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Caring letters for suicide prevention: Implementation of a multi-site randomized clinical trial in the U.S. military and veteran affairs healthcare systems

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ABSTRACT

Caring letters is a suicide prevention intervention that entails the sending of brief messages that espouse caring concern to patients following discharge from treatment. First tested more than four decades ago, this intervention is one of the only interventions shown in a randomized controlled trial to reduce suicide mortality rates. Due to elevated suicide risk among patients following psychiatric hospitalization and the steady increase in suicide rates among the U.S. military personnel, it is imperative to test interventions that may help prevent suicide among high-risk military personnel and veterans. This paper describes the design, methods, study protocol, and regulatory implementation processes for a multi-site randomized controlled trial that aims to evaluate the effectiveness of a caring emails intervention for suicide prevention in the military and VA healthcare systems. The primary outcome is suicide mortality rates to be determined 24 months post-discharge from index hospital stay. Healthcare re-utilization rates will also be evaluated and comprehensive data will be collected regarding suicide risk factors. Recommendations for navigating the military and VA research regulatory processes and implementing a multi-site clinical trial at military and VA hospitals are discussed.

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1. Introduction

The risk for suicide and repeat suicide attempts is elevated among post-hospitalized psychiatric patients. Luxton, Trofimovich and Clark [1] reported the suicide rate among the U.S. active-duty service members between the years 2001 and 2011 with histories of psychiatric hospitalization to be five times the average for the entire US military active-duty population. Valenstein et al. [2] examined suicide rates among 887,859 U.S. military veterans who were in treatment for depression at the Department of Veterans Affairs (VA) hospitals between 1999 and 2004 and found the suicide rate within 12 weeks after a psychiatric hospital discharge to be approximately five times that of the overall treatment population and 54 times the rate for the general U.S. population during the same period. Studies of civilian populations report even higher rates of suicide following psychiatric hospitalization compared to controls [3,4], and

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consistent with the aforementioned studies, the highest risk is generally reported within the first few weeks following hospital discharge [5]. These data highlight the need for targeted treatments and interventions for suicidality after psychiatric inpatient stays.

The caring letters concept is a suicide prevention intervention that specifically addresses suicide risk during the post-hospitalization period. The intervention involves the routine sending of brief messages of caring concern to patients who are discharged from inpatient psychiatric treatment [5,6]. The caring letters concept was first tested in a study led by psychiatrist Jerome Motto approximately four decades ago [6,7]. In Motto's trial, civilian psychiatric inpatients were sent brief caring postal letters following treatment discharge (initially monthly, decreasing to quarterly) for five years. Compared to a control group with no further contact, the "caring letters" group had a significantly lower suicide rate for the first two years of the trial. Motto's caring letters [6,7] and a contact study by the World Health Organization (WHO; [8]) that involved a series of personalized phone or in-person contacts are the only studies that have reported reduced suicide mortality rates in randomized controlled trials [9,10]. Several other caring contact interventions that have tested various contact methods (e.g., post-cards, telephone, texting, or a combination of contact modalities) have been shown to prevent suicidal behaviors [5]. However, there have not been any replications of the original Motto caring letters intervention or studies with large enough sample sizes to include suicide mortality rates as an outcome.

Given the potential for caring contacts to be an effective suicide intervention for post-hospitalized service members and veterans, we launched a five year randomized controlled trial (RCT) that is based on Motto's original study but updates the contact modality with emailed letters rather than postal letters. This paper describes the design, methods, and protocol for this on-going Military Operational Medicine Research Program (MOMRP) grant funded multi-site trial. We also describe the military specific research regulatory process and provide recommendations for implementing multi-site clinical trials in the Department of Defense (DoD) and VA.

2. Research design and methods

2.1. Study design

This study is a RCT that tests the effectiveness of the caring contacts intervention to prevent suicide and suicidal behavior among U.S. service members and veterans. The trial is registered on the United States National Institutes of Health Clinical Trials Registry, (ClinicalTrials.gov Identifier # NCT01473771) available online at: http://clinicaltrials.gov/show/NCT01473771. The study sites include Madigan Army Medical Center (MAMC), Tripler Army Medical Center (TAMC), Landstuhl Regional Medical Center (LRMC), Navy Medical Center San Diego (NMCSD), VA Palo Alto, and VA Western New York. These study sites were selected because they represent diverse military populations (the military sites serve Army, Navy, Air Force and Marine Corps) and because there were no other competing clinical trials recruiting at the inpatient psychiatry units at these sites. The overall study design is shown in Fig. 1. The Consolidated Standards of Reporting Trials (CONSORT) statement guidelines are being followed. The study is being conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Methodology for the RCT was first tested in a pilot study conducted by Luxton et al. [11] at the National Center for Telehealth & Technology (T2) and MAMC. The purpose of the caring letters pilot program was to evaluate the feasibility of the caring letters concept within a military treatment facility setting including the feasibility of using email for contacts and to test the protocol procedures. The pilot study also tested the procedures of having a research team member embedded on the inpatient treatment unit and it provided an opportunity to develop and test safety protocol procedures (see Section 2.5 for a full discussion of the safety procedures). The results of the pilot study indicated that email was the preferred method of follow-up contact (participants were given a choice between email and postal letters). Data regarding patient replies to caring emails were also examined to assess what may be expected in a full trial of the intervention. Approximately 20% of the pilot study participants replied to emails and all replies consisted of positive statements regarding the caring messages. By the end of the pilot study, there were a total of three participant replies that indicated that the participant was (or may become) in crisis (e.g., increase in depressive symptoms and return of suicide-related thoughts). These were all resolved by notifying the treatment team who followed up the patients to assure that they were reconnected to care services. Although the pilot study did not include a usual care comparison group nor was it powered to test a suicide preventative influence of the contacts, the results supported the feasibility of the caring

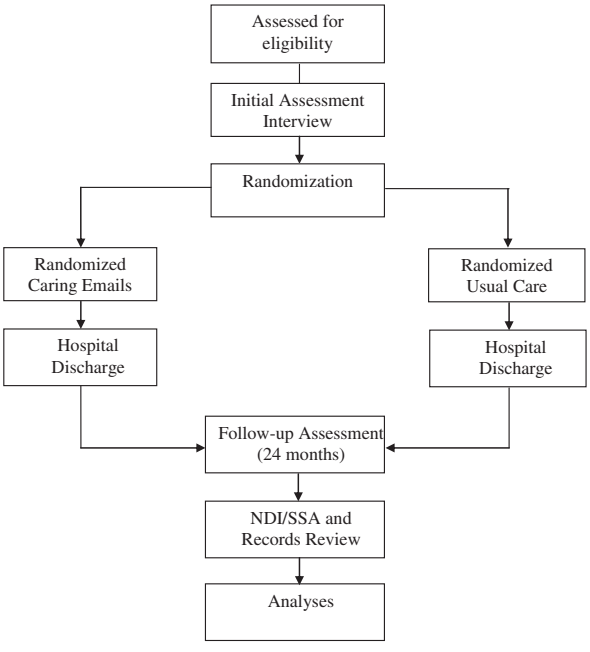

Fig. 1. Study conceptual design.

email procedures and provided initial data that informed expansion to the current RCT.

In the RCT, eligible participants are randomized to either of two groups: a caring letters intervention group or a no-contact usual care group. The research hypotheses for the trial are as follows: 1) During the two year follow-up after the index hospital discharge, the frequency of suicide will be significantly lower in the intervention group compared to those in the usual care group, 2) The frequency of medically admitted self-inflicted injuries will be lower in the intervention group compared to the usual care group, and 3) The time to suicidal behavior, if any, will be longer among participants in the intervention group compared to those in the usual care group. Data is also collected regarding psychosocial and other suicide risk variables in order to examine potential moderators of treatment effect (see Section 2.3). No a priori stratification based on patient participant characteristics was planned. We will, however, examine subgroups after two years including comparison of groups that may have continued in care following hospitalization and those that did not, as well as differences between men and women in outcomes.

2.2. Caring letters condition

Participants randomized to the caring letters group are sent a total of 13 emails based on a pre-determined schedule that begins when the participant is discharged from the in-patient psychiatry unit. The schedule of email contacts replicates the first two years of the original Motto trial (monthly for four months, then every two months for eight months, and then every three months), however we elected to send one additional email during the first week after hospital discharge when suicide risk is the highest. The emails are prepared and sent by the research coordinator at each site who met with and interviewed the patient during their hospital stay. An example caring email is shown below.

Dear [patient's name],

We appreciated the opportunity to get to know you while you were at the hospital. We hope things are going well for you.

We remember how you said that you enjoy hiking around the South Puget Sound. With the return of the summer weather, we hope you're getting a chance to get out there and explore some new trails. Anyway, we just wanted to send a quick e-mail to let you know we are thinking about you and wishing you well.

If you wish to drop us a note, we would be glad to hear from you.

Sincerely, Cassidy and Laura

Please note that the following resources are always available to you:

Military OneSource: www.militaryonesource.com *1-800-833-6622 Many helpful resources for active duty and families.*

Suicide Prevention Lifeline: www.suicidepreventionlifeline.org *1-800-273-TALK (8255) A crisis line for anyone (Press 1 for Military).*

The Defense Centers of Excellence (DCoE) Outreach Center: 1-866-9660-1020 or www.dcoe.health.mil/24-7help.aspx

DoD/VA Suicide Outreach: www.suicideoutreach.org

Please know that I make every attempt to respond to my emails each business day. If for some reason you need immediate assistance, please reach out to the resources listed above.

Also, you should refrain from replying with any sensitive personally identifiable material or confidential information to include medical information over the internet. If you choose to send such information via email, you do so at your own risk.

If you will be changing your contact information (email address, phone number, postal address), feel free to let us know so that we can stay in contact with you.

The emails are sent to email addresses that participants provide and the addresses may be to personal email accounts or to military email accounts (all military personnel have an email account). While regular access to email is expected among military personnel, we expect greater variance of email access in the veteran population (i.e., this may be a particular issue for homeless veterans). If a participant states that they do not have email access, they are not eligible for enrollment into the study. To date, only a very small percentage of screened patients were not eligible for the study due to lack of email access. There is not a way to be certain whether a participant received or read an email; however, we are collecting data regarding "undeliverable" email system replies and via self-report during a final follow-up survey (see Section 2.3). At enrollment, all participants are asked if they wish to provide an alternate email account in case a primary account returns email as "undeliverable". We also include a statement in each outgoing caring email that lets participants know that updated contact information is welcome (Table 2).

Table 1
Inclusion and exclusion criteria for participant enrollment.

Inclusion criteria
(a) Current psychiatric inpatients
(b) Possess an active email account
(c) Informed consent
(d) Active duty military, veteran, retiree, national guard or reserve status
Exclusion criteria
(a) Not competent to consent
(b) Adverse behavioral problems (e.g. aggressive/hostile behavior on the unit to be safely approached by research coordinator)
(c) The primary psychiatric nurse or attending psychiatrist considers the study to be clinically inappropriate (e.g. due to paranoia about mail/email)
(d) Currently under arrest/incarceration. A person in any form of detention will immediately be withdrawn from the study and no data will be used during the period of detention/incarceration
(e) Involuntary committed for psychiatric care status (72 h hold) unless released by provider or changed to voluntary status

Table 2
Schedule of measures and survey instruments.

Assessment measure	Baseline	Post intervention
Demographics	X	
Background	X	
Education &Work History	X	
Medical & Psychiatric History	X	
Suicide Attempt Self-Injury Count (SASI-C)	X	
Depression and Anxiety Ratings	X	
Patient Experience Survey	X	
Patient Health Questionnaire (PHQ-9)	X	X
Rudd Suicide Ideation Scale (RSIS)	X	X
Interpersonal Needs Questionnaire (INQ)	X	X
Acquired Capability for Suicide Scale (ACSS)	X	X
Positive Assets Search Semi-Structured Interview Tool (PASSIT)	X	
Soldier's Perception of Unit Cohesion Scale	X	
Patient Satisfaction Questionnaire	X	
Final Satisfaction Survey	X	

As shown in the example caring email, the emails also include contact information for help and crisis resources. Although this type of information was not included in the original Motto caring letters study, the rationale was to include them as a reminder of the available help resources that could be kept for retrieval if the patient ever wished to use the information. An auto reply email is also sent with this information to any patient who replies to a caring email account.

2.3. Usual care condition

Patients randomized to the treatment as usual group provide consent to participate but they do not receive the caring emails. Both groups will receive follow-up contact two years after index hospital discharge in the form of a survey. We limited the contact period to two years because it was in the first two years of the original caring letters study [7] that a significant effect was found. There is no additional contact made with participants in either group (i.e., for trial retention) beyond the caring contacts and two-year follow-up contact.

2.4. Recruitment methods

The target sample size is 4730 participants (2365 per study group). Each inpatient unit staff identifies potential participants based on study inclusion and exclusion criteria (see Table 1) and then gives the embedded research coordinator approval to approach potential participants. The research coordinator then schedules a time to meet with eligible patients to assess their interest in participating in the study. Informed consent is obtained and then the research coordinator completes a semi-structured psychosocial interview with each participant in a private area on each treatment unit. After the interview, the site research coordinator emails the study project manager to request a blind randomization assignment to either the contact or no-contact condition. The randomized assignment is emailed from the main coordinating site to the site research coordinator and documented.

2.5. Measures and outcomes data

Study data are collected during three phases: during the initial interview, during the two-year intervention period, and two years after the index hospitalization (see Table 1.). During the initial interview, data regarding participant demographics, psychosocial background/functioning, as well as scores on several clinical measures are collected. Participants are administered the *Positive Assets Search Semi-Structured Interview Tool* (PASSIT; Luxton, Armstrong, & June, unpublished) which is a semi-structured interview tool consisting of 27 questions with additional open-ended follow-up questions. Participants are asked to respond to questions about positive activities in their life. The content domains include social support/activities, school and work, religion/spirituality, recreation/leisure activities, and personal attributes with sub-domains that include coping skills, giving/benevolence, past successes, and hope. The PASSIT is intended to be used as a tool to help patients identify positive aspects of their life and to provide personalized information to aid the research team in creating personalized content for the caring emails. Participants are administered the *Patient Health Questionnaire* (PHQ-9; [31]) to assess depression symptoms as well as the Lifetime Parasuicide Count (LPC; [30]) to obtain information about history of suicidal behavior. Participants are also administered the *Interpersonal Needs Questionnaire* (INQ; [12]) and the *Acquired Capability for Suicide Scale* (ACSS; [13]) as well as the *Soldier's Perceptions of Unit Cohesion Scale* [15] in order to examine how thwarted belongingness, perceived burdensomeness, capability for lethal self-injury, and perceived unit cohesion and stigma (military participants only) may influence outcomes. Following the initial interview, participants complete a brief survey that assesses self-reported feelings of connection with the research coordinator who interviewed them. Participants place this survey into a sealed envelope to be sent to the main coordinating site.

During the two-year follow-up period, data are collected on the number of email replies, content of any replies, and frequency of undeliverable emails. We also track the number of email replies that resulted in activation of our safety protocol (see Section 2.5). At the end of the two-year intervention period, suicide and all-cause mortality rates will be assessed. Suicide counts will be based on death certificates recorded in the Centers for Disease Control and Prevention (CDC) National Death Index Plus (NDI-Plus). We will first use the Social Security Administration Death Master File (DMF) to identify deaths and then submit records to the NDI-Plus to ascertain mortality cause. The International Statistical Classification of Diseases and Related Health Problems (ICD-10) will be used to identify suicides from the NDI-Plus data. In addition, the number of suicide attempts, time to suicidal behavior, and mental health treatment utilization rates will be compared across conditions. This data will be obtained from patient medical records as well as a final survey. We will use the definitions for suicide ("death caused by self-directed injurious behavior with intent to die as a result of the behavior") and suicide attempt ("non-fatal self-directed injurious behavior with any intent to die as a result") as adopted by the CDC [14]. A suicide attempt may or may not have resulted in injury.

After the two-year intervention period, participants in both conditions are asked to complete a final survey. In order to allow for the maximum response rate, the research team will call all participants, state that we are conducting a follow-up, and ask them to participate in a follow-up survey interview. If we are unable to reach participants by phone or email, the research team will mail a cover letter and a paper version of the final survey and include a postage paid return envelope. The US Postal Service's "Return Service Requested" will be used to identify forwarding addresses. The interview/survey includes the PHQ-9, RSIS, INQ, and the ACSS. Participants will also be asked to report treatment utilization (e.g., re-hospitalizations) during the last two years. Medical records of participants receiving care in the DoD or VA will also be reviewed by study staff at each site to assess the accuracy of the self-reported data regarding treatment utilization within the two-year period since the index hospitalization. Participants (caring emails condition only) will also be asked to provide feedback regarding whether they think this program should be provided to other military personnel and veterans. A unique identifier code is used on the paper survey instead of personal identifiers to assure participant privacy. Similar strategies for maximizing response during follow-up are used in the Millennium Cohort Study [19].

2.6. Statistical methods

In Motto's study, the two-year cumulative mortality for suicide was approximately 4%. Given the difference in study populations, we used a 2% estimate of suicide mortality to estimate a sample size that will provide sufficient statistical power to determine whether the caring letters intervention is associated with reduced suicide mortality rates. With a two-tailed $\alpha = 0.05$ and power $= 0.80$, and a small amount of variation in treatment assignment explained by any included covariates (by dint of randomization), and a hypothesized odds ratio of 0.50, the total target sample size is 4730 participants. We also consider all-cause mortality to be an appropriate outcome for this study given the practical constraints of recruiting a large sample in a defined, finite population, competing risks [20] and the potential for underestimating suicide rates due to the misclassification of deaths by suicide [21,22]. Under the same assumptions as the suicide-specific mortality sample size calculation, with the exception of an estimate of 4% for cumulative all-cause mortality (compared to the approximately 8% observed in Motto's study), the total sample size would be 2300 subjects. With this sample size, we would have adequate power to detect minimum hazard ratios of 0.56 for time-to-event analyses of mortality and 0.85 for time-to-event analysis of rehospitalization, assuming a 50% incidence of rehospitalization in the population.

Prior to the main analyses, we will conduct univariate and bivariate descriptive statistics to examine distributions of key variables. Baseline differences across groups will also be examined to assure that randomization yielded no imbalances between groups. Additional preliminary analyses will examine differences in participants between the six selected study sites and the intraclass correlation of study outcomes as a function of study site. The main hypotheses of this study focus on two aspects of suicidal behavior: (1) the cumulative incidence and (2) the incidence density. For the hypotheses associated with the incidence of suicide and rehospitalization (Hypotheses 1 and 2) we will use a generalized linear model with a Binomial distribution and a log link to estimate the risk ratio as a function of treatment group assignment. To examine multiple hospitalizations, we will use the count of events for each individual as the outcome and modify the generalized linear model to incorporate an appropriate error distribution for the analysis. Given the possibility of low counts and a preponderance of zeroes, we will evaluate the appropriateness of Poisson and Negative Binomial distributions and their zero-inflated analogs in estimating a rate ratio to compare the treatment groups. To examine incidence density (Hypothesis 3), we will use time-to-event modeling to compare the treatment groups. Provided that the model assumptions are met, we will use a Cox proportional hazards model to examine time to suicide, time to first rehospitalization, and time to either type of event. In these models, participants who die from other causes or who drop out of the study will be censored at the date of death or study exit to account for different contributions of person-time for each individual. These models will yield hazard ratios to compare the two treatment groups. An alternative modeling option would be a Poisson regression model with the natural logarithmic transformation of accumulated person-time included as an offset given the anticipation of a low frequency of events occurring in the observation period [16]. A secondary analytic option for time-to-event analysis will include discrete time models which will examine the event rates over defined intervals. These models will be particularly advantageous to describe specific time periods of increased risk and will be informed based on the continuous hazard function that will be developed in examining the continuous time-to-event models. For the discrete time analysis, we will use a Poisson regression with the cumulative person-time included as an offset variable. All models will include a clustered robust variance estimator to account for study participant nonindependence and any covariates identified as imbalanced or as strong independent determinants of the outcome. Missing data as a function of loss to follow-up or unavailability of data within medical records will be evaluated for type of missingness. Assuming that missing at random assumptions are reasonable, we will implement full information maximum likelihood estimation methods. If the data are determined to be missing not at random, we will use methods such as selection modeling to estimate the missing data mechanism and incorporate this into any final analysis [17]. We will use 95% confidence intervals to evaluate both precision and statistical significance of the derived point estimates.

Secondary analyses include examination of the associations between incidence of suicidal behavior and treatment seeking with unit cohesiveness (active-duty participants only), and perceived connection with the caring letters research coordinators. The association between the constructs of thwarted belongingness, perceived burdensomeness, capability for lethal self-injury, and suicidal behavior will also be examined. We will use latent variable modeling methods to examine the measurement models of the aforementioned constructs and the structural relationships between constructs.

2.7. Safety protocol

A safety protocol was developed for this study that specifies procedures for responding to email replies from participants

that contain disclosure of threat to harm self or others, or indicate the participant is in crisis. The safety protocol calls for immediate notification of the inpatient treatment team or the Suicide Prevention Coordinator (at the VA sites) when such a reply is received so that they may contact the participant and assist with additional care or initiating a welfare check. In the Caring Letters Project pilot study, there were just three occasions when a participant replied to an email with information that indicated that the participant was potentially in or may become in a crisis state. The inclusion of links to additional support resources can also be included. It is also important to not reinforce excessive responses and interchanges that are not consistent with the intervention intent. Excessive responses were not a problem in the caring letters pilot study and we have not experienced any issues associated with this during the trial.

An additional risk that was considered when designing the trial is the potential for some participants to perceive the ending of the caring contacts as abandonment or loss of a relationship [18]. Thus, as in Motto's trial, the letter frequency decreases over time which, through titration of the intervention, may reduce any sense of loss that may be experienced by the patient. The 12th letter includes the paragraph, "Just to let you know, we will send out one last note after this one. Please know that it has been a pleasure for us to reach out to you and we hope you are out in the world doing well for yourself." The 13th letter includes the paragraph:

> "*This is officially our last email to you and we hope that you have enjoyed getting our little notes over this time. As we said in our last email, it has been a true joy for us to drop you a few lines here and there to let you know that we truly care about you and hope you are doing well. If you wish to write us and let us know how you have been doing over the years, we would be glad to hear from you*."

The study consent process also discloses the two year length of the intervention so that it is known to the participants that the contacts will cease.

2.8. Email and data management

A centralized email system is used to provide email accounts for each site to send the caring emails. The two VA sites have their own account systems (.va.gov). All sites have an email address that references the location (e.g. MAMC.ContinuingCare@). The centralized email system allows the project manager at the lead investigative site to monitor for any potential crisis emails while a site research coordinator is out of the office. Incoming emails are monitored during business hours only. This is disclosed to participants during the informed consent process and all outgoing emails provide a reminder that the emails are not monitored 24/7.

Data management for this multi-site trial is conducted by each of the individual sites and by the main coordinating site (T2). Research staff at the main coordinating site are responsible for generating and providing all study materials (folders, surveys, etc.) to each individual site and each site is responsible for storing the paper copies of study materials (informed consent forms and interview/survey data). Materials are stored in locked, limited access storage at each site. Data collected on the paper forms are entered into a secure database at each site. The research coordinators input all data collected during the initial interview, patient satisfaction survey and final survey into the database. The research coordinators then enter data into the database and send an encrypted copy of the local database to the lead investigative site monthly for inclusion into a master database. Each site also maintains an excel database that includes a master subject log, weekly log for tracking of sent emails and documentation of recruitment efforts.

2.9. Research staff training

A standardized training procedure was developed and is documented in a study procedure manual. The training involves the combination of self-study, observation of mock interviews and practice interviews. The research coordinator from each site has a current CITI Training Certificate or other accepted human research subjects training, HIPAA training, and is approved on the study protocol through the Institutional Review Board (IRB).

Prior to meeting with study participants, research coordinators receive training regarding informed consent procedures, structured interviewing, research conduct and ethics, safety, and crisis response. The research coordinator observes mock interviews and practices interview procedures with the Principal Investigator (PI), the site Principal Investigator (Site PI) or a previously trained research coordinator. Additional readings regarding psychological interviewing (i.e., [23]), research methods (i.e., [24]), and caring contacts theory and methods (i.e., [5,11]) are also required. Each inpatient psychiatry unit also has specific safety rules and procedures to follow in order to maintain a safe environment for the participants and employees. Site specific safety training is provided during initial training.

After successful completion of all required training components, the research coordinators are then approved to begin enrolling and interviewing participants at their respective sites. To help assure fidelity of consenting and data collection procedures, the research coordinators are asked to send a de-identified copy of source documents following enrollment of their first participant for a quality assurance review by the lead site project manager. Any queries are reviewed with the site research coordinator and corrections are made.

3. Research regulatory process

The regulatory process for a federally funded research protocol at multiple Military Treatment Facilities (MTF) and VA healthcare systems is complex. The first step in the process was to submit the protocol and all documents for the lead investigative site for local IRB review and approval. Approval documents were then sent to Human Research Protection Office (HRPO) and a Cooperative Research and Development Agreement (CRADA) was sent to the Clinical Investigation Regulatory Office (CIRO) for review. Final approval documents were released to the lead site and enrollment began at the lead site. Once full approval was received for the lead investigative site, the remaining sites were able to begin the submission process. An IRB deferral process was requested for the remaining three military sites

(LRMC, TAMC, and NMCSD). The deferral process involved the execution of an Institutional Agreement for IRB Review (IAIR), which allows for an institution with a Federal Wide Assurance (FWA) to rely on the IRB of another institution. This agreement had to be signed by the Institutional Officer (IO) at MAMC and each respective DoD site. The deferral process took an average of 4–6 weeks. Once the IAIR was executed at both sites, the protocol was reviewed on an administrative level at the respective sites. If there were any site specific requirements, those were addressed. The IRB approval process took approximately 10 months to obtain full IRB and HRPO approval. The two VA sites were required to submit the protocol to their local Research & Development Offices (VA R&D) for scientific merit review and use their local VA IRBs. Approval documents were provided to HRPO for review and approval prior to commencing enrollment into the trial.

The four MTFs and VAWNYHS all use IRBnet for submission and maintenance of all regulatory documents. This web-based platform allows sites to upload IRB documents, obtain electronic signatures of investigators, and submit documents to the IRB. The IRB also uploads all approval documents to this same system. HRPO has oversight and is able to review all documents in each protocol package. The system also sends automated email notifications and reminders for actions such as digital signatures, amendment submissions, and continuing review dates for each project.

The protocol was determined to be a minimal risk human use protocol, thus a Data Safety Monitoring Board was not required by the grant sponsor or the IRBs. All participating sites are required to provide notification of serious or unexpected adverse events and unanticipated problems involving risks to participants or others within 24 h to all respective IRBs.

4. Discussion

At the time of this writing, all six sites are in the recruitment phase with more than 900 participants enrolled across all sites. Recruitment is scheduled to end in 2016. The time to full approval and recruitment start was 22 months, which was much longer than anticipated. There were many complexities involved due to multiple IRBs and organizations (Army, Navy, and VA) that all have unique requirements and procedures. For example, to our knowledge, this is the first trial in the DoD that involved a Navy IRB deferral to an Army IRB. We recommend coordinating with the regulatory offices (HRPO) and initiating the deferral process as soon as possible. It was also helpful to have a hospital staff member in the role of PI at each site to facilitate both the IRB and implementation processes at each location. We also recommend the use of IRBnet or a similar system because this greatly improves the efficiency of coordination, tracking, and submission of IRB documents. Also, while the initial approvals of each site occurred on different dates, we synchronized the continuing review so that all four sites would complete continuing review on the same date annually. This makes the continuing review process more streamlined and time efficient. It was also helpful to have a point of contact at HRPO who could address questions regarding review process and status.

In addition to determining the effectiveness of the caring contacts intervention at reducing suicide mortality and rehospitalization rates, the trial will also provide useful data regarding the underlying theoretical mechanisms for how caring contacts may work to prevent suicide and suicidal behavior. Luxton, June and Comtois [5] discuss three basic mechanisms for how caring contacts may have a preventative influence. First, the caring contacts may facilitate a sense of social connection and belongingness that has a suicide preventative effect. This is consistent with Motto's [6] emphasis on the importance of human social connection in suicide prevention. As with Motto's study, the letters are written to communicate that the staff remembers the patient and that they continue to maintain positive feelings towards them. Unconditional expression of concern about a person's well-being may reduce feelings of isolation and helplessness and increase feelings of belongingness and acceptance that help to mitigate suicidal behavior.

Second, the caring emails may serve as reminders of treatment availability that can help patients to seek assistance when in crisis. This is already evident in our RCT; we occasionally receive email responses from participants that indicate possible current or future crisis state (i.e., indicating worsening of depression symptoms or other risk behaviors such as alcohol use). In all cases, the research coordinators followed the safety protocol and the participants were contacted by treatment staff for follow-up. In each case, the participant did not explicitly indicate suicidal thoughts or intent, but did express worsening depressed mood. Participant crisis replies have been seldom in the trial, but nonetheless underscore how the intervention can provide an additional layer of support following hospital discharge.

Third, some patients may not view their experience with mental health treatment in a positive light. The caring, personal messages may help to change attitudes about the overall treatment system and thus help patients feel more open to seeking additional treatment when it is needed [5]. As suggested by Kapur et al. [25], follow-up messages from a treatment setting that provided less than optimal care may not be effective and possibly have an unintended deleterious effect by exacerbating negative feelings associated with care. Upon completion of the trial, we will be able to assess the association between attitudes towards care and outcomes of the study.

Motto also theorized that one caring note would not have much impact, but that the cumulative effect of repeated caring contacts would exert the greatest influence [6]. Published caring contact intervention studies vary greatly in regard to frequency and timing of caring contacts, thus, the optimal “dose” is not fully understood. The present study will allow us to examine the rates of suicidal behaviors based on post-hospitalization time periods and therefore help us to determine what frequency and number of contacts may be optimal for this type of intervention.

The present study will also provide extensive data regarding other psychosocial factors associated with suicide risk among military service members and veterans. In particular, we will be able to test the Interpersonal Psychological Theory of Suicide [13,26]. The theory emphasizes the importance of belongingness (interpersonal connections) in suicide risk and states that individuals with an acquired

capability for self-harm, perceptions of being a burden, and perceptions of thwarted belongingness are more likely to attempt or complete suicide than are others. Thwarted belongingness refers to a person's belief that he or she has infrequent positive social interactions and the perception that he or she is not cared for by others [27]. Individuals who die by suicide often harbor feelings of disconnect from others in such a way that they may believe that there is no one who truly cares about them or that no one can relate to them and understand their situation which leads to feelings of isolation [28,29]. We will also be able to examine whether perceptions of unit cohesion are associated with suicide behavior and whether a patient's perceived connection with care providers (i.e., the research coordinator who interviewed them) influences treatment seeking and suicidal behaviors.

The results of this study have the potential to inform the implementation of caring contact programs at military, VA, and civilian inpatient psychiatry units, as well at other treatment settings that encounter high risk for suicide patients including emergency departments, primary care clinics, and counseling centers. The use of multiple contact modalities (e.g., email, texting, telephone, and postal mail) has been proposed and may prove to be the best option given patient preferences for and access to technology-based forms of contact [5,18]. The use of SMS texting to deliver caring messages for suicide prevention is currently being evaluated in outpatient military clinics (ClinicalTrials.gov Identifier # NCT01829620). Post-treatment caring contact interventions could also coincide with interventions that specifically address the assessment and treatment of suicidality during inpatient treatment (e.g., post-admission cognitive therapy [32] and collaborative assessment and management of suicidality: CAMS; [33]). A two-pronged approach of addressing suicidality while in care and caring contact interventions that support recovery and prevention after treatment may prove to be most advantageous.

The greatest strength of the caring contacts intervention is its simplicity and portability. This straight-forward intervention is based on the notion that even the most basic expression of care and compassion for others can have a powerful, live-saving influence. This intervention also has the advantage of being able to reach military service members and veterans who choose not to continue in care, those who may not have easy access to care, and those who move frequently. This intervention may also be free of the stigma that is sometimes associated with other mental health interventions. The intervention is also inexpensive to implement and it has the potential to reduce future costs associated with psychiatric re-hospitalizations by preventing suicide behaviors and facilitating help-seeking on an outpatient basis. The caring contacts intervention, if shown to be effective among service members and veterans, could become part of the overall suicide prevention strategy in the military and VA health systems.

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References

[1] Luxton DD, Trofimovich L, Clark LL. Suicide risk among U.S. service members following psychiatric hospitalization, 2001–2011. Psychiatr Serv 2013;64:626–9. http://dx.doi.org/10.1176/appi.ps.201200413.
[2] Valenstein M, Kim HM, Ganoczy D, McCarthy JF, Zivin K, Austin KL, et al. Higher-risk periods for suicide among VA patients receiving depression treatment: prioritizing suicide prevention efforts. J Affect Disord 2009;112:50–8.
[3] Goldacre M, Seagroatt V, Hawton K. Suicide after discharge from psychiatric inpatient care. Lancet 1993;342:283–6.
[4] Ho T. The suicide risk of discharged psychiatric patients. J Clin Psychiatry 2003;64:702–7.
[5] Luxton DD, June JD, Comtois KA. Can post-discharge follow-up contacts prevent suicide and suicide behavior?: a review of the evidence. Crisis J Crisis Interv Suicide Prev 2013;34:32–41. http://dx.doi.org/10.1027/0227-5910/a000158.
[6] Motto JA. Suicide prevention for high-risk persons who refuse treatment. Suicide Life Threat Behav 1976;6:223–30.
[7] Motto JA, Bostrom AG. A randomized controlled trial of postcrisis suicide prevention. Psychiatr Serv 2001;52:828–33.
[8] Fleischmann A, Bertolote JM, Wasserman D, De Leo D, Bolhari J, Botega NJ, et al. Effectiveness of brief intervention and contact for suicide attempters: a randomized control trial in five countries. Bull World Health Organ 2008;86:703–9.
[9] Comtois KA, Linehan MM. Psychosocial treatments of suicidal behaviors: a practice-friendly review. J Clin Psychol 2006;62:161–70.
[10] Joiner Jr TE, Van Orden KA. The interpersonal–psychological theory of suicidal behavior indicates specific and crucial psychotherapeutic targets. Int J Cogn Psychol 2008;1:80–9.
[11] Luxton DD, Kinn JT, June JD, Pierre LW, Reger MA, Gahm GA. The caring letters project: a military suicide prevention pilot program. Crisis J Crisis Interv Suicide Prev 2012;33:5–12.
[12] Van Orden KA, Cukrowicz KC, Witte TK, Joiner TE. Thwarted belongingness and perceived burdensomeness: construct validity and psychometric properties of the Interpersonal Needs Questionnaire. 2012;24:197–215.
[13] Van Orden KA, Witte TK, Gordon KH, Bender TW, Joiner Jr TE. Suicidal desire and the capability for suicide: tests of the interpersonal–psychological theory of suicidal behavior among adults. J Consult Clin Psychol 2008;76:72–83.
[14] Crosby AE, Ortega L, Melanson C. Self-directed violence surveillance: uniform definitions and recommended data elements, version 1.0. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2011.
[15] Wright KM, Cabrera OA, Bliese PD, Adler AB, Hoge CW, Castro CA. Stigma and barriers to care in soldiers postcombat. Psychol Serv 2009;6:108–16. http://dx.doi.org/10.1037/a0012620.

[16] Holford TR. Multivariate methods in epidemiology. Oxford University Press; 2002.
[17] Enders CK. Applied missing data analysis. New Yord: The Guilford Press; 2010.
[18] Luxton DD. Caring letters for military suicide prevention. In: Sullivan, James, Bongar, editors. The Oxford Handbook of Suicide in Military and Veteran Populations. New York: Oxford University Press; 2014 [in press].
[19] Littman AJ, Boyko EJ, Jacobson IG, Horton JL, Gackstetter GD, Smith B, et al. Assessing nonresponse bias at follow-up in a large prospective cohort of relatively young and mobile military service members. BMC Med Res Methodol 2010;10(1):99. http://dx.doi.org/10.1186/1471-2288-10-99.
[20] Hosmer DW, Lemeshow S, May S. Applied survival analysis: regression modeling of time-to-event data. 2nd ed. Hoboken, NJ: John Wiley & Sons, Inc.; 2008.
[21] Carr JR, Hoge CW, Niebuhr D, Belenky G, Potter R, Gardner J. Suicide surveillance in the U.S. military—reporting and classification biases in rate calculations. Suicide Life Threat Behav 2004;34:233–42.
[22] Eaton K, Messer S, Wilson A, Hoge C. Strengthening the validity of population-based suicide rate comparisons: an illustration using U.S. military and civilian data. Suicide Life Threat Behav 2006;36(2): 182–91.
[23] Stewart CJ, Cash WB. Interviewing: principals and practice. 12th ed. New York: McGraw-Hill; 2008.
[24] Shaughnessy JJ, Zechmeister EB, Zechmeister JS. Research methods in psychology. 8th ed. New York: McGraw-Hill; 2009.
[25] Kapur N, Cooper J, Bennewith O, Gunnell D, Hawton K. Postcards, green cards and telephone calls: therapeutic contact with individuals following self-harm. Br J Psychiatry 2010;197:5–7.
[26] Joiner Jr TE. Why people die by suicide. Cambridge, MA: Harvard University Press; 2005.
[27] Baumeister RF, Leary MR. The need to belong: desire for interpersonal attachments as a fundamental human motivation. Psychol Bull 1995;117:497–529.
[28] Conner K, Britton P, Sworts L, Joiner Jr TE. Suicide attempts among individuals with opiate dependence: the critical role of felt belonging. Addict Behav 2007;32:1395–404.
[29] Joiner Jr TE, Hollar D, Van Orden KA. On Buckeyes, Gators, Super Bowl Sunday, and the Miracle on Ice: "Pulling Together" is associated with lower suicide rates. J Soc Clin Psychol 2006;25:180–96.
[30] Linehan MM, Comtois KA. Lifetime parasuicide count. Seattle: University of Washington; 1994.
[31] Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. J Gen Med 2001;16:606–13.
[32] Ghahramanlou-Holloway M, Cox D, Greene F. Post-admission cognitive therapy: a brief intervention for psychiatric inpatients admitted after a suicide attempt. Cogn Behav Pract 2012;19:233–44.
[33] Jobes DA. Managing suicidal risk: a collaborative approach. New York: Guilford; 2006.