%)	8 (80%)	23 (77%)
Hispanic White	0 (0%)	0 (0%)	0 (0%)
Black	4 (20%)	1 (10%)	5 (17%)
American Indian or Alaskan Native	1 (5%)	0 (0%)	1 (3%)
Multiracial	0 (0%)	1 (10%)	1 (3%)
Health insurance			
Private, employee provided	3 (15%)	1 (10%)	4 (13%)
Private, other	6 (30%)	2 (20%)	8 (27%)
Medicare	6 (30%)	4 (40%)	10 (33%)
Medicaid	2 (10%)	2 (20%)	4 (13%)
Other	3 (15%)	0 (0%)	3 (10%)
None	0 (0%)	1 (10%)	1 (3%)
Marital status			
Married	14 (70%)	6 (60%)	20 (67%)
Separated/divorced	3 (15%)	3 (30%)	6 (20%)
Widowed	2 (10%)	0 (0%)	2 (7%)
Single/never married	1 (5%)	1 (10%)	2 (7%)
Highest level of education			
Some high school	0 (0%)	2 (20%)	2 (7%)
High school graduate or GED	4 (20%)	1 (10%)	5 (17%)
Some college	11 (55%)	3 (30%)	14 (47%)
College graduate (4 years or more)	4 (20%)	2 (20%)	6 (20%)
Graduate school/ Advanced degree	1 (5%)	2 (20%)	3 (10%)
Household income			
< \$25,000	6 (30%)	0 (0%)	6 (20%)
\$25,000–\$50,000	5 (25%)	4 (40%)	9 (30%)

(Continues)

TABLE 1 | (Continued)

Variable	No. (%)		Overall (N = 30)
	Proactive ID + DMHI (N = 20)	Proactive ID + UC (N = 10)	
\$50,000–\$75,000	4 (20%)	2 (20%)	6 (20%)
\$75,000 = \$100,000	1 (5%)	0 (0%)	1 (3%)
> \$100,000	3 (15%)	4 (40%)	7 (23%)
Don't know/not sure	1 (5%)	0 (0%)	1 (3%)
Employment status			
Full-time	2 (10%)	1 (10%)	3 (10%)
Unemployed	6 (30%)	1 (10%)	7 (23%)
Disabled	4 (20%)	4 (40%)	8 (27%)
Employed part time	1 (5%)	1 (10%)	2 (7%)
Retired	6 (30%)	3 (30%)	9 (30%)
Other	1 (5%)	0 (0%)	1 (3%)
Rurality			
Non-rural	16 (80%)	10 (100%)	26 (87%)
Rural	4 (20%)	0 (0%)	4 (13%)
Baseline depression severity (PHQ-9), mean (SD)	12.8 (3.3)	14.0 (2.7)	13.2 (3.1)
Baseline depression severity (PHQ-9 score)			
Moderate (8–14)	14 (70%)	4 (40%)	18 (60%)
Moderately severe to severe (15–27)	6 (30%)	6 (60%)	12 (40%)
Concomitant mental health treatment ^a			
Psychotherapy	7 (35%)	2 (20%)	9 (30%)
Pharmacotherapy	15 (75%)	9 (90%)	24 (80%)
Cancer type ^b			
Brain	2 (10%)	1 (10%)	3 (10%)
Breast	3 (15%)	0 (0%)	3 (10%)
Colon	1 (5%)	1 (10%)	2 (7%)
Gynecologic	1 (5%)	1 (10%)	2 (7%)
Lung	1 (5%)	1 (10%)	2 (7%)
Multiple myeloma	2 (10%)	2 (10%)	4 (13%)
Neuroendocrine	2 (10%)	1 (10%)	3 (10%)
Pancreas	1 (5%)	1 (10%)	2 (7%)
Prostate	4 (20%)	0 (0%)	4 (13%)
Renal	1 (5%)	1 (10%)	2 (7%)
Other ^b	2 (10%)	1 (10%)	3 (10%)
Type of likely incurable cancer			
Advanced	5 (25%)	3 (30%)	8 (27%)
Metastatic	15 (75%)	7 (70%)	22 (73%)

(Continues)

TABLE 1 | (Continued)

Variable	No. (%)		Overall (N = 30)
	Proactive ID + DMHI (N = 20)	Proactive ID + UC (N = 10)	
Time since diagnosis of likely incurable cancer, median (IQR), years	2.5 (1.5, 3.6)	2.5 (2.2, 5.4)	2.5 (1.8, 4.1)
Current cancer therapy ^a			
Chemotherapy	7 (35%)	3 (30%)	10 (33%)
Hormone therapy	4 (20%)	0 (0%)	4 (13%)
Immunotherapy	2 (10%)	2 (20%)	4 (13%)
Targeted therapy	8 (40%)	3 (30%)	11 (37%)
None (treatment break)	5 (25%)	4 (40%)	9 (30%)
Duration of cancer-directed therapy, median (IQR), years	4.0 (2.0, 8.7)	2.2 (2.0, 3.7)	2.5 (2.0, 5.5)
ECOG performance status			
0	7 (35%)	4 (40%)	11 (37%)
1	4 (20%)	3 (30%)	7 (23%)
2	4 (20%)	0 (0%)	4 (13%)
3	1 (5%)	0 (0%)	1 (3%)
Unknown	4 (20%)	3 (30%)	7 (23%)
Charlson comorbidity index			
0	15 (75%)	6 (60%)	21 (70%)
1	3 (15%)	2 (20%)	5 (17%)
2	0 (0%)	1 (10%)	1 (3%)
≥ 3	2 (10%)	1 (10%)	3 (10%)
Cell phone type			
iPhone	11 (55%)	7 (70%)	18 (60%)
Android	9 (45%)	3 (30%)	12 (40%)
Mobile device health proficiency	37.0 (32.4, 40.0)	39.0 (33.8, 40.0)	37.8 (33.0, 40.0)
Questionnaire-16 score, median (IQR)			

^aPercentages can sum > 100% as a participant can have more than one current therapy.

^bOther = 1 (DMHI) Hematologic, 1 (DMHI) Melanoma, 1 (UC) Sarcoma.

baseline to week 4 = −1.0; 90% CI: −2.8 to 0.8). Proactive ID + DMHI improved HRQOL over time (change in FACT-G7 score from baseline to week 4 = 2.0; 90% CI: 0.8–3.2). Proactive ID + DMHI also improved HRQOL relative to proactive ID + UC (mean difference in change in FACT-G7 score from baseline to week 4 = 2.9; 90% CI: 1.1–4.7).

4 | Discussion

In this pilot RCT, we demonstrated that a proactive ID + DMHI approach to treating depression is feasible and acceptable

TABLE 2 | Moodivate acceptability and engagement (n = 20).

Acceptability measure	Mean (SD)
Number of Moodivate app sessions	35.9 (26.6)
Time per Moodivate session, minutes	3.6 (2.3)
Total time using the Moodivate app, minutes	107.1 (89.7)
Number of goals created within Moodivate	4.0 (6.0)
Number of activities created within Moodivate	3.2 (4.4)
Number of activities scheduled within Moodivate ^a	66.8 (114.7)
Number of activities completed ^a	28.3 (41.0)
Use of app within week following download (engagement)	
	No. (%)
Week 1	20 (100%)
Week 2	17 (85%)
Week 3	17 (85%)
Week 4	16 (80%)

^aNumber of activities created refers to the number of unique activities created (e.g., “go for a 10-min walk”). However, each activity created could be scheduled and completed > 1 time (e.g., the person could schedule the activity of “go for a 10-min walk” daily for 7 days). As a result, it is possible for the number of activities scheduled and completed to exceed the number of activities created.

among ILLIC and results in high levels of app engagement. These preliminary data demonstrate that this treatment paradigm may improve depression severity relative to proactive ID + UC in this patient population. Although we are cautious to over-interpret these results, particularly the wide confidence intervals, the finding that 45% of patients in proactive ID + DMHI experienced a clinically meaningful improvement in depression severity, which is 9-times the odds of patients in proactive ID + UC, suggests that the benefits of this intervention have the potential to be realized by a large proportion of patients with advanced and metastatic cancer suffering from depression.

4.1 | Implications (Clinical and Research)

The proactive ID + DHMI approach to treating depression among ILLIC is appealing at a population level because it addresses many of the barriers to screening for depression among cancer survivors seen with current standard of care approaches [42–45]. Although the strong recruitment, retention, and engagement data confirm the feasibility and acceptability of the proactive ID + DMHI approach for this patient population, our data also highlight opportunities to improve intervention reach in two key areas. First, the overall response rate to the proactive outreach was low, as only 25% of ILLIC with likely elevated depressive symptoms completed the screening eligibility assessment. Second, even among those who completed the assessment who likely had elevated rates of depression per EHR documentation, an additional 37.5% did not have elevated depressive symptoms upon confirmatory eligibility assessment. These data suggest that additional research is necessary to tailor

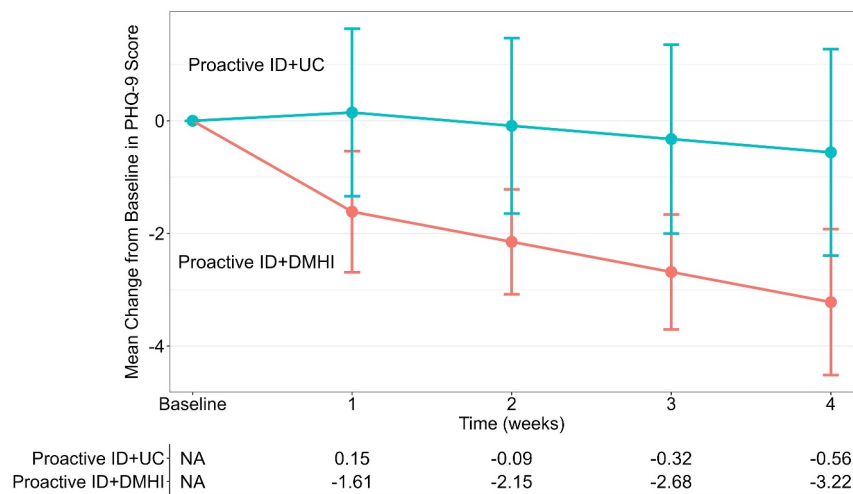


FIGURE 2 | Mean change from baseline of PHQ-9 scores for patients in proactive ID + DMHI versus proactive ID + UC. Line graph demonstrating the mean change from baseline in PHQ-9 scores over time by intervention allocation with 90% CIs. Proactive ID + DHMI arm: $n = 20$ patients at all timepoints; Proactive ID + UC arm: $n = 10$ at all timepoints except $n = 9$ at week 4.

message content and/or method of delivery to promote reach while concurrently refining methods to enhance the accuracy of identifying individuals with likely elevated depressive symptoms using structured and unstructured data within the EHR.

Our study also extends normative data about mobile device proficiency among cancer survivors, a key feasibility concern for expanding DMHI usage. Our sample was highly proficient in terms of their mobile device use, with proficiency scores similar to a community-based sample of people < 65 years from a study published in 2016 [38]. However, as overall population-level norms or cancer survivor-specific norms for the MDPQ-16 have not been established, it is unclear whether our study sample with a median age of 57.5 years is exceptionally proficient or rather merely representative in terms of mobile device proficiency in the current age. It is also unknown whether mobile device proficiency systematically differed between those who enrolled in the study and those who did not. Future studies evaluating DMHI in this patient population should characterize mobile device proficiency among participants and those who decline to understand how to maximize intervention reach.

Our study adds to the growing evidence base supporting the efficacy of DMHIs for treating depression among cancer survivors [23–26]. Prior studies evaluating DMHI for treating depression among cancer survivors have been small and single arm, establishing feasibility and acceptability. Building on these single arm data, Zion et al. conducted a decentralized RCT of 449 patients with nonmetastatic stage I–III cancer survivors, demonstrating that a cognitive behavioral stress management (CSBM) app reduced anxiety and depression severity relative to sham educational control [25]. This important study provided a solid evidence base for DMHIs among cancer survivors but was limited through its inclusion of individuals without clinically significant depressive symptoms, exclusion of those with severe depression, and reliance on social media and internet platforms for recruitment (i.e., untethered to clinical oncology care).

To our knowledge, our trial is the first to show the potential effectiveness of DMHIs for treating depression specifically in the

growing survivor population of ILLIC. In their large RCT, Zion et al. excluded individuals with stage IV and metastatic cancer because of the need for additional tailoring of their CSBM-based DMHI to meet the unique needs of this population [25]. In particular, relevant considerations for ILLIC include how longstanding treatment-related toxicity (e.g., chemotherapy induced cognitive dysfunction, cancer-related fatigue), need for ongoing cancer-directed therapy (e.g., busy daily schedules with clinical appointments), and prognostic uncertainty (e.g., fear of cancer progression) may affect the delivery and efficacy of DMHIs for depression treatment. Herein, we provide novel data demonstrating that a BA-based DMHI tailored to the unique needs of survivors living with advanced and metastatic cancer has potential as a novel treatment paradigm.

Although there is a growing interest in the ILLIC population, their long-term toxicity profile and comorbidity burden remain poorly understood [3, 6]. Despite being on cancer-directed therapy for a median of 2.5 years, our study sample had relatively good performance status (75% ECOG 0–1) and low severity of comorbidity burden (40% Charlson Comorbidity Index score = 0). However, these measures of performance status and comorbidity burden are likely not the optimal measures to characterize the relevant treatment toxicities experienced by this patient population in terms of their mental health care as they fail to capture relevant toxicities such as chemotherapy induced cognitive dysfunction and cancer-related fatigue (Charlson Comorbidity Index) or do so in a manner that is too gross to notice small differences that may be relevant to seeking mental health care (ECOG performance status). Future studies that explore the psychosocial needs for the growing ILLIC population should continue to refine measures that precisely characterize the relevant toxicity profile.

4.2 | Limitations

Consistent with its pilot nature, the study had a single-site design, small sample size and short follow-up. We are therefore cautious to over-interpret these encouraging but preliminary

findings. Further evaluation of proactive ID + DMHI in a fully powered efficacy trial featuring a sample of survivors with diverse demographic characteristics and longer-term follow-up is necessary to confirm the efficacy signal and enhance the external validity of these preliminary findings. Although we showed a potential benefit of proactive ID + DMHI relative to proactive ID + UC, we cannot elucidate the marginal benefit of this approach relative to UC without proactive identification (as patients in both arms were identified as having elevated depressive symptoms via proactive ID) nor to a control that would account for nonspecific treatment effects of receiving a mobile app (i.e., an attention control). Although self-guided DMHIs allow on-demand access to treatment, prior studies in non-cancer samples have demonstrated highly variable patient engagement [46, 47]. The relationship between levels of engagement with self-guided DMHIs and improvement in depression severity is not known and should be studied in future work. Finally, we were unable to passively and systematically collect information about the types of activities that patients create, schedule, and complete, limiting our ability to understand the relationship between activity scheduling and completion with improvement in depression severity.

5 | Conclusion

Data from this pilot RCT suggest that proactive ID + DMHI may result in a clinically meaningful improvement in depressive symptoms among ILLIC. These promising preliminary data support conducting a large effectiveness trial to establish proactive ID + DMHI as a novel, evidence-based paradigm for treating depression among ILLIC.

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Conflicts of Interest

E.M.G. reports research support and honorarium from Castle Biosciences; research support and travel from Stryker, and advisory and speaker bureau fees from Merck, all outside of the submitted work. J.D. is a co-owner of Behavioral Activation Tech LLC, a small business that develops digital interventions for behavioral health treatment. Underlying intellectual property for the Moodivate intervention is owned by the University of Maryland, College Park. Behavioral Activation Tech LLC, has agreed to an exclusive license with the University of Maryland, College Park for the commercialization of Moodivate.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information S1: pon70309-sup-0001-suppl-data.docx.