Ethics/Regulatory Call with Dr. Simons' Demonstration Project – Suicide Prevention
Date: May 17, 2013
MINUTES

Participants:

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☒	Rob Califf (Duke)	☒	Irene Stith-Coleman (OHRP)	☒	Tammy Reece (Coord Center)	☐	
☒	Greg Simon (Group Health)	☒	Jane Pearson (NIH)	☒	Cheri Janning (Coord Center)	☐	
☒	Barbara Young (Group Health, IRB)	☒	Dave Chambers (NIH)	☐		☐	
☒	Tonya Matthews (Group Health)	☒	Catherine Meyers (NIH)	☐		☐	
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These minutes were circulated to all participants on the call for two rounds of review and they reflect all corrections that were received.

AGENDA ITEMS	DISCUSSION	ACTION ITEM
Review of Demonstration Project	• Dr. Simon gave an overview of the Suicide Prevention project. All eligible patients will be randomly assigned in equal proportions (1:1:1) to either of the two prevention intervention conditions or to continued usual care (control). Following a modified Zelen design, participants will be assigned automatically at the time that eligible participants are identified prior to obtaining consent; those assigned to either of the active intervention conditions will be asked to consent to participation. Outcomes will be analyzed according to original treatment assignment, regardless of willingness to accept either intervention	

	and regardless of level of intervention participation. • The study will enroll approximately 16,000 adults whose responses to item 9 of the PHQ depression scale (regarding thoughts of death or suicide) indicate elevated risk. • Centers involved include: Group Health Cooperative, the University of Washington, the University of Pittsburgh, Health Partners, and Kaiser Permanente Colorado. • Trial design: Participants will be randomly assigned to one of three arms: usual care (UC); UC plus online interactive program and coaching; or UC plus systematic outreach for structured risk assessment. • Primary endpoint: Suicide attempt (fatal or nonfatal) in the year following enrollment. • IRB approval has been obtained for UH2 and UH3 phases. • No concerns were raised about the trial design.	
Minimal risk	• Regarding the use of medical records information to identify participants, Dr. Simon indicated that this falls within the definition of minimal risk, as these data are collected and recorded during healthcare encounters. • Dr. Simon stated that none of the interventions are believed to expose participants to greater than minimal risk. Although the interventions differ in intensity and mode of delivery, each is based on best available evidence regarding the prevention of suicide attempts. • For participants assigned to the UC control group, treatment will be identical to what would have been delivered had the study not occurred. • No treatment or intervention will be restricted or withheld, and treating providers will still be responsible for any assessment and follow-up care they would normally provide.	

	• No concerns were raised about a minimal risk determination for this study.	
Consent (patient and physician)	• The project is requesting waivers of consent for: assignment to usual care or one of the intervention groups; participation in the usual care group; and access to health records to ascertain outcomes. In addition, the project is requesting a waiver of documentation of consent for participation in either of the intervention groups. • These waivers or alteration will not adversely affect the rights or welfare of the subjects. Study participants (in the UC group or either intervention group) will be free to receive any treatment or services that are normally available. • In each of the intervention conditions, the initial contact with each participant will clearly identify this as a research activity and will clearly state that participation is voluntary. Participants assigned to the UC 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 the risk of violating confidentiality. • The research could not practicably be carried out without the waiver or alteration. • No concerns were raised regarding the planned waivers of consent or waivers of documentation of consent.	• Additional information regarding the consent process will be sent to OHRP to help clarify consent issues.
HIPAA	• The study is using a closed data system. • Dr. Simon believes that criteria for 45 CFR 164.512 are satisfied and that a waiver of HIPAA is acceptable. No concerns were mentioned.	

Monitoring and oversight	• Study intervention is one and the same with safety monitoring. • The study will not have much power until enrollment is halfway completed; this would probably be an appropriate point to start systematically reviewing safety data. • Concerns were raised about the need for a systematic and objective review for safety.	• The study will require a Data and Safety Monitoring Plan, which will be developed by the study team, and approved by NIMH prior to study implementation. NIMH will determine the level of independent oversight appropriate for the project, and whether a DSMB will be appointed for trial oversight.
Issues beyond the Suicide Prevention Trial	• None voiced.	
Conclusion of meeting	• Follow-up needed as noted in action items.	• A case study will be drafted to provide guidance for others on the process and value of open dialogue with regulators.

SUPPLEMENTARY MATERIAL
FOR SUICIDE PREVENTION TRIAL

All eligible patients will be randomly assigned in equal proportions (1/3 – 1/3 – 1/3) to either of the two prevention intervention conditions or to continued usual care. This assignment will occur automatically at the time that eligible participants are identified (as described above). Following a modified Zelen design (Zelen 1979; Zelen 1990; Ellenberg 1997; Adamson, Cockayne et al. 2006; Carter, Clover et al. 2007; Hatcher, Sharon et al. 2009; Hatcher, Coupe et al. 2011; Hatcher, Sharon et al. 2011; Hatcher, Sharon et al. 2011), participants will be assigned prior to obtaining consent, and those assigned to one of the active intervention conditions will be asked to consent to intervention participation. Outcomes will be analyzed according to original treatment assignment, regardless of willingness to accept either intervention and regardless of level of intervention participation. As we discuss above, this approach (pre-consent randomization) may raise ethical concerns. We believe, however, that such an approach is both scientifically necessary and ethically justified (Ellenberg 1997; Adamson, Cockayne et al. 2006; Hatcher, Sharon et al. 2009; Sim and Dawson 2012).

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 trial enrollment to those who volunteer to receive prevention interventions, any findings regarding intervention acceptability or adherence would have no scientific value. And any findings regarding intervention effects on the primary outcome would have questionable validity and limited generalizability.

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

- *The research involves no more than minimal risk to the subjects* – According to 45CFR46.102: "*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."
  - Regarding the use of medical records information to identify participants – This falls clearly within the definition of minimal risk as these data were collected and recorded during health care encounters.
  - Regarding the assignment of potential participants to different treatment groups – We must separately consider how this definition of minimal risk applies to the active interventions and to the usual care control condition. For participants assigned to one of the active intervention conditions, we do not believe that any of the interventions expose participants to greater than minimal risk. While the interventions differ in intensity and mode of delivery, each is based on best available evidence regarding prevention of suicide attempt. In addition, engagement in any intervention activities will be completely voluntary. 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. Consequently, we do not believe that receiving an offer to participate in either programs involves more than minimal risk (as defined by 45CFR46). For participants assigned to the usual care control group, treatment will be identical to what would have been delivered had the study not occurred. No treatment or intervention will be restricted or withheld, and treating providers will still be responsible for any assessment and follow-up care they would normally provide. While those eligible for the trial are (by definition) at risk, assignment to the usual care group does not increase risk beyond what would have existed if the trial had not occurred. We should emphasize that ***the proposed trial does not involve randomly assigning patients at risk of suicide attempt to a no-treatment control group***. Instead, it involves assignment to a control group that will receive exactly the same treatment that would have otherwise occurred.
- *The waiver or alteration will not adversely affect the rights or welfare of the subjects* – All study participants (in the usual care group or any 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. Participation in study activities will have no effect on insurance benefits or access to usual care.

- *The research could not practicably be carried out without the waiver or alteration* – As discussed above, a trial of selective prevention limited to those who actively consent to receive prevention interventions would have little to no scientific value.
- *Whenever appropriate, the subjects will be provided with additional pertinent information after participation* – In each of the intervention conditions, the initial contact with each participant will clearly identify this as a research activity and will clearly state that participation is voluntary. Details regarding this notification/consent process are described below. 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.

In the attached section regarding protection of human subjects, we provide additional detail regarding justification for the proposed waivers of consent and also describe procedures for monitoring and protecting participant safety.

We considered and rejected the option of group- or cluster-level randomization (such as randomizing providers or clinics to intervention or usual care conditions). The proposed interventions are applied at the level of the individual patient rather than the provider or clinic, so cross-over or spill-over of intervention effects within clinics or providers should not occur. Consequently, there is no scientific advantage in cluster-level randomization. Cluster-level randomization could, however reduce statistical power. While cluster-level randomization would seem to avoid ethical concerns regarding pre-consent randomization, it only obscures (rather than resolves) the ethical concern. Cluster-level randomization still implements randomization prior to informed consent, it simply does so in a less obvious way. For the same reason, we do not propose any community consent procedure. Such a procedure might obscure the ethical issue (pre-consent randomization) but would not actually offer additional protection to those eligible for the study(Sim and Dawson 2012).

Adamson, J., S. Cockayne, et al. (2006). "Review of randomised trials using the post-randomised consent (Zelen's) design." Contemp Clin Trials **27**(4): 305-19.

Carter, G. L., K. Clover, et al. (2007). "Postcards from the EDge: 24-month outcomes of a randomised controlled trial for hospital-treated self-poisoning." Br J Psychiatry **191**: 548-53.

Ellenberg, S. S. (1997). "Informed consent: protection or obstacle? Some emerging issues." Control Clin Trials **18**(6): 628-36; discussion 661-6.

Hatcher, S., N. Coupe, et al. (2011). "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 **12**: 117.

Hatcher, S., C. Sharon, et al. (2009). "Beyond randomized controlled trials in attempted suicide research." Suicide Life Threat Behav **39**(4): 396-407.

Hatcher, S., C. Sharon, et al. (2011). "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 **12**: 135.

Hatcher, S., C. Sharon, et al. (2011). "Problem-solving therapy for people who present to hospital with self-harm: Zelen randomised controlled trial." Br J Psychiatry **199**(4): 310-6.

Sim, J. and A. Dawson (2012). "Informed consent and cluster-randomized trials." Am J Public Health **102**(3): 480-5.

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

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

SPECIFIC AIMS FOR UH2 PLANNING PHASE

Suicide ranks 10th among all causes of mortality in the US, accounting for over 38,000 deaths in 2010. Suicide attempts result in 600,000 emergency room visits and nearly 200,000 hospitalizations each year. Reducing this potentially preventable morbidity and mortality is a public health priority.

While evidence supports both universal (or primary) prevention programs and indicated (or tertiary) prevention programs, no effective selective (or secondary) prevention programs have been identified. Developing and testing effective selective prevention strategies would address the most important gap in a multi-level suicide prevention strategy. Recent developments create a new opportunity 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 allows 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.

We propose a large, pragmatic trial to examine two specific selective prevention programs. Both programs are based in a re-conceptualization of suicidal ideation as an enduring vulnerability rather than a short-term crisis. The trial would be conducted in 3 or more large, integrated health care systems. We propose to enroll approximately 16,000 adults for whom responses to item 9 of the PHQ depression scale (regarding thoughts of death or suicide) indicate elevated risk. Participants will be randomly assigned to continued usual care or to usual care plus one of the two prevention programs:

- A systematic outreach and care management program including structured assessment linked to specific care pathways. The program would be based on successful suicide prevention efforts Henry Ford Health System. The assessment component would be derived from the Columbia Suicide Severity Rating Scale. Outreach and care management protocols would follow those developed by the Group Health research team.
- An online psychoeducational program focused on development of emotion regulation skills, supported by personalized coaching to promote engagement and adherence. The online program will focus on specific Dialectical Behavior Therapy (DBT) skills shown to mediate the effect of DBT on preventing suicide attempts.

Both programs are supplements to usual care - in addition to any immediate risk assessment or treatment provided by primary care or mental health providers. Both programs will capitalize on existing electronic records systems to improve efficiency and assure quality. The primary outcome will be suicide attempt (fatal or non-fatal) during the year following enrollment – ascertained automatically from computerized records.

The proposed trial will confront several significant challenges, including:

- Protecting human subjects while preserving scientific integrity
- Addressing health system concerns regarding risk management and liability
- Developing consensus across health systems regarding risk assessment and care management processes
- Integrating preventive interventions with ongoing clinical care
- Making interventions accessible to a diverse and geographically dispersed population
- Delivering interventions at a cost acceptable to health system stakeholders
- Relying on computerized health system records for ascertainment of outcomes

We propose a one-year planning phase to address these challenges and evaluate the feasibility of study procedures and the proposed prevention programs. Specific aims of the planning phase include:

- Obtain IRB approval for preparatory activities
- Test and refine procedures for identifying potential study participants from electronic medical records
- Refine study eligibility criteria to maximize efficiency
- Test and refine procedures for ascertaining suicide attempts from electronic health system records
- Develop and field-test a brief online intervention to develop emotion regulation skills
- Develop and test a structured program of suicide risk assessment and risk-based care management
- Engage with health system leaders regarding best practices for intervention implementation
- Revise interventions based on stakeholder input and findings of feasibility testing
- Implement intervention delivery tools in existing electronic medical records systems

- Develop protocols and tools for monitoring intervention quality
- Obtain IRB approval for the multi-site pragmatic trial

SPECIFIC AIMS FOR IMPLEMENTATION (UH3) PHASE

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. Reducing this potentially preventable morbidity and mortality is a public health priority.

Recent developments create a new opportunity 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 structure 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 a nationwide infrastructure large enough to adequately evaluate population-based selective prevention.

We identify two distinct approaches to selective prevention of suicide attempt. This first (exemplified by the successful suicide prevention program at the Henry Ford Health System) focuses on more accurate assessment of risk and establishment of standard treatment pathways for high-risk patients. The second (exemplified by the Dialectical Behavior Therapy or DBT treatment developed by Marsha Linehan) focuses on patient-centered interventions to develop emotional regulation skills.

We propose a large, pragmatic trial to examine two specific selective prevention programs. Both programs are based in a re-conceptualization of suicidal ideation as an enduring vulnerability rather than a short-term crisis. The trial would be conducted in 3 or more large, integrated health care systems. We propose to enroll approximately 16,000 adults for whom responses to item 9 of the PHQ depression scale (regarding thoughts of death or suicide) indicate elevated risk. Participants will be randomly assigned to continued usual care or usual care plus one of the two prevention programs:

- A systematic outreach and care management program (via secure messaging and telephone) including structured assessment linked to specific care pathways. Program structure and content will be based on a model successfully implemented at Henry Ford Health System. The assessment component will be informed by the recently developed Columbia Suicide Severity Rating Scale. Recommended care pathways will include specific guidance regarding type and timing of recommended service (e.g. in-person evaluation by specialty mental health provider within 7 days). Electronic medical records will be used to support and monitor intervention quality. Outreach and assessment will continue through the one-year intervention period, with frequency depending on risk level.
- An online psychoeducational program focused on development of emotion regulation skills and prevention of suicidal behaviors, supported by coaching to promote engagement and adherence. The online program will incorporate the specific skills components of DBT that have been shown to mediate treatment effects on suicidal behaviors. This content will be delivered via 4 online sessions including video demonstrations and interactive exercises. Based on previous research with online interventions, we anticipate that coaching support will be necessary to promote initial engagement and continued participation. This coaching will be delivered by telephone and/or secure online messaging following a specific motivational enhancement protocol.

Both programs are supplements to usual care - in addition to any immediate risk assessment or treatment provided by primary care or mental health providers. Both programs will capitalize on existing electronic records systems to improve efficiency and assure quality. The primary outcome will be suicide attempt (fatal or non-fatal) during the year following enrollment – ascertained automatically from computerized records.

A pragmatic trial of selective prevention of suicide attempts would fill a major gap in current suicide prevention efforts. Methods developed through such a trial could dramatically accelerate suicide prevention research.

The proposed research also is completely consistent with the principles of pragmatic trials, including:

- Population-based identification of study participants using health system records
- Automated assignment to intervention or usual care groups – regardless of motivation to receive intervention
- Flexible and scalable interventions suitable for delivery to diverse, geographically dispersed populations
- Comparison to current usual practice
- Simple and generalizable models for intervention delivery and quality control

- Comparisons based on initial group assignment, regardless of intervention participation
- Population-based outcome ascertainment using computerized health system records