CLINICAL STUDY PROTOCOL

PRAGMATIC TRIAL OF POPULATION-BASED PROGRAMS TO PREVENT SUICIDE ATTEMPT

Version Number: 13
Version Date: 9/23/2016

Principal Investigator: Gregory Simon MD MPH, Group Health Research Institute

Supported by:

The National Institute of Mental Health

UH3 MH007755-02

Grant Number: UH3 MH007755-02
Protocol Number: n/a

Name of Coordinating Center [CC]: Group Health Research Institute
Name of Data center [DCC]: Group Health Research Institute

Principal Investigator [PI] & Clinical Site *[list all]*:

PI Name	Site #	Location	Phone	E-mail
Gregory Simon	1	Group Health Cooperative	206-287-2979	Simon.g@ghc.org
Arne Beck	2	Kaiser Permanente Colorado	303-614-1326	Arne.Beck@kp.org
Rebecca Rossom	3	HealthPartners	952-967-5006	Rebecca.C.Rossom@HealthPartners.com
Gregory Clarke	4	Kaiser Permanente Northwest	503-335-6673	Greg.Clarke@kpchr.org

Study Phase and Target enrollment:

Phase of clinical investigation: N/A (effectiveness trial of system-level intervention).

Target enrollment: 19,500 Patients

Project Uses Ionizing Radiation: ■ No ☐ Yes (*attach RSC/RDRC documentation)*
- ☐ Medically-indicated only
- ☐ Research-related only
- ☐ Both

IND/IDE ■ No ☐Yes *(attach FDA documentation)*

Drug/Device: _____
Specify the assigned name and/or #, when applicable, the code number of the investigational drug(s).
IND #_____
Drug/Device supplied by: _____

Regulatory Approvals:

Multi-institutional Project ☐ No ☒ Yes

Group Health Cooperative
Date of IRB approval _____*(attach IRB documentation)*

Kaiser Permanente Colorado
Date of IRB approval _____*(attach IRB documentation)*

Health Partners
Date of IRB approval _____*(attach IRB documentation)*

Kaiser Permanente Northwest
Date of IRB approval _____*(attach IRB documentation)*

NIMH Data and Safety Monitoring Board	☐ No	■ Yes
Samples are being stored	■ No	☐ Yes

Précis:

Objective - This pragmatic clinical trial will evaluate the effectiveness of two population-based outreach programs for preventing suicide attempts among patients identified as at-risk for suicide.

Study population - The study will be conducted at Group Health (the lead site) and at HealthPartners, KP Colorado, KP Northwest. Electronic health records will be used to identify outpatients aged 18 or older who respond to a routinely administered PHQ depression questionnaire by reporting thoughts of death or self-harm "most of the days" or "nearly every day."

Design - Eligible patients will be automatically assigned to continue in usual care (1/3) or to usual care plus either of the two intervention programs (1/3 each). Those assigned to usual care will not be contacted at all by study staff and will continue to receive usual care from treating primary care and mental health providers. Both intervention programs involve outreach by Epic secure messaging (with optional telephone outreach for those not reading messages). The Care Management intervention includes routine outreach to assess ongoing risk of suicide attempt, and care management to monitor and facilitate ongoing engagement in outpatient follow-up. The Care Manager will coordinate care with treating Group Health providers (ongoing usual care) using Epic Staff Messaging (or telephone contacts if necessary). The Skills Training intervention uses an online skills training program to support patients in developing and using self-management skills for emotion regulation and crisis management. A Coach will monitor each participant's use of the program and send periodic messages (using Epic secure messaging) to encourage and support use of the program and practice of program skills. Each intervention continues for up to one year.

Outcome measures - In all three groups (Usual Care, Care Management, and Skills Training) computerized health system records will be used to identify medically-treated suicide attempts over 18 months following randomization. Procedures for invitation, consent, and intervention delivery are described in more detail below.

Table of Contents

List of Abbreviations

- GHRI – Group Health Research Institute
- KPCO – Kaiser Permanente Colorado
- KPNW – Kaiser Permanente Northwest
- PHQ9 – Patient Health Questionnaire 9

Introduction/Background/Significance

Suicide ranks 10th among all causes of mortality in the US, accounting for over 38,000 deaths in 2010. Non-fatal suicide attempts result in 600,000 emergency room visits and nearly 200,000 hospitalizations each year. Recent developments have opened new opportunities to develop and evaluate population-based selective prevention programs for suicidal behavior. First, increasing use of standard depression severity measures and recording of results in electronic medical records will allow timely and efficient identification of people at risk for suicidal behavior. Second, efficient and scalable interventions (both structured risk assessment / care management programs and low-intensity emotion regulation skills training) have shown promise for reducing risk of suicide attempt in at-risk populations. Third, the NIMH-funded Mental Health Research Network has established an infrastructure to adequately evaluate population-based prevention.

1. Study objective

Evaluate the effectiveness of two population-based outreach programs for reducing risk of suicide attempt among patients who report frequent thoughts of death or self-harm on PHQ9 questionnaires completed during routine care.

2. Subjects:

a. Description of study populations - At the four participating health systems, electronic health records will be used to identify outpatients aged 18 or older who respond to a routinely administered PHQ depression questionnaire by reporting thoughts of death or self-harm "most of the days" or "nearly every day." Following a modified Zelen design, those identified will be automatically assigned to continue in usual care OR offered one of the two outreach interventions while continuing in usual care. Analyses will compare risk of subsequent suicide attempt according to initial assignment, regardless of participation in intervention programs or other treatment received.

b. Inclusion criteria – We propose to automatically enroll all health system patients who:

- Complete PHQ questionnaire and respond to item 9 (regarding thoughts of death or self-harm) "more than half the days" or "nearly every day"
- Are currently enrolled in the health system
- Are aged 18 or older
- Have used health system online messaging services in the prior 12 months

c. Exclusion criteria – We propose to exclude those who:

- Have a recorded diagnosis of dementia or developmental delay
- Have already been enrolled by virtue of a previous PHQ questionnaire

3. Study Design and Methods:

a. Study overview

We propose to conduct a multi-site pragmatic clinical trial to evaluate two population-based programs to prevent suicide attempts among patients who report suicidal ideation during outpatient visits. While the two proposed prevention programs differ in specific content and mode of delivery, both emphasize systematic outreach and follow-up to reduce ongoing risk (in contrast to the traditional emphasis on acute or emergent management). Each intervention is intended to supplement usual care by primary care and mental health providers. Patients receiving continued usual care will serve as the comparison or control group. Key aspects of the proposed pragmatic trial include:

- Potential participants will be automatically identified from records of PHQ depression questionnaires routinely administered during outpatient primary care and mental health visits.
- All those eligible will be randomly assigned to continue in usual care or to receive usual care plus one of the two prevention programs (using a modified Zelen design).
- A DBT skills training intervention will include systematic outreach, an online program to develop emotion regulation skills, and a structured coaching program to support engagement and adherence.
- A risk assessment and care management intervention will include systematic outreach, structured assessment of risk of suicide attempt, and ongoing care management to facilitate engagement in specified risk-based care pathways.
- For both prevention programs, intervention delivery and quality control will be supported by specific tools integrated into the Epic electronic medical records systems already in use at all sites.
- The primary outcome, diagnosis of probable suicide attempt during the 18 months following randomization, will be assessed using electronic medical records and insurance claims data.
- Secondary analyses will examine intervention effects on use of mental health services and on alternative definitions of suicide attempt, as well as test for possible biased ascertainment.
- Analyses will examine the consequences of original assignment to intervention conditions, regardless of participation in intervention programs.

A diagram illustrating the overall study design is attached as an Appendix.

b. Recruitment

Each week, a the study programmer/analyst at each site will use electronic medical records data to identify adult outpatients who completed a PHQ depression questionnaire in the previous week and reported thoughts of death or self-harm “most of the days” or “nearly every day.”

Those identified will be automatically assigned to continued Usual Care or to Usual Care plus one of two intervention programs (Care Management or Skills Training).

For those assigned to the Care Management group, the Care Manager will send an invitation message including essential elements of informed consent (see Appendix b for invitation message with informed consent language). Those who actively consent will continue in the Care Management program, those who actively decline will not be contacted again, and those who neither consent nor decline may be invited up to two more times over the next two months.

For those assigned to the Skills Training group, the Coach will send an invitation message including essential elements of informed consent (see Appendix c for invitation message with informed consent language). Those who actively consent will continue in the Skills Training program, those who actively decline will not be contacted again, and those who neither consent nor decline may be invited up to two more times over the next two months.

c. Screening

As described above, participants will be identified automatically from health system electronic medical records. There will be no study contact with participants to assess eligibility or any inclusion or exclusion criteria. Those identified will be automatically assigned to one of the three study groups (Risk Assessment intervention, Skills Training intervention, or continued usual care).

d. Intervention Procedures

CARE MANAGEMENT INTERVENTION PROGRAM

Intervention Overview – The aim of this program is to provide systematic monitoring of suicide risk linked to risk-based care pathways. A structured care management program (delivered by online messaging and/or telephone) will include motivational interventions to promote engagement in recommended treatment pathways and coordination of care with responsible providers. The program is a supplement to (not a substitute) for usual medical and mental health care. The design of the program draws from the research team's extensive experience with systematic outreach, motivational enhancement, and care management to promote engagement in and adherence to mental health treatment. Outreach messages also include content from "caring letter" interventions previously shown to reduce suicidal behavior.

Organizational Structure – Services will be delivered by intervention clinicians based in each health system, using tools embedded in each system's Epic EMR system. GHRI investigators will be responsible for training and supervision of intervention staff at all sites. Clinical liaisons at KPCO, KPNW and HealthPartners will assist with adaptation of intervention procedures and coordination with local clinicians and leaders.

Care Management Clinician Qualifications, Training, and Supervision – Care managers will be masters-prepared mental health clinicians, recruited (whenever possible) from the workforce of participating health care systems. Each care manager will receive standard training required of mental health clinicians in her/his health

care system (use of EMR systems, records privacy, relevant regulatory compliance, etc). Project-specific training for delivery of this preventive intervention will include 8 hours of initial training (two 4-hour sessions) followed by two 2-hour booster sessions by videoconference (all organized by Evette Ludman). This low-intensity training is consistent with the principles of pragmatic trials and is intended to maximize the chances of eventual dissemination and implementation. Dr. Ludman has extensive experience with implementation of care management programs using similar low-intensity training. During the intervention period, care managers will participate in quality control meetings to monitor caseload-level indicators of successful intervention delivery (described below).

Outreach Contacts – A series of structured outreach contacts will be scheduled throughout the 12-month intervention period, with the interval between contacts determined by risk level at last contact, engagement in care, and interim PHQ scores recorded in the medical record. The algorithm for contact intervals (implemented and evaluated in pilot testing) calls for intervals between outreach contacts ranging from as brief as one week (for high-risk participants not yet engaged in care) to three months (for low-risk participants engaged in care and showing resolution of suicidal ideation on subsequent PHQ questionnaires). Initial contact attempts will be made through online messaging with telephone follow-up for those not reading or responding to online messages.

Assessment Tools – Each outreach contact will begin with a structured assessment of risk using an adapted version of the Columbia Suicide Severity Rating Scale. Online administration of an adapted CSSR was successfully implemented in the pilot phase.

Risk-Based Care Pathways – A specific algorithm will link risk levels (as determined by the C-SSR) to specific pathways for follow-up care – following the care pathways developed and successfully implemented in the Henry Ford program and adapted based on feedback from health system clinical leaders. Recommended follow-up options will range from immediate emergency department assessment for highest-risk participants, decreasing to as-needed outpatient follow-up for those with complete resolution of suicidal ideation.

Motivational Interventions – We anticipate that simple recommendations for follow-up care will not be sufficient to prompt engagement in care – especially among people with suicidal ideation and significant depression. As in our previous care management interventions, outreach messages will include structured motivational enhancement content (motivational assessment, algorithm-based motivational enhancement messages) suitable for secure message or telephone.

Integration with Usual Care – Following each contact, care managers will communicate assessment findings and recommended follow-up care to treating providers using provider-to-provider messaging within the Epic EMR. Messages will be clearly labeled as informational only ("FYI") or requests for specific action. Direct telephone communication will be used for communication of urgent needs. Care managers will also communicate directly with primary care and mental health nursing staff and reception/appointing staff (using EMR-based messaging or telephone) to facilitate recommended follow-up care. The purpose of the intervention is to prompt appropriate follow-up treatment by responsible outpatient providers.

Care managers will serve as treatment facilitators rather than direct treatment providers.

Management of Clinical Emergencies - For emergent needs, all health systems have capacity for in-person emergency room assessment, 24-hour access to on-call mental health providers, and mobile crisis teams. Care management algorithms will include specific recommendations for use of these services.

Caseload and Workflow – A study site enrolling 5000 participants would offer this intervention to approximately 1700 participants, or approximately 12 per week during the anticipated 33-month enrollment period. While the number of contacts per participant will vary widely (depending on risk level and engagement in care), our experience in the pilot phase suggests an average of approximately 5 contacts per participant over the 12-month period. Consequently, enrollment of 12 patients per week would generate a steady-state workload of 60 care management contacts per week. Based on extensive experience with telephone and online messaging care management programs, we estimate that approximately 24 hours of care manager time per week (or 0.60 FTE) will be required to complete those 60 contacts (including time for record-keeping, administrative tasks, and meetings).

Embedded EMR Tools – Care managers will take advantage of each health system's electronic medical records system for communicating with participants via secure online patient-provider messaging, real-time monitoring of engagement in treatment, communication with treating clinicians by provider-to-provider messaging, and documenting all care management contacts. In addition to increasing efficiency, these embedded communication tools create a comprehensive electronic record of all intervention activity. Care managers will also take advantage of the Epic EMR capacity for care automation and workflow management using other specific tools:

- Risk assessment questionnaires embedded in Epic patient-provider messaging tools
- Customizable "smart phrases" allow care managers to generate algorithm-driven messages to both patients and clinicians, automatically personalizing messages with patient identifiers and allowing additional personalization by the care manager.
- Customized patient lists support contact and workflow management by organizing information regarding contact dates, risk assessment results, expected date and type of next provider contact, provider contacts completed, provider contacts scheduled, and prescriptions filled or refilled. These lists identify participants overdue for care manager outreach and those failing to engage in recommended care pathways. Outreach contacts can be immediately "launched" from this EMR interface.

Each of these tools is a standard feature of the Epic EMR, so complex programming will not be necessary to generate project-specific tools for workflow management and quality control.

Quality Monitoring – Day-to-day clinical and administrative supervision of care managers will be the responsibility of investigators and delivery system colleagues at each site. Care managers from all sites will also participate in a bi-weekly project-wide quality control meeting led by Drs. Ludman and Simon. This meeting will use the EMR tools described above to review timeliness of intervention service delivery and adherence to care management protocols across sites. Site investigators will meet twice per month to review specific indicators of intervention implementation (see sections 14 and 15 below).

SKILLS TRAINING INTERVENTION PROGRAM

Intervention Components – The aim of this program is to efficiently deliver an online intervention to develop specific emotion regulation skills derived from Dialectical Behavior Therapy. Skills training will be delivered through an interactive, self-contained online program but will be supported by outreach and coaching (via online messaging and telephone) to provide support and promote engagement in the online program. The program is a supplement to (not a substitute for) usual medical and mental health care. Program content draws from the research team's extensive experience with structured outreach programs, online psycho-educational programs, and structured motivational interventions.

Organizational Structure – As described above regarding the care management intervention, coaching will be delivered by distinct staff at each study site supported by centralized training and supervision.

Online Skills Training Program – Content will focus on four core skills found to mediate the clinical benefits of dialectical behavior therapy: mindfulness, mindfulness of current emotion, paced breathing, and opposite action. Following our experience with development of previous interactive programs to develop self-management skills, each specific skill topic (e.g. using opposite action as a strategy to manage strong negative emotions) will be presented in a separate module – with each module including text and graphic descriptions, video demonstrations, online exercises, and tools to generate personalized printed homework assignments. The program will include four modules designed for completion over a period of six to twelve weeks. Each module also includes video testimonials and encouragement from people with lived experience of suicidal ideation and suicidal behavior.

Coaching Support – Previous research regarding online interventions for depression and anxiety disorders demonstrates that online interventions have efficacy similar to traditional in-person therapies – but only for those who engage in and adhere to the online treatment. Personalized outreach to promote engagement and adherence are critical to the success of online interventions. Compared to a therapist role, this coaching role is both less intensive (fewer, briefer contacts) and narrower (focused on motivating program use and reinforcing use of program tools). A series of structured outreach contacts will be scheduled over the first 6 months of the intervention period, with the number of and intervals between contacts determined by level of engagement in the online program. Initial contact attempts will be made through online messaging (for participants using online messaging) or telephone (for those not reading or responding to online messaging). In addition to specific motivational content (described below), each contact will include expressions of support based on previous "caring letter" programs. Coaches supporting the online intervention will be bachelors- or masters-prepared mental health clinicians. To preserve integrity of the two intervention programs, no individual clinician will perform both coaching and care management (described above) functions. Each coach will receive standard training required of mental health clinicians in her/his health care system (use of EMR systems, records privacy, relevant regulatory compliance, etc). Project-specific training for delivery of this preventive intervention will include 8 hours of initial

training (two 4-hour sessions) followed by two 2-hour booster sessions by videoconference (by Evette Ludman and Ursula Whiteside). The training will focus on program objectives, use of program procedures and tools, and principles of motivation enhancement interventions. This low-intensity training program is consistent with the principles of pragmatic trials and is intended to maximize the chances of eventual dissemination and implementation. Our recent trials have successfully implemented similar care management programs using similar low-intensity training. Coaches will participate in biweekly quality control meetings to monitor caseload-level indicators of intervention delivery (described below).

Motivational Interventions – Coaching protocols will include scripted messages for motivational assessment and motivational enhancement based on those used successfully in our previous outreach and coaching programs. These messages will focus on specific behavioral goals (initial enrollment in online program, completion of specific online modules, practice of emotion regulation skills). Messages will be suitable for delivery either by telephone or online messaging.

Integration with Usual Care – As described above, coaches will communicate with treating mental health and/or general medical providers following each participant's enrollment in the online program. These standardized messages will briefly describe the program content, invite treating clinicians to reinforce use of programs skills, and invite treating clinicians to contact the care manager for additional information. Because the coaching program does not include specific recommendations regarding follow-up treatment, messages from coaches will not include recommendations for providers. If, however, coaching contacts discover clear need for evaluation or intervention by mental health or general medical providers, coaches will communicate that need to participants and providers and will facilitate necessary follow-up care.

Management of Clinical Emergencies – The coaching program does not include specific assessment of suicidal ideation or suicidal behavior. Nevertheless, it is possible that coaching contacts may discover need for urgent or emergent intervention. For emergent needs, all health systems have capacity for in-person emergency department assessment, 24-hour consultation with on-call mental health providers, and mobile crisis teams. Coaching algorithms will include specific recommendations for use of these services.

Caseload and Workflow – As with the risk assessment and care management program described above, a study site enrolling 5000 participants would offer this program to approximately 12 new participants each week. While the number of contacts per participant will vary (depending on engagement in the online program), we anticipate an average of 6 total contacts. Consequently, enrollment of 12 patients per week would generate a steady-state workload of 72 care management contacts per week. Based on extensive experience with telephone and online messaging care management programs, we estimate that approximately 24 hours of care manager time per week (or 0.60 FTE) will be required to complete those 72 contacts (including time for record-keeping, administrative tasks, and meetings).

Technology Platform – The skills training intervention has been implemented using the DatStat Illume content management system, a standard commercial content

management system for delivery of tailored online surveys and educational interventions.

Quality Monitoring - Day-to-day clinical and administrative supervision of coaches will be the responsibility of investigators and delivery system colleagues at each site. Coaches from all sites will also participate in a twice-monthly quality monitoring meeting led by Drs. Ludman and/or Whiteside. This meeting will use Epic EMR tools and reports generated by DatStat Illume to monitor intervention participation and adherence to coaching protocols across sites. Site investigators will meet twice per month to review specific indicators of intervention implementation (see sections 14 and 15 below).

TREATMENT AS USUAL

Participants assigned to continue treatment as usual will not be contacted by study staff. No additional services will be offered, but no services normally available will be restricted or withheld. Treating mental health and primary care providers will be aware of participants' thoughts of death or self-harm, since results of PHQ9 questionnaires were entered by providers during in-person or telephone encounters. Follow-up care (including referral to outpatient mental health specialty care or inpatient mental health care) will be at the judgment of the treating primary care or mental health providers. Study staff do not have permission to view records of usual care participants, and usual care will not be monitored by study staff.

e. Coordination of Care / End of Participation

The intervention programs are intended as supplements to (not replacements for) ongoing care by treating mental health and primary care clinicians. In both intervention programs, intervention clinicians (care managers or coaches) will coordinate care with other treating clinicians throughout the 12-month intervention period. This coordination will typically occur through electronic provider-to-provider messaging in the electronic medical record, but telephone contacts may be necessary for more urgent concerns. For each participant, an initial message to treating clinicians will describe the purpose, content, and procedures of the intervention program. In the Care Management intervention, each cycle of outreach for risk assessment and care management will include a summary message to treating providers regarding current risk level and follow-up plan. As necessary (according to each participant's risk level and engagement in care), the Care Manager may send additional messages to treating providers to arrange appropriate follow-up care. In the Skills Training intervention, the Coach will send periodic messages to treating providers regarding each participant's progress in the online program – with the number and timing of those messages varying according to each participant's pattern of progress.

In both programs, a standard process will notify study participants and treating providers regarding the end of intervention services. That process will include:

- A message to treating clinicians regarding the end of the intervention period, summarizing the participant's involvement in the program and the plan for follow-up care

- A message to the participant regarding the end of intervention services (e.g. outreach contacts, coaching messages) and plans for follow-up care
- Documentation in the electronic medical record

4. Storage of data

At each site, electronic health records will be used to identify participants (described above) and assess outcomes (described below). The study programmer/analyst at each site will maintain a list of participant identifiers linked to study identifiers. These lists will be stored in password-protected directories in each health system's HIPAA/HITECH compliant computer networks. Identifiable information will only be available to study staff with clear need to know (programmer/analysts and intervention clinicians). Identifying information will not be shared across sites. Analytic datasets will be completely de-identified (including appropriate procedures to prevent backwards-identification). All identifying information will be discarded once final analytic files are created.

Information used for delivery of the Care Management intervention will be stored within the electronic health records of each healthcare system and will be protected by the same technical safeguards and policies/procedures that protect the privacy of participants' other medical record information.

The online Skills Training program will not receive or store any identifiable information. Within that program, each participant will be identified only by a study identifying number.

5. Risks and discomforts

- Risks associated with participant identification and recruitment – As described above, participants will be identified from health system electronic medical records. Use of records for this purpose may create a risk of violating patient/participant confidentiality. Procedures for protection of participants' health information are described in #5 above.

- Risk associated with Care Management intervention program - The Care Management program includes less-intensive versions of intervention components that have been previously found effective in high-risk populations. Intervention recommendations are based on best practice and are intended to be beneficial. It is possible, however, that some participants may find specific aspects of the intervention to be unhelpful or upsetting. This possibility will be described in invitation and consent messages. Participants will be free to decline any portion of either program and will be free to withdraw from either program at any time.

- Risk associated with Skills Training intervention program - The Skills Training program includes less-intensive versions of intervention components that have been previously found effective in high-risk populations. Skills training modules and coaching messages are based on best practice and are intended to be beneficial. It is possible, however, that some participants may find specific aspects of the intervention to be unhelpful or

upsetting. This possibility will be described in invitation and consent messages. Participants will be free to decline any portion of either program and will be free to withdraw from either program at any time.

- Risks associated with use of health records for ascertainment of outcomes - As described above, study outcomes (fatal and non-fatal suicide attempts) will be identified from electronic medical records and insurance claims data. Use of records for this purpose may create a risk of violating patient/participant confidentiality. Procedures for protection of participants' health information are described in #5 above.

6. Participant safety monitoring within intervention programs

Participants assigned to the Usual Care control group will not be contacted, and no real-time information will be available regarding suicide risk or treatment received. Consequently, no real-time monitoring of participant safety is possible.

Within the two intervention groups, specific procedures for safety monitoring will vary according to the nature and timeliness of data available to intervention staff.

In the Care Management intervention, participants will be asked to complete periodic standardized assessments of suicide risk, and these assessments may reveal high risk of self-harm (Columbia Suicide Severity Rating Scale score of 4 or 5) in responses to either an online assessment or a telephone assessment with a Care Manager. In addition, participants may spontaneously reveal indicators of risk during online or telephone communication with Care Managers. If indication of high risk is received via online communication, the Care Manager will receive this information no later than the next working day, depending on when the assessment is completed. Immediately on receipt of this information, the care manager will initiate an outreach contact (either by online message or telephone, depending on the participant's previous communication behavior and preferences). The goal of this outreach contact is to arrange appropriate follow-up care, including (if clinically indicated) urgent assessment in the emergency department or by a local 24-hour mobile crisis team. If indication of high risk is received during a live telephone call, the Care Manager will immediately work with the participant to arrange appropriate follow-up care, including (if clinically indicated) urgent assessment in the emergency department or by a local 24-hour mobile crisis team. In each of these high-risk cases, Care Managers will document outreach contacts, recommended follow-up care, and appropriate resolution. All Care Managers will be experienced mental health providers with appropriate training and licensure for assessment of suicide risk or other urgent mental health need. Care Managers are not, however, direct providers of mental health or general medical care for study participants. The clinical role of Care Managers is limited to outreach, structured assessment, and facilitation of appropriate follow-up care through standard recommendations made to participants and those participants' treating clinicians. At each site, clinical supervisors will be available to Care Managers for as-needed clinical consultation.

The Skills Training intervention does not include any specific assessment of suicide risk or risk of self-harm. Nevertheless, participants may spontaneously reveal indicators of risk during online or telephone communication with Coaches. If indication of high risk is received via online communication, the Coach will receive this information no later than the next working day. Immediately on receipt of this information, the care manager will initiate an outreach contact (either by online message or telephone, depending on the participant's previous communication behavior and preferences). The goal of this outreach contact is to arrange appropriate follow-up care, including (if clinically indicated) urgent assessment in the emergency department or by a local 24-hour mobile crisis team. If indication of high risk is received during a live telephone call, the Coach will immediately work with the participant to arrange appropriate follow-up care, including (if clinically indicated) urgent assessment in the emergency department or by a local 24-hour mobile crisis team. In each of these high-risk cases, Coach will document outreach contacts, recommended follow-up care, and appropriate resolution. All Coaches will be experienced mental health providers with appropriate training and licensure for assessment of suicide risk or other urgent mental health need. Coaches are not, however, direct providers of mental health or general medical care for study participants. The clinical role of Coaches is limited to outreach and encouragement to use the online skills training program through standard recommendations made to participants. At each site, clinical supervisors will be available to Coaches for as-needed clinical consultation.

At each site, local clinical supervisors will review all instances of outreach to high-risk cases within 2 working days to assure compliance with study procedures and clinical appropriateness of Coaches' or Care Managers' assessments and recommendations. As described in section 14 below, reports of all outreach to high risk cases at all sites will be reviewed by an independent medical monitor bi-monthly, as well as monthly by the intervention implementation team (including clinical and health system representatives from all sites) . Study staff responses to high-risk cases will be reported three times each year to the DSMB.

As described above, the likelihood of detection of high-risk cases will be much greater in those assigned to Care Management than in those assigned to Skills Training. And there will be no detection of high-risk cases in the Usual Care group as study staff will have no contact with these participants. Consequently, data regarding study response to high-risk cases cannot be used for any valid comparison across treatment groups.

In addition to this real-time safety monitoring within the two intervention programs, health system records will be used to systematically identify suicide attempts and suicide deaths in all three treatment groups. These data will be reported to DSMB as described in section 15 below.

7. Outcome measures

- **Primary outcome measures**

The primary trial outcome will be fatal or non-fatal suicide attempt up to 18 months following randomization, ascertained from computerized medical records, computerized

records of insurance claims, and death certificate data. Three specific criteria will be used to identify medically treated nonfatal suicide attempts.

- Outpatient or inpatient encounter with ICD9 diagnosis of definite self-inflicted injury (E950-E958)
- Outpatient or inpatient encounter with ICD9 diagnosis of possible self-inflicted injury (E950-E958
- Emergency department or inpatient encounter with ICD diagnoses of poisoning (960-989) or open wound (870-897) associated with diagnosis of suicidal ideation (V62.84)

Our pilot work has validated the use of these criteria at the three study sites. As discussed above, enrollment will be limited to those for whom EMR and insurance data will be available. In addition suicide deaths not identified by the above will be identified by death certificate cause-of-death codes of definite self-inflicted injury (X60 to X84) or possible self-inflicted injury (Y10 through Y34).

Health system records will also be used to identify censoring variables: health system disenrollment and death from causes other than suicide.

Consistent with the principles of pragmatic effectiveness trials, outcomes will be assessed for all randomized participants, including those who decline intervention services or drop out of intervention services. As described in section 10 below, analyses will compare risk of suicide attempt according to initial treatment assignment, regardless of level of participation in intervention services.

- **Secondary outcome measures**

Specific secondary analyses are planned to:

- Describe intervention effects on care process (both use of specific intervention services and traditional mental health services)
- Examine intervention effects using alternative outcome definitions (broader and narrower criteria for defining suicide attempts)
- Estimated incremental cost and incremental net benefit
- Test for possible biased outcome ascertainment due to intervention effects on care-seeking behavior

<u>Intervention effects on care processes:</u>

- **Intervention uptake and adherence** – Data generated within both intervention programs will be used to assess specific measures of uptake and adherence described in section 14 below. For the Skills Training Intervention, additional analyses will describe proportions initiating and completing each module of the skills training program as well as use of specific components (video demonstrations, interactive exercises, printable homework) within each module. These findings will inform any subsequent revisions to both programs and to estimate resources needed for any future implementation.
- **Use of specific health services** – Increasing use of follow-up care is an explicit goal of the risk assessment and care management intervention. While the skills training intervention will not specifically attempt to increase service use, it is possible that skills training might either increase or decrease care-seeking.

Therefore, we propose to compare each of the intervention groups to the usual care group regarding these specific categories of health services utilization:
- Mental health specialty outpatient visits
- Emergency department visits
- Primary care visits associated with any mental health diagnosis (ICD9 diagnosis 290 to 316)
- Hospitalizations associated with any mental health diagnosis (ICD9 diagnosis 290 to 316)

Based on experience with similar analyses, we anticipate skewed distributions for each of these utilization measures, so appropriate transformations or non-parametric analyses (e.g. poisson regression, comparison of ranks) will be required.

Intervention effects on alternative outcome definitions: The effect of treatment on secondary time-to-event outcomes will be estimated using proportional hazards models, paralleling the analysis plan described for the primary outcome.

- **Broader categories of injury/poisoning diagnoses** – As discussed above, failure to record any cause-of-injury code (E-code) or mis-coding of self-inflicted injuries as accidental may lead to under-ascertainment of suicide attempts from EMR or claims data. While our pilot data support the use of E-codes at the three study sites, we must acknowledge that coding practice could change during the study period [1]. Consequently, we propose to examine between-group differences in risk of two broader categories of injury/poisoning diagnoses that do not depend on E-codes:
  - One alternative analysis will examine all diagnoses of open wound (ICD9 870 thru 897) or poisoning (ICD9 960 thru 989), regardless of cause-of-injury code[2]. These specific codes were selected because preliminary research across MHRN sites (described above) found that these type-of-injury codes accounted for over 90% of encounters where cause-of-injury code indicated self-inflicted injury.
  - An additional analysis will examine all the broader category of all diagnoses of injury or poisoning (ICD9 800 thru 999), regardless of cause-of-injury code.
- **Restriction to suicide attempts with greater potential lethality –** Given the possibility of biased outcome ascertainment due to differential care-seeking prompted by exposure to the intervention (see below), an additional secondary analysis will compare groups after limiting to suicide attempts resulting in death or leading to medical or psychiatric hospitalization (presuming that differential care-seeking would have less influence on more serious suicide attempts).

Incremental cost and incremental net benefit – Following methods used in several of our previous effectiveness trials, health system accounting and claims records will be used to calculate costs of all health services provided or paid for by the health system, and study personnel records will be used to estimate actual costs of intervention program delivery. These data will be used to estimate incremental cost of each intervention program (cost for intervention group minus cost for usual care control group) considering the narrower category of mental health treatment costs (intervention program costs, mental health specialty care costs, costs of general medical visits or hospitalizations with mental health diagnoses, and costs of psychotropic medications) as well as the broader category of total costs (intervention program costs plus total health services costs). If either intervention program demonstrates a reduction in risk of suicide attempt, then these data will be used

to estimate incremental net benefit (probability of net benefit for different valuations an additional suicide attempt avoided).

Testing for Biased Outcome Ascertainment – It is possible that either of the intervention programs might affect participants' threshold for care-seeking regarding self-injury or suicide attempt. For example, care management and risk assessment contacts might result in participants assigned to that condition presenting to emergency departments following overdose or self-injury episodes that would have otherwise gone undiagnosed and unrecognized. Such an effect might bias our ascertainment of outcomes from electronic records and thereby bias our comparison of either intervention with usual care. Consequently, we propose to examine severity of identified suicidal behavior as indicated by need for inpatient treatment and means of attempt (firearms/jumping/hanging vs other means), a proxy for potential lethality. If exposure to the intervention lowered care-seeking thresholds, we would expect to see a lower proportion of more serious suicide attempts (leading to hospitalization or by more potentially lethal means) among suicide attempts identified in the intervention groups.

8. Statistical Analysis

- **Analysis of data/ study outcomes**

Participants assigned to each of the two intervention programs will be separately compared to those assigned to continued usual care. Primary analyses will examine risk of suicide attempt for up to 18 months after randomization. Estimated intervention effects will be based on original group assignment (an "as randomized" analysis), regardless of subsequent treatment or level of participation in either intervention program. Criteria for defining suicide attempts and pilot data supporting the validity of those criteria are described in section 8 above. We plan to use proportional hazards models to describe time until first suicide attempt following randomization and to compare the risk of suicide attempt or completion between groups. Individuals will be censored at time of health system disenrollment, death from cause other than suicide, or administratively, at 18 months following randomization. Selection of an 18-month limit for outcome ascertainment is based on our observation that the association between score on item 9 of the PHQ (used to determine eligibility and assess baseline risk) and risk of subsequent suicide attempts declines to a modest level after 18 months. Proportional hazards models will adjust for initial response to PHQ item 9 (2 vs. 3), study site, sex, age group (18-29, 30-64, 65+), race/ethnicity (Non-Hispanic White, Black, Asian American, Hispanic, other), and visit type at which the qualifying PHQ measure was completed (primary care vs. mental health specialty). Previous research and our preliminary data indicate that risk of suicide attempt can be expected to vary by these characteristics, and adjustment for these factors in survival models will account for any imbalance in these factors across randomization groups.

Note regarding intervention uptake or adherence: Consistent with the principles of pragmatic trials, this effectiveness trial intends to address a policy question regarding effectiveness: Should health systems implement population-based outreach programs to reduce risk of suicide attempt? In such a trial, analyses must be based on initial assignment or intent-to-treat, regardless of any participant's receipt of any intervention services. Among participants assigned to intervention conditions, those who actively engage in all intervention services,

those who never actively engage in interventions, and those who drop out of intervention services must still be considered as assigned to the intervention condition. Intervention drop-out or non-adherence is not considered a threat to validity but a valid indicator of real-world effectiveness (i.e. effectiveness = efficacy times reach). As discussed in section 16 below, low rates of intervention uptake or high rates of drop-out would be expected to reduce effectiveness. DSMB monitoring should evaluate whether rates of intervention uptake or drop-out indicate that effectiveness or benefit of either intervention program is not plausible.

- **Power analysis**

Availability of detailed data from study sites regarding patients meeting proposed eligibility criteria allows us to base sample size estimates on simulations using observed data. This approach, which is similar to the bootstrap, enabled us to estimate power in a population with event rates, censoring distributions, and covariate patterns expected in the actual study sample. Proposed eligibility criteria identified 4,643 patients with item 9 scores equal to 3 and another 5,661 with item 9 scores equal to 2 in 2012. Records identified 670 suicide attempts over an 18 month follow-up period. We first estimated the baseline hazards and covariate effects using a proportional hazards model to describe events in these complete datasets, including patient level covariates: item 9 PHQ score (2 or 3), site (HP,GH,KPCO, KPNW), age (18-29,30-64,65+), sex, race/ethnicity (Black American, Asian American, Hispanic, other), and visit type (primary care vs. specialty). Next, we simulated trial data under 8 scenarios (intervention and control sample sizes equal to 5000, 6000, 7000, and 8000; and hazard ratios equal to 0.75 and 1.0), simulating 1000 trials for each scenario. To generate these data, we randomly selected patients from the complete dataset, with replacement, into intervention and control groups of specified sizes. When a patient with an observed event was selected (so that there was no censoring time), we randomly selected a censoring time from patients with no event who had the same covariate distribution (i.e., "hot deck" imputation). Next, we simulated events for each patient in the simulated trial using an inverse-probability look-up using the cumulative hazard based on the estimated baseline hazards combined with observed covariates and estimated covariate effects, observed censoring times, and simulated treatment group and proposed treatment effects. For each simulated dataset, we estimated both adjusted and unadjusted treatment effects using a proportional hazards model. The estimated power and alpha level (false positive rate) are based on the proportion of times an intervention effect is detected if the true hazard ratio is 0.75 (the smallest effect we would hope to detect) or 1.0 (no true intervention effect). As shown in the table below, a sample of approximately 6500 per group (19,500) should allow at least 80% power to detect a hazard ratio of 0.75 or smaller with a false positive rate of 5%.

Number per group	Hazard Ratio	Event rate in usual care	Event rate in intervention	Power unadjusted	Power adjusted for covariates
5000	0.75	0.032	0.024	0.685	0.686
6000	0.75	0.033	0.024	0.764	0.772
7000	0.75	0.033	0.024	0.818	0.821
8000	0.75	0.033	0.024	0.868	0.869
5000	1.00	0.032	0.032	0.059	0.057
6000	1.00	0.032	0.033	0.040	0.042
7000	1.00	0.033	0.033	0.056	0.052
8000	1.00	0.032	0.032	0.041	0.038

9. Human Subjects Protection

- **Subject selection** – As described above, potential participants will be identified automatically from health system records of PHQ9 depression scores. All eligible participants will be included without respect to sex, race, and ethnicity. Children under 18 will not be included, because the proposed interventions are not appropriate for children under 18. Those aged 18 and over will be included without respect to age.
- **Justification for exclusion of children** – The proposed interventions are not clinically appropriate for children under age 18.
- **Justification for exclusion of other vulnerable subjects -** Potential participants who appear to lack capacity to consent (because of diagnosis of dementia or developmental delay) will be excluded.
- **Qualifications of investigators**

Gregory Simon MD MPH will serve as overall Principal Investigator for the project and as Lead Investigator for the Group Health site. Dr. Simon is a psychiatrist and mental health services researcher with extensive experience in the design, implementation, and evaluation of organized care programs for people with mental health conditions. Dr. Simon will assist Dr. Ludman (below) in the training and monitoring of intervention program clinicians at all sites, will participate in supervision of intervention clinicians at the Group Health site, and will serve as primary clinical liaison to Group Health mental health and primary care leadership regarding study procedures and activities.

Evette Ludman PhD will serve as co-investigator at the Group Health site. Dr. Ludman is a clinical psychologist with extensive experience in the design, implementation, and evaluation of organized care programs for people with mental health conditions. She has specific expertise in the training and supervision of clinicians providing telehealth interventions in multi-site studies. Dr. Ludman will lead the training and monitoring of intervention program clinicians at all sites and will lead clinical supervision of intervention clinicians at the Group Health site.

Rebecca Rossom MD will serve as lead investigator for the HealthPartners site. Dr. Rossom is a psychiatrist and mental health researcher with expertise in the implementation and evaluation of organized care programs for people with mood disorders, especially those based in primary care. She practices psychiatry in the HealthPartners Medical Group. Dr. Rossom will lead clinical supervision of intervention clinicians at the HealthPartners site and will serve as primary clinical liaison to HealthPartners mental health and primary care leadership regarding study procedures and activities.

Arne Beck PhD will serve as lead investigator for the KP Colorado site. Dr. Beck is a mental health services researcher with extensive experience in the implementation and evaluation of organized care programs for depression. Dr. Beck will serve as the primary liaison to the KP Colorado mental health and primary care leadership regarding study procedures and activities. Because Dr. Beck is not a practicing clinician, David Price MD will lead clinical supervision of intervention clinicians at the KP Colorado site.

Gregory Clarke, PhD will serve as lead investigator for the KP Northwest site. Dr. Clarke is a mental health services researcher with extensive experience in the implementation and evaluation of organized care programs for depression. Dr. Clarke will serve as the primary liaison to the KP Northwest mental health and primary care leadership regarding study procedures and activities. Because Dr. Clarke is not a practicing clinician, TBD, MD will lead clinical supervision of intervention clinicians at the KP Northwest site.

10. Anticipated Benefit

- Direct benefit - The Care Management and Skills Training programs are reduced-intensity versions of interventions previously proven effective in high-risk populations. We hope that these programs will have direct benefit to participants, but that benefit is not proven. Consequently, no benefit will be promised, and participants will be clearly informed that benefits of the programs are not proven.

- Indirect benefits – The proposed research would be the first randomized evaluation of population-based secondary or selective prevention programs to reduce risk of suicide attempt. The programs to be tested were designed to maximize potential for rapid dissemination (minimizing cost and utilizing existing tools embedded in commonly used electronic medical records systems). In addition, data collected during the trial should yield important insights regarding the effectiveness of various outreach strategies and the performance of risk assessment measures.

11. Classification of risk

- All participants are, by definition, at increased risk of suicide attempt. But the research does not involve more than minimal risk.

  For the Usual Care group – Each participant will receive the same care s/he would have received if the study had not occurred. The only potential risk to participants is the initial use of records data to identify the study sample and the later use of records data to identify suicide attempts.

  For the Care Management and Skills Training intervention groups – Each of the two interventions represents a lower-intensity version of an intervention proven effective for patients at high risk of suicide attempt. Each is based on best-practice recommendations for outreach and follow-up. In both interventions, each participant will be repeatedly advised that intervention participation is voluntary. At any time, participants may decline further intervention contact, and all such requests will be immediately and permanently respected.

  During our pilot phase, investigators formally consulted with the NIH Collaboratory Regulatory and Ethics core and leadership of the Office for Human Research Protection of DHHS regarding risk determination and received notification that proposed procedures

(including pre-consent randomization to intervention groups and alteration of consent for intervention participation) did not create more than minimal risk.

- **Overall risk and benefit consideration –** The minimal risks to participants (described above) are reasonable in relation to the significant potential indirect benefit of the proposed research.

12. Consent documents and process

- **Designation of those obtaining consent** – N/A (see below)

- **Consent procedures**

Following a modified Zelen design, participants will be assigned prior to any contact, and those assigned to one of the active intervention conditions will be offered intervention services. Each participant offered intervention services will be free to accept or decline any element of the intervention program (see Appendix b for consent language in the Care Management intervention invitation and Appendix c for the consent language for the Skills Training intervention invitation). Outcomes (medically treated suicide attempt over up to 18 months following randomization) will be assessed using electronic health system record. Outcomes data will be collected (anonymously) for all randomized participants, regardless of level of intervention participation. Outcomes will be analyzed according to original treatment assignment, regardless of level of intervention participation. We believe waiver of consent for random assignment to the intervention or usual care groups is scientifically necessary and ethically justified.

Regarding scientific necessity: For both of the low-intensity interventions being studied, acceptability to participants and level of continued participation are essential components of real-world effectiveness. If we limited enrollment to those who volunteer to receive prevention interventions, findings regarding intervention acceptability or effectiveness would have questionable validity and limited generalizability. In other words, we cannot study effectiveness of outreach only among those who volunteer to receive it.

Regarding ethical justification: The "Common Rule" for protection of research participants (45 CFR 46.116d) lists specific requirements for waiver of the usual requirement for individual informed consent:

- *The research involves no more than minimal risk to the subjects* – For participants assigned to one of the active intervention conditions, we do not believe that any intervention activities expose participants to greater than minimal risk. Each program is based on best available evidence regarding prevention of suicide attempt. In addition, each participant will be free to engage – or not engage – to the degree s/he finds the program to be helpful. Participants offered any of the active interventions will be free to receive any other service or treatment without restriction. For participants assigned to the usual care control group, treatment will be identical to what would have been delivered had the study not occurred. While

those eligible for the trial are (by definition) at risk, assignment to usual care does not increase risk.

- *The waiver or alteration will not adversely affect the rights or welfare of the subjects* – All study participants (in the usual care group or either of the active intervention groups) will be free to receive any treatment or services normally available. No treatment or service will be restricted or withheld.
- *The research could not practicably be carried out without the waiver* – As discussed above, limiting the trial to those who actively consent to receive outreach would yield an invalid test of effectiveness.
- *Whenever appropriate, the subjects will be provided with additional pertinent information after participation* – In each intervention, outreach communications will clearly identify the program as research and clearly state that participation is voluntary. Participants assigned to the usual care group will not be contacted. For this group, after-the-fact notification that the study occurred would offer no additional protection, and attempting to contact participants would increase risk of violating confidentiality.

We considered and rejected the option of randomizing providers or clinics to intervention or usual care conditions. The proposed interventions are applied at the level of the individual patient, so cross-over or spill-over of intervention effects within clinics or providers should not occur. Because patients seen in specialty mental health care often see multiple providers (psychiatrist and psychotherapist), provider-level randomization could introduce cross-over or contamination.

13. Data and Safety monitoring

- **Local Data and Safety monitoring** – As described in Section 6 above, clinical supervisors at each site will monitor timeliness and appropriateness of Coaches' and Care Managers' outreach and clinical interventions for all high-risk cases (i.e. patients with Columbia risk scores >=4 OR patients spontaneously reporting high risk of self-harm to intervention staff). Each such case will be reported to the local clinical supervisor within two working days. In addition, the Intervention Implementation team (including investigators and health system representatives from each site) will review tabular reports of responses to high-risk cases at each monthly meeting.

- **Independent Medical Monitor-** An independent medical monitor or safety officer will provide ongoing supervision of each site's adherence to intervention protocols, safety monitoring procedures, and good clinical practice. Specific duties of the safety officer will include:
  - Bi-monthly review of all study responses to high-risk cases
  - Bi-monthly review of any protocol violations
  - Participation in preparation of DSMB reports, including review of counts and rates of systematically ascertained suicide attempts and suicide deaths (other study staff will not have access to these reports)

- **DSMB monitoring –** The NIMH DSMB will review study progress three times yearly, with each review to consider:

- Progress in recruitment - Reports to the DSMB will detail overall recruitment progress, progress at each site, and recruitment of identified racial/ethnic minority groups.
- Quality/fidelity of intervention delivery – For participants assigned to the Care Management intervention, reports to the DSMB will include:
    - % declining intervention services at initial invitation
    - % not responding to up to three intervention invitations
    - % withdrawing from intervention services after enrollment
    - % more than 30 days overdue for most recent outreach contact

  For participants assigned to the Skills Training intervention, reports to the DSMB will include:
    - % declining intervention services at initial invitation
    - % not responding to up to three intervention invitations
    - % withdrawing from intervention services after enrollment
    - % more than 30 days overdue for most recent intervention contact
- Quality/fidelity of safety monitoring procedures – As described in section 6 above, reports to the DSMB will include tabular descriptions of timing and outcome of each Care Manager or Coach outreach contact for high-risk cases (i.e. patients with Columbia risk scores >=4 OR patients spontaneously reporting high risk of self-harm to intervention staff). These reports will include:
    - Risk indicator (Columbia Suicide Severity Rating Scale or spontaneous report)
    - Source of risk indicator (online message or telephone)
    - Time from receipt of risk indicator to outreach attempt
    - Study staff response
    - Final resolution

  The DSMB will use these data to assess quality/fidelity of safety procedures and (as indicated) recommend changes to those procedures.
- Evidence of harm (increased risk of suicide attempt) attributable to intervention – As described in section 15 below, reports to the DSMB will include counts and rates for suicide attempts and suicide deaths for participants assigned to all three intervention groups (based on assignment, regardless of actual intervention participation). These interim reports will not include data for participants who actively decline intervention services. The waiver of consent allowing use of these data will only permit access to those data at one time at the end of the trial.

- **Criteria for stopping the study or suspending enrollment or procedures**
- Insufficient progress in recruitment - If recruitment progress reports indicate unsatisfactory progress, the DSMB may choose to suspend overall recruitment or suspend recruitment at a specific study site.
- Inadequate intervention engagement or uptake – If reports indicate that uptake of either intervention is so low that significant effectiveness or benefit is not plausible (i.e. high rate of declining intervention or low rate of engagement/initiation), then the DSMB may choose to suspend delivery of one or both intervention conditions at one or more study sites.

- Inadequate quality/fidelity of intervention delivery – If intervention quality reports indicate significant deficiencies, the DSMB may choose to suspend delivery of one or both intervention conditions at one or more study sites.
- Inadequate quality/fidelity of safety monitoring procedures - If reports regarding safety procedures for high-risk cases indicate significant deficiencies, the DSMB may choose to suspend delivery of one or both intervention conditions at one or more study sites.
- Preliminary evidence of harm from either intervention (when compared to usual care) – If reports regarding suicide attempts and suicide deaths indicate the possibility of harm (increased risk of suicide attempt or death) for either intervention condition, the DSMB may request more formal interim analyses or may choose to either suspend trial recruitment or end randomization to one of the intervention conditions.

14. Quality Assurance

- **Monitoring intervention quality and fidelity –** At each study site, clinical supervisors will provide direct supervision for Coaches and Care Managers through weekly supervision meetings, including review of reports regarding all high-risk cases. Across all sites, monthly implementation team meetings (including investigators and health system leaders from each site) will review reports of quality metrics for each intervention program (described in section 14 above).

- **Monitoring compliance with high-risk outreach procedures** – As described in sections 6 and 13 above, all instances of outreach to high risk cases (participants with Columbia risk scores of 4 or 5 and those spontaneously reporting high risk) will be reviewed by site clinical supervisors within two working days and by the independent medical monitor within 15 days. Summary reports of these events reviewed monthly by the cross-site intervention implementation committee.

- **Monitoring quality of outcome data –** The Mental Health Research Network (in which all 3 study sites participate) conducts regular quality assessment regarding health system data for key mental health diagnosis and treatment indicators (including rates of suicide attempt and suicide death).

15. Adverse event and unanticipated problem reporting

Availability of Data Regarding Expected Adverse Events – In contrast with adverse event data collected and reported by traditional clinical trials, data regarding adverse events in this pragmatic trial will be limited in detail and delayed in time. Data regarding diagnoses of probable or possible suicide attempts (see section 7 above) and suicide deaths will be periodically extracted from health system administrative databases regarding encounter diagnoses and insurance claims. Given that these data are collected under a waiver of consent and waiver of HIPAA authorization, investigators are only allowed to extract and store the minimum information necessary to address study hypotheses. Consequently these data will be limited in detail. Because insurance claims data may be submitted up to three months following a health care encounter, data regarding suicide attempt diagnoses from insurance claims may be delayed by up to three months. Because suicide

deaths are most often identified by linkage with state death certificate data, data regarding suicide deaths may be delayed by several months.

Definition and Reporting of Serious Adverse Events (SAEs)– All suicide attempts (regardless of potential lethality or perceptions of "suicidal intent") will be considered serious adverse events. Only SAEs identified through the health system administrative databases will be reviewed by the independent Medical Monitor and reported to the DSMB. The only data available from the data extraction regarding each of these events will include: group assignment, time since randomization, and 3-level severity rating (fatal attempt, nonfatal attempt resulting in hospitalization, nonfatal attempt not resulting in hospitalization). Over the course of the study, these data will be available for all randomized participants, regardless of group assignment or level of participation in either intervention program – excluding those who actively decline participation in the intervention programs. Reports to the DSMB will include a tabular description of the number, rates, types, and timing of events in each of the three treatment groups. These interim reports will not include data regarding participants who actively decline intervention services. Because outcome data for that group are obtained under waiver of consent, access to those data is limited a single data extraction at the end of the study period.

Definition and Reporting of Other Adverse Events – Potential adverse events not rated as serious (e.g. inadvertent violation of privacy, participant report of distress or upset due to intervention procedures) will be recorded by intervention clinicians and reported to the DSMB in tabular form. Given known differential ascertainment across treatment groups (more frequently in the Care Management intervention group, less frequently in the Skills Training intervention group, not at all in the Usual Care group) any comparison of event rates or event characteristics across treatment groups would be irretrievably biased and uninterpretable.

Reporting Responses to High-Risk Cases – As described in sections 6 and 13 above, reports to the DSMB will include tabular descriptions of intervention clinician (Care Manager or Coach) response to each high-risk case, including:

- Initial risk indicator (scheduled Columbia Suicide Severity Rating Scale or spontaneous report to study staff)
- Source of risk indicator (online message or telephone)
- Time from receipt of risk indicator to outreach attempt
- Study staff response
- Final resolution (e.g. urgent visit scheduled and attended, patient declined suggestion of urgent visit, etc.)

As described in sections 13 and 14 above, the DSMB will use these data to assess quality/fidelity of safety procedures and (as indicated) recommend changes to those procedures. As explained in section 6 above, these high risk scenarios will be identified more frequently in the Care Management intervention group, less frequently in the Skills Training intervention group, and not at all in the Usual Care group. Consequently, any

comparison of event rates or characteristics across treatment groups would be irretrievably biased and uninterpretable.

Reporting Unanticipated Problems – In addition to adverse events described above, any other unanticipated problems (e.g. significant deviations from the study protocol) will be reported to the independent Medical Monitor and responsible IRBs within 7 days and to the DSMB within 15 days.

16. Alternatives to participation

The Care Management and Skills Training interventions are intended as supplements to (not replacements for) ongoing care by treating mental health and primary care providers. Each participant offered either of the interventions will be free to (and will be encouraged to) continue to receive any care s/he finds helpful. No treatment normally available will be withdrawn or withheld.

Participants assigned to usual care will not be contacted, and treating providers will not be notified. Each participant will receive the care s/he would have received if the study had not occurred. No treatment normally available will be withdrawn or withheld.

For all participants, health system records will be used to anonymously extract data regarding medically treated suicide attempts over up to 18 months following randomization.

17. Confidentiality

- **For research data and investigator medical records** (repeated from #5 above)

At each site, electronic health records will be used to identify participants (described above) and assess outcomes (described below). The study programmer/analyst at each site will maintain a list of participant identifiers linked to study identifiers. These lists will be stored in password-protected directories in each health system's HIPAA/HITECH compliant computer networks. Identifiable information will only be available to study staff with clear need to know (programmer/analysts and intervention clinicians). Identifying information will not be shared across sites. Analytic datasets will be completely de-identified (including appropriate procedures to prevent backwards-identification). All identifying information will be discarded once final analytic files are created.

Information used for delivery of the Care Management intervention will be stored within the electronic health records of each healthcare system and will be protected by the same technical safeguards and policies/procedures that protect the privacy of participants' other medical record information.

The online Skills Training program will not receive or store any identifiable information. Within that program, each participant will be identified only by a study identifying number.

Consistent with the NIH Collaboratory data-sharing policy, an appropriately de-identified analytic dataset will be made available to any interested investigators no later than the acceptance for publication of the manuscript describing primary trial results. Summary results will also be posted on clinicaltrials.gov.

20. Conflict of Interest

a. Distribution of NIH Guidelines

NIH guidelines on conflict of interest have been distributed to all investigators.

b. Conflict of interest

Investigators have no conflicts of interest or relevant financial interests.

c. Role of a commercial company or sponsor – N/A

21. Technology Transfer and Data Sharing

Consistent with the NIH Collaboratory resource sharing policy, all intellectual property or technology resources developed by this project (e.g. computer code, intervention algorithms) will be placed in the public domain and will be freely shared with any investigators or health systems following completion of the trial.

We anticipate that the Collaboratory Coordinating Center may create a common process and platform for sharing of data created by all Collaboratory UH2/UH3 projects. If no such process is established, then we propose the following process for this specific project:

- Data will be distributed through the public website of the Mental Health Research Network (described above)
- Those downloading specific datasets will be asked to briefly describe the intended use of data (in order to document dissemination efforts and inform future dissemination activities)
- We will request (but we cannot strictly require) that users acknowledge the role of NIH funding in any publications or presentations using project data

We describe below plans for distributing data regarding specific outcomes (and plans for protecting privacy of potentially identifiable information).

- Datasets for primary analyses will be freely shared with any interested researcher or member of the public using an unsupervised public data archive model. Data will be available no later than publication data of primary study findings. This person-level dataset will include the following variables:
  - Time to suicide attempt or death
  - Time to censoring for disenrollment or death from other cause
  - Age group
  - Sex
  - Race/ethnicity
  - Site of care (mental health specialty, primary care, other)

  - Treatment history (current or past depression or other mental health treatment)
  - Year of enrollment
  - Intervention assignment (Skills Training, Risk Assessment/Care Management, Usual Care)

  We do not propose to include study site (health system) in this publicly available dataset given concerns by participating health systems that such data could be used for inappropriate comparisons of suicide attempt rates across health systems. We acknowledge the importance of examining variation in intervention effects across health systems, and datasets including health system identifiers will be available on request, following a supervised data archive, subject to specific agreements regarding use and re-disclosure.
- The above-described public-use datasets will also contain time-to-event variables for proposed broader definitions of suicide attempt (psychotropic drug poisoning, open wound or poisoning, any injury or poisoning).
- We do not plan to release any data regarding suicide death. First, the anticipated number of suicide deaths will be too small to support any meaningful conclusions regarding intervention effects. Second, data regarding dates and cause of death may be available through other sources (e.g. state vital records), allowing potential re-identification of study participants.
- Person-level datasets regarding use and costs of specific health services could also allow backward-identification of study participants. But study data regarding these outcomes may have scientific or public health value to other investigators. Consequently, we will make such datasets available at the time study findings in this area are published. But those datasets will be available only upon request and will be subject to formal agreements regarding protection of privacy and re-disclosure (i.e. supervised data archive model).

All datasets for public distribution will completely satisfy HIPAA standards for de-identification. Consequently no data use or data transfer agreements will be required.

22. Research and Travel Compensation

No compensation or reimbursement will be offered.

23. Governance Plan

Trial Steering Committee – The Steering Committee will supervise all scientific and administrative aspects of the proposed trial. Members will include the overall lead investigator (Simon), investigators from each study site (Beck, Rossom, Ludman) and one or more NIMH program representatives. The Committee will meet (by teleconference) monthly across all project years to review: implementation of study procedures, progress of recruitment, delivery of interventions, quality of outcome data, and data analysis. This team of investigators has an extensive history of successful collaboration through the NIMH-funded Mental Health Research Network, including recent completion of a 4-site effectiveness trial of behavioral activation psychotherapy for depression in pregnancy.

Group Health Research Institute Management Team – The GHRI project managers (Richards and Kirlin) and overall lead investigator (Simon) will be responsible for administrative operations including:

- Financial management, including monitoring of budgets and spend rates at all sites
- Regulatory compliance, including human subjects and privacy protection
- Communication, including scheduling and reporting of other committee and team meetings

Intervention Implementation Committee – Continuing the work of the Healthcare System Engagement Committee in the UH2 phase, the Intervention Implementation Committee will supervise quality and fidelity of intervention implementation across all study sites. Members will include mental health delivery system representatives from each study site, lead investigators from each study site, and the overall lead investigator. The committee will meet (by teleconference) monthly during months 1 through 24 and bimonthly thereafter. Members of this committee will also serve as liaisons to mental health, primary care, and informatics leaders in each study site.

DBT Skills Implementation Team – Drs. Ludman and Whiteside will meet (by teleconference) regularly with coaches from each site. Meetings will occur biweekly in months 3 through 18 and monthly thereafter. This group will be the primary venue for administrative and clinical supervision of coaches supporting the online DBT skills training program. As described in the Progress Report / Transition Request, this meeting will include structured review of specific indicators of the quality and fidelity of intervention implementation as well as coach-initiated review of specific cases. Meeting organization will follow the format used successfully by Drs. Simon and Ludman in several previous trials of coaching and care management interventions delivered by telephone and online messaging.

Risk Assessment/Care Management Implementation Team - Dr. Ludman and Ms. King will meet (by teleconference) regularly with care managers from each site. Meetings will occur biweekly in months 3 through 18 and monthly thereafter. This group will be the primary venue for administrative and clinical supervision of care managers supporting the Risk Assessment / Care Management intervention. As described in the Progress Report / Transition Request, this meeting will include structured review of specific indicators of the quality and fidelity of intervention implementation as well as care manager-initiated review of specific cases. Meeting organization will follow the format used successfully by Drs. Simon and Ludman in several previous trials of coaching and care management interventions delivered by telephone and online messaging.

Data Quality and Analysis Team – This group, including Drs. Simon, Shortreed, and Penfold, will be responsible for ongoing monitoring of study data quality during months 1 thru 42. The team will meet quarterly during this period to monitor:

- Rates of use and patterns of response for PHQ depression questionnaires in participating health systems
- Background rates of diagnoses of suicide attempts in participating health systems
- Changes in coding practices that might affect ascertainment of suicide attempts

This group will also lead data analysis during months 42 through 48 – when meetings will be merged with those of the Steering Committee.

IRB Oversight – The Group Health Cooperative IRB will have primary responsibility for initial and continuing review of all study procedures and study execution. The IRB will review and approve all clinical protocols and invitation/consent messages (included as attachments to this DSMB protocol). Any unanticipated problems will be reported to this IRB within 7 days. Any unexpected adverse events (as described above) will be reported at each annual review. Annual reviews will evaluate progress toward recruitment goals, successful delivery of intervention programs, and adherence to safety monitoring procedures.

The trial will report to the NIMH Data and Safety Monitoring Board rather than to a locally-constituted DSMB. The NIMH DSMB will conduct:

- Initial review of all study procedures and materials
- Detailed annual review of study progress (including review of recruitment progress and adverse events)
- Additional twice-yearly abbreviated review of study progress (including review of adherence to safety monitoring procedures as described above)
- Reviews of unanticipated problems that will be reported to the DSMB within 15 days.

Matrix Relationships – The overall lead investigator (Simon) and Steering Committee will make regular reports on trial progress to:

- NIMH Program and Operations Staff
- The Healthcare Systems Collaboratory Pragmatic Trials Steering Committee
- The Mental Health Research Network Steering Committee

24. Key References

References regarding Zelen design:

Zelen M. A new design for randomized clinical trials. N Engl J Med. 1979;300(22):1242-5.

Zelen M. Randomized consent designs for clinical trials: an update. Stat Med. 1990;9(6):645-56.

Adamson J, Cockayne S, Puffer S, Torgerson DJ. Review of randomised trials using the post-randomised consent (Zelen's) design. Contemp Clin Trials. 2006;27(4):305-19.

Ellenberg SS. Informed consent: protection or obstacle? Some emerging issues. Control Clin Trials. 1997;18(6):628-36; discussion 61-6.

References regarding use of Zelen design in studies of suicide prevention programs:

Carter GL, Clover K, Whyte IM, Dawson AH, D'Este C. Postcards from the EDge: 24-month outcomes of a randomised controlled trial for hospital-treated self-poisoning. Br J Psychiatry. 2007;191:548-53.

Hatcher S, Coupe N, Durie M, Elder H, Tapsell R, Wikiriwhi K, Parag V. Te Ira Tangata: a Zelen randomised controlled trial of a treatment package including problem solving therapy compared to treatment as usual in Maori who present to hospital after self harm. Trials. 2011;12:117. PMCID: PMC3103449.

Hatcher S, Sharon C, House A, Collings S, Parag V, Collins N. The ACCESS study a Zelen randomised controlled trial of a treatment package including problem solving therapy compared to treatment as usual in people who present to hospital after self-harm: study protocol for a randomised controlled trial. Trials. 2011;12:135. PMCID: PMC3117717.

25. **Attachments/Appendices**

a. Study Diagram
b. Invitation/Consent language for Risk Assessment Intervention
c. Invitation/Consent language for Skills Training Intervention
d. Detailed protocol for Risk Assessment Intervention
e. Detailed protocol for Skills Training Intervention