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Design and Rationale for a Randomized Controlled Trial to Reduce Readmissions among Patients with Depressive Symptoms

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Abstract

Background—The Re-Engineered Discharge (Project RED) reduces 30-day readmission rates by 30 percent. However, our data indicates that for patients displaying depressive symptoms during hospitalization, Project RED is less effective in preventing unplanned readmission. We aim to examine the effectiveness of RED-D, a modified brief Cognitive behavioral therapy (CBT) protocol delivered as a post-discharge extension of the Re-Engineered Discharge, in reducing 30-day readmissions rates and emergency department (ED) use as well as depressive symptoms for medical patients with comorbid depressive symptoms.

Methods—This paper details the study design and implementation of an ongoing, federally funded randomized controlled trial of our post-discharge mental health intervention, RED-D, compared to the RED plus usual care. This research has two primary objectives: (1) to determine whether RED-D delivered telephonically by a mental health professional immediately following discharge is effective in reducing hospital readmission and emergency department use for patients displaying depressive symptoms during their inpatient stay, and (2) to examine whether this approach yields a clinically significant reduction in depressive symptoms. We intend to recruit 1200 participants randomized to our intervention, RED-D (n=600), and to RED plus usual care (n=600).

Conclusions—Hospitalized patients with depressive symptoms are at increased risk for 30-day readmission. We aim to conduct a randomized clinical trial to evaluate the comparative effectiveness of RED-D, our post-discharge modified brief CBT intervention compared to RED alone in reducing readmissions and depressive symptoms for this at-risk population.

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Introduction

Recent efforts to streamline hospital discharge processes and bridge gaps in care transitions have improved patient safety and significantly reduced 30-day readmissions rates. Evidence from the randomized controlled trial of the Re-Engineered Discharge (Project RED), indicates that a systematic approach to the discharge process can reduce the risk of 30-day readmission for general medical patients by 30 percent [1]. Despite receiving RED, general medical patients who display comorbid depressive symptoms during an acute hospitalization remain at increased risk for readmission [2], and require care transition support that targets depressive symptoms and limits the impact of psychosocial sequelae of depressive episodes.

Depression is linked to readmission in certain patient populations including the elderly [3–4], and those with specific diagnoses (e.g. Congestive Heart Failure (CHF), Chronic Obstructive Pulmonary Disease (COPD), Myocardial Infarction (MI)) [5–12]. Functional decline associated with chronic medical illness is often accompanied by depressive symptoms, which arise in 20% to 50% of chronically ill persons [13–16]. Depressive symptoms can reduce a patients' ability to cope with physical symptoms and adhere to medical treatment, causing increased health care utilization and cost [17–23]. Project RED clinical trial data demonstrate a striking association between the presence of depressive symptoms and rates of 30-day rehospitalization [2], specifically, we found that for hospitalized patients with mild or moderate to severe depressive symptoms, the incidence rate ratio (IRR) for readmission was 1.49 (95% confidence interval [CI]: 1.11–2.00), and 1.96 (95% CI:1.51–2.49) respectively, when compared with hospitalized patients with no depressive symptoms [2]. This finding prompted the authors to hypothesize that even a small improvement in depressive symptoms may reduce a patient's risk of readmission.

Medical patients with comorbid depression often present with physical health concerns and fewer chronic mental health difficulties than patients with a primary mental health diagnosis. Although traditional psychotherapy approaches such as CBT, which aims to address the thoughts, emotions, and behaviors that contribute to and reinforce depressive symptoms, and interpersonal therapy are effective for treating depression [24], they do not typically address physical concerns of medically ill patients with comorbid depression. By contrast, interventions for chronic disease self- management do address physical and emotional concerns of patients with medical illness however [25], such models do not typically offer the level of psychological support for medically ill patients with major depressive symptom burdens. A modified mental health intervention focused on the physical and emotional health needs of medical patients with comorbid depressive symptoms is therefore required.

We aim to conduct a randomized controlled trial to examine the effect of the Re-Engineered Discharge for hospitalized patients with Depressive Symptoms (RED-D), a 12-week mental health intervention, compared to RED plus usual care on rates of 30-day readmission and emergency department (ED) visits, and on comorbid depressive symptom burden of hospitalized general medical patients. RED-D involves a modified brief CBT approach with elements of self-management education, patient navigation, and the collaborative care model, delivered telephonically by a mental health professional. Herein, we describe the design and methods protocol for our five-year study now underway.

Methods

The Re-Engineered Discharge for patients with Depression (RED-D) study was developed to examine the clinical efficacy of an evidence-based mental health intervention delivered as an extension of the Re-Engineered Discharge (RED) following discharge for general medical patients displaying depressive symptoms during an acute hospitalization. The RED-D intervention is initiated post-discharge with patient navigation support to promote adherence to the discharge plan and minimize the psychosocial and clinical sequelae resulting from depressive symptom burden, which impairs self-management capabilities. Simultaneously and subsequently, RED-D addresses the patient's need for treatment of comorbid depression that results from living with chronic progressive functional decline and illness using a modified brief CBT approach with components of self-management and mindfulness education in a collaborative care model. RED-D's collaborative care component enhances communication between the RED-D mental health professional and the patient's primary care health providers (PCP).

The study is being conducted at an urban safety-net hospital, Boston Medical Center (BMC), and includes patients admitted to the general medical service, observation unit, or surgical unit. Over a five-year period we seek to recruit a total of 1200 patients who have been admitted to BMC and display moderate to severe depressive symptoms during an acute hospitalization. Of these, 600 are randomized to the control arm, which involves the Re-Engineered Discharge process delivered by a nurse, followed by usual care. The remaining 600 patients are randomized to the intervention arm, and in addition to the RED discharge, receive the telephone-based RED-D protocol for 12 weeks following hospital discharge. Prior to the start of the study, a statistician used SAS [26] to generate a blocked randomization schedule and prepared and numbered two sets of sealed study allocation envelopes in accordance with this schedule. Once a patient is enrolled, the research assistant opens the next envelope and the patient is assigned to either the control or intervention condition. The Institutional Review Board (IRB) of Boston University School of Medicine approved the RED-D study.

Potential study participants are identified each day through unit registries of patients admitted during the previous 24 hours. Research assistants approach potentially eligible patients during the index hospitalization. Interested participants complete the Patient Health Questionnaire-9 (PHQ-9) screen for depressive symptoms [27]. If patients receive a score of 10 or higher on the PHQ-9, they are required to provide informed consent to participate in further screening to determine their eligibility. If patients meet all of the eligibility criteria, including a PHQ-9 score ≥ 10 , and are not subject to any exclusion criteria, they are enrolled in the study. Participants are excluded if they are scheduled to be discharged to another care facility, are planning to leave the greater Boston area within six months, are unable to communicate in English, are undergoing active cancer therapy or dialysis, or have cognitive, bipolar, psychotic, or active substance use disorders. At the time of submission, 356 patients have been recruited and enrolled to date.

INTERVENTION AND CONTROL CONDITIONS

Rationale for the RED-D Intervention—RED-D is a manualized, patient-centered mental health intervention which consists of patient navigation, self-management education, and a modified brief CBT protocol delivered using a collaborative care model that is initiated following hospital discharge for the treatment of comorbid depressive symptoms in hospitalized patients. RED-D is delivered telephonically for 12 weeks by a midlevel mental health professional in weekly sessions of up to one hour in duration. We designed a telephone-based protocol to increase patient engagement and adherence to the intervention. The weekly sessions comprise of patient navigation support and six modules of modified brief CBT for depression. The dose and duration of navigation and brief CBT is determined by the patient's symptom burden, navigation needs, and readiness for engagement in depression treatment consistent with traditional psychotherapy treatment. This approach ensures the maximum impact of the CBT component which, if initiated too soon following discharge, has been associated with a high drop-out rate [28]. To ensure the fidelity of the RED-D intervention, we supply the mental health professional with a comprehensive and structured 12-week protocol manual. We will randomly digitally record weekly phone sessions between the mental health specialist and the study participant for quality improvement and to ensure intervention fidelity. The study psychiatrist and family medicine physicians will review these recordings to evaluate the degree of congruence with the protocol manual. In addition, the RED-D mental health specialist will track the occurrence of each component of the intervention for each telephone contact to support the assessment of the extent to which each of the components is emphasized during each call and at what specific times during the post-discharge period these components are most useful.

(i) Patient Navigation: Depressive symptoms can impair essential self-care behaviors which jeopardize a patient's ability to implement his or her discharge plan at home. Furthermore, the sequelae of unmet self-care needs resulting from depression can persist long after depressive symptoms have subsided, making it difficult for a patient to engage effectively in depression treatment. To address this concern, the RED-D intervention begins with the mental health professional's assessment of the participant's needs for health system navigation support and the professional's provision of the required level of support to promote adherence to the discharge plan and follow up care. Patient navigation is an evidence-based intervention, which has been shown to improve health outcomes and reduce health and healthcare disparities [29]. Patient navigation refers to the assistance offered to patients in "navigating" the complex health-care system, overcoming barriers in accessing quality care and treatment (e.g., arranging financial support, coordinating among providers and setting, arranging for translation services, etc.), and coaching patients on adherence to their treatment plan and follow up care [29]. Patient navigation minimizes the potential psychosocial sequelae of depressive symptoms by assisting a patient in managing and stabilizing his/her medical condition, which constitutes a crucial foundation for beginning CBT. By undertaking this role, the mental health professional has the opportunity to establish rapport with the participant before initiating depression treatment using CBT.

(ii) Adapted Brief CBT: The six CBT modules include Orientation to CBT, The Thought-Feeling Connection, Transforming Negative Thoughts, Behavior Activation, Physical

Symptoms and Stress Management, and Relationships. Patients with medical illness and comorbid depressive symptoms have physical as well as emotional health needs, and these concerns are heightened during and immediately following an acute hospitalization. To successfully manage their hospital discharge plan and avoid unintended setbacks, patients require adequate psychosocial functioning, which can be impaired in the setting of comorbid depression. We adapted a brief version of CBT to enable patients to address depressive symptoms, which are generated or exacerbated by their medical illness experience. To support patients' development of coping skills for living with their medical illness, functional decline and troublesome physical symptoms, we integrated a CBT approach informed by principles of self-management education and mindfulness meditation practice. Self-management education and mindfulness meditation are evidence-based interventions for individuals living with chronic conditions designed to improve coping, reduce stress, increase self-efficacy in disease management, and improve long-term health outcomes [30]. Within the six CBT modules of the RED-D protocol, self-management education and mindfulness practices are integrated into homework and in-session activities, whereby participants are encouraged to problem solve to address the emotional challenges of experiencing ongoing physical symptoms and illness. To monitor the patient's response to treatment, the mental health professional regularly reassesses their depressive and anxiety symptoms and pain symptoms using the validated assessment tools the 16-item Quick Inventory of Depressive Symptomatology (QIDS) [31], and the 11-point numerical pain rating scale (Pain NRS) [32], respectively.

(iii) Collaborative Care: To integrate the RED-D intervention with the participant's primary and mental health care, we incorporated elements of the Collaborative Care Model, a validated strategy for coordinating care between care settings and providers [33–34]. In accordance with this model, the mental health provider is responsible for proactively monitoring participants' therapeutic response to depression treatment, and communicating these findings to the patient's primary and mental health care providers. This is done with a biweekly completion of the QIDS depression screen. The study team employs the evidence-based approach to depression pharmacotherapy from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial [35] to assess the patient's response to treatment, and to decide whether the patient warrants consideration for the initiation or titration of medication for depression. If for example, a participant exhibits persistently high levels of depressive symptoms and is not currently on antidepressant therapy, the mental health professional will discuss the case with the study's supervising physician and psychiatrist. If these specialists are in agreement, the mental health professional will notify the primary care provider and/or the patient's primary psychiatric provider by electronic message or letter, of the persisting depressive symptom burden, and will provide evidence-based recommendations for augmenting or adjusting therapy. Such communication has been demonstrated to support the timely response of providers to persistent or worsening symptoms of depression [36], adherence to medications and greater patient satisfaction with care [37], as well as improved concordance and a dose-response relationship between medication use and depression outcomes [33], and will improve the continuity between our intervention and the participant's primary and mental health care providers.

(iv) RED (usual care): All participants will receive RED regardless of study arm assignment. The RED is an evidence-based, 12 component hospital discharge process that has been recognized as a national best practice by the National Quality Forum. A Discharge Nurse Educator (DNE) coordinates the discharge plan with the hospital team, and educates and prepares the participant for their discharge. The DNE also schedules a follow-up appointment for the participant with the participant's primary care provider (PCP), and shares the patient's discharge summary with their PCP. Finally, RED culminates with a phone call from the DNE two days post-discharge to complete medication reconciliation and to provide guidance on managing any complications that have arisen.

Outcome measures, Sample Size and Data Analysis

1. Sample Size Calculations: Our study considers two outcomes as our primary endpoints – 30-day hospital readmission, and hospital reutilization (defined as combined 30-day hospital readmission plus ED visits). The 30-day readmission rate is measured by incident rate ratio (IRR). To calculate the IRR, we divide total hospital utilizations by total person-time. We measure person-time in months, making total person-months equal to the number of participants in each study group. We used the Poisson test and proportions test to test for significance of primary outcomes and secondary outcomes, respectively. This trial assumes 80% power and an alpha of 0.05. Our previously published data indicated a readmission rate of 19.88% for adult patients who screened positive for moderate to severe depressive symptoms and received the Re-Engineered Discharge (RED) [2]. Based on prior work, we hypothesize that RED-D will reduce the odds of rehospitalization for those with depressive symptoms at 30 days from 19.88% to 13.88% – a 30% reduction. We selected the 30- rather than 90-day time marker, because the 30-day all cause readmission rate is used in hospital benchmarking and research. Our required sample size, accounting for an estimated 20% potential dropout rate, was calculated using this hypothesized change in the odds of rehospitalization at 30 days. To achieve this reduction in rehospitalizations with 80% power, it is necessary to enroll 600 participants in each arm of the study, for a total sample size of 1200.

2. Analyses of outcomes: The primary analysis will be the intention-to-treat (ITT) two-sided comparison of outcome proportions between the two groups, conducted using a Logistic regression. We anticipate a balance of measured and unmeasured patient baseline characteristics due to randomization and the equal allocation of participants. The Bonferroni correction for multiple testing is conservative because the primary endpoints of reutilization and readmission are highly correlated, and we will therefore use the Benjamini-Hochberg approach. We will further analyze readmissions by generating cumulative hazard curves for time to multiple events (rehospitalizations) and compare them using a log-rank test. This method corresponds to the Wei, Lin, and Weissfeld marginal data model for ordered multiple events, which allows each event to have a separate underlying hazard [38]. If baseline characteristics are not balanced at baseline, we will assess whether these characteristics are potential confounders of the relationship between the intervention and the reutilization and readmission outcomes. We will determine whether the primary ITT analysis presented should be adjusted for confounding variables. In addition, we will evaluate patient characteristics as potential interaction terms in the logistic regressions for

both outcomes. Analogous methods will be applied to test our second objective, whether RED-D can produce a clinically meaningful improvement in depressive symptoms, as measured using the PHQ-9 and Generalized Anxiety Disorder 7-item scale (GAD-7) [39] at 30, 90, and 180 days following discharge, measured in comparison to patients receiving the RED discharge alone (usual care). Specifically, we will assess the mean change in PHQ-9 scores from baseline to follow up at 30 days, 90 days and 180 days among participants in each study arm. We will use 2-sided significance tests and consider an overall alpha of 0.05. All data will be analyzed using SAS [26].

To determine the fidelity of our intervention and success in recruitment and randomization, we intend to track and analyze a number of process measures (see Table 1). These include: percent of eligible participants actually enrolled, drop-out before completion of the study, comparison of baseline characteristics by study arm. We will determine success in delivering the RED to all enrolled participants including: percent receiving RED discharge education from RED nurse, percent attending PCP visit within two weeks of discharge, percent contacted for post-discharge phone call, and percent of participants with completed discharge summaries sent to their PCP within 24 hours of discharge. To determine fidelity of the RED-D intervention and adherence to the protocol, we identified a number of process measures including total post-discharge RED-D sessions attended telephonically, total time spent by RED-D mental health specialist in patient navigation vs CBT activities per week, and total time spent on weekly calls.

Our final analysis will involve a cost-benefit analysis to investigate whether the RED-D intervention is more cost saving than the RED intervention alone. In estimating cost savings associated with the RED and RED-D interventions, we are aware that the principal source of savings will likely result from a reduction in rehospitalizations during the 180 days following discharge. We will obtain the total costs associated with these inpatient admissions from administrative records for most inpatient events, and from insurance companies for non-BMC events. Since patterns of outpatient care may differ systematically with the type of intervention - in particular, with differential usage of pharmacotherapy and mental health specialists - we will also obtain this information from hospital administrative records, patient reports and insurance companies. Additional costs of the two treatment arms will be estimated through calculations of the cost of staff time and other resources used. Cost-savings will be estimated using t-test comparisons of the mean costs for the groups; given the randomization of patient assignment, these should provide unbiased estimates.

Discussion

Despite receiving a streamlined discharge process, general medical patients who display comorbid depressive symptoms during an acute hospitalization remain at an increased risk for readmission [2]. Herein, we propose to conduct a randomized controlled trial of our unique behavioral health intervention, Project RED-Depression (RED-D). RED-D is a blend of patient navigation support and brief, modified cognitive behavioral therapy for depression initiated immediately following hospital discharge. This intervention addresses a gap in care for comorbid depressive symptoms among individuals admitted to general medical services who are at increased risk for readmission.

Our innovative mental health approach supports patients in self-managing their discharge plan during the often challenging transition from hospital to home, and simultaneously addresses ongoing psychosocial and clinical concerns related to chronic medical illness and functional decline. By using a telephone-based intervention, we hope to demonstrate the feasibility of improving access to mental healthcare and the possibility of greater treatment adherence compared with in-person CBT protocols, as demonstrated by other CBT research. Alternative access to mental healthcare may be important to individuals at increased risk of readmission such as those with advanced chronic disease, poor functional status, or those who are debilitated following an acute hospitalization. One possible obstacle to a telephone-based delivery of the RED-D intervention is the potential reluctance of participants who use cellular phones to dedicate paid cellular minutes to time spent in treatment with the RED-D mental health specialist. To minimize loss-to-follow-up or refusals to participate in the study for this reason, we are screening potential participants during the enrollment process to identify individuals who anticipate a problem using cell phone minutes for study purposes due to limited-use cell phone plans. In such cases, we will offer use of a study cell phone which will be programmed to accept only incoming study-related calls. To date, this option has not been needed.

Another potential concern for the RED-D study is that individuals who screen positive for depressive symptoms (PHQ-9 score ≥ 10) will no longer display significant depressive symptom burden following hospital discharge, that is, these participants will not fulfill criteria for clinical depression. Indeed, there is little data on the natural history of depressive symptomatology from acute hospitalization to the immediate post-discharge period particularly among individuals who may not have a prior history of depression. Nonetheless, our prior work shows that hospitalized individuals who exhibit a significant burden of depressive symptoms during admission have nearly twice the rate of readmissions compared with those who score in the non-depressive range (PHQ-9 score < 5) [40]. Based on this data, we hypothesize that individuals with high burdens of depressive symptoms during acute hospitalization will experience poor psychosocial and physical functioning leading to an increased risk of readmission due to challenges implementing discharge care plans. For this reason, in addition to CBT to address depressive symptoms, we have included a component of patient navigation in our RED-D protocol to support adherence to discharge plans. Furthermore, we emphasize that the primary objective of our study is the avoidance of readmission for this target population and therefore, we will examine the impact of our RED-D intervention on depressive symptom burden as a secondary outcome.

To examine the natural history of depressive symptom burden during the care transition, we are measuring depressive symptoms using the same validated depression screening tool, the PHQ-9, which we used in our original Project RED clinical trial. The PHQ-9 demonstrates high sensitivity and specificity for detecting clinical depression. In addition, we are using a clinical interview by our study team mental health specialists to confirm the presence of clinical criteria for major depression. This protocol allows us to examine the proportion of enrolled participants who meet clinical criteria for depression as well as the percentage of participants who experience persistent depressive symptoms at 30-days post-discharge. Finally, for participants randomized to the intervention arm, we will conduct biweekly assessments of depressive symptoms using the QIDS instrument validated in the STAR*D

11 clinical trial. We expect that this comprehensive data on depressive symptom status will allow us to examine the impact of RED-D on depression itself compared with usual care.

Despite these potential challenges, Project Re-Engineered Discharge for Depression, RED-D, will be among the first interventions designed to target comorbid depressive symptoms in the post-hospital discharge setting. Positive findings would garner support for the expansion of mental healthcare access for individuals with positive depression screens during acute hospitalization and enable advocacy for the universal screening of patients admitted to acute care facilities. With a growing emphasis on the integration of behavioral health with medical care services, particularly primary care, our RED-D protocol could represent a logical extension of a comprehensive primary care model such as the Patient-centered Medical Home. In particular, RED-D could prove to be an effective solution for the significant barriers to mental healthcare access for marginalized and underserved populations such as those living in rural communities or living with disabilities. Further studies of the feasibility, implementation and dissemination opportunities for a protocol such as RED-D will be needed to confirm the sustainability of this program in diverse clinical settings.

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Figure 1.
An overview of the RED-D Intervention

Table 1

Study Outcomes and Outcome Measures

Outcome	Outcome Measures
Clinical Efficacy	<p>To determine whether the RED-D intervention is more effective than RED (i.e. usual care) in reducing all-cause 30 day hospital reutilization or readmission:</p> <p>a) We examine BMC's administrative database (SDK), and contact the patient's insurance company in case the patient is readmitted or uses the ED elsewhere.</p>
Patient Efficacy	<p>To assess whether RED-D produces a clinically meaningful improvement in depressive symptoms, we use:</p> <p>a) Patient Health Questionnaire-9 Depression score (PHQ-9)</p>
RED-D Fidelity	<p>To evaluate the mental health specialist's execution of the protocol we monitor:</p> <p>a) total post-discharge RED-D sessions attended telephonically,</p> <p>b) total time spent by RED-D mental health specialist in patient navigation vs CBT activities per week,</p> <p>c) total time spent on weekly calls.</p>
RED-D Success in Recruitment and Randomization	<p>a) percent of eligible participants actually enrolled,</p> <p>b) drop-out before completion of study,</p> <p>c) comparison of baseline characteristics by study arm.</p>
RED Success	<p>a) percent receiving RED discharge education from RED nurse,</p> <p>b) percent attending PCP visit within two weeks of discharge,</p> <p>c) percent contacted for post-discharge phone call,</p> <p>d) percent of participants with completed discharge summaries sent to their PCP within 24 hours of discharge.</p>
RED-D Cost-Benefit	<p>a) total costs associated with inpatient admissions from administrative records for most inpatient events, and from insurance companies for non-BMC events.</p> <p>b) Additional costs of the two treatment arms will be estimated through calculations of the cost of staff time and other resources used.</p>