The Challenge of Clinical Research and Suicidality: Participant Feedback on a Safety Protocol

Rachel Vanderkruik, PhD, MSc[a,*]; Marlene P. Freeman, MD[a]; Katherine A. Dunn, BS[a]; Charlotte A. Clifford, BA[a]; Sona Dimidjian, PhD[b]; and Lee S. Cohen, MD[a]

ABSTRACT

Objective: Clinical studies of depression have historically excluded participants with suicidal ideation. Research participant safety protocols are critical to allow for the much-needed study of suicide risk. This report summarizes participant feedback about the safety protocol used in a national, remote study of perinatal women with suicidal ideation.

Methods: Upon completion of the study, participants who had triggered the suicidality safety protocol during the study were invited to complete a brief survey with questions about their experiences with the protocol. The survey included 4 Likert-scale questions and 1 open text question where participants could provide feedback, suggestions, and comments to the research team. Participant feedback survey data were collected between October 2021 and April 2022, and this research was funded by the National Institute of Mental Health.

Results: Of the 45 participants enrolled in the UPWARD-S study, 16 triggered the safety protocol. All eligible participants (N = 16) completed the survey. Among respondents, most were at least neutral to very comfortable with the call from the study psychiatrist (75% [n = 12]) and reported that the call had a "positive impact" on their well-being (69% [n = 11]). After the call with the study psychiatrist, 50% of participants (n = 8) reported that they increased engagement with treatment for depression, and the other 50% reported no change in treatment. We also report on themes from the qualitative feedback regarding suggestions of how to modify or improve the safety protocol.

Conclusions: Learning from the experiences of research participants will provide unique insight into satisfaction with, and impact of, the implemented suicidality safety protocol. Findings from this study could inform the refinement and implementation of safety protocols used in depression studies as well as future research on the impact of such protocols.

J Clin Psychiatry 2023;84(4):22m14737

To cite: Vanderkruik R, Freeman MP, Dunn KA. The challenge of clinical research and suicidality: participant feedback on a safety protocol. *J Clin Psychiatry. 2023;84(4):22m14737.*

To share: https://doi.org/10.4088/JCP.22m14737

[a]Ammon-Pinizzotto Center for Women's Mental Health, Massachusetts General Hospital, Boston, Massachusetts

[b]Renée Crown Wellness Institute, University of Colorado Boulder, Boulder, Colorado

**Corresponding author:* Rachel Vanderkruik, PhD, MSc, Massachusetts General Hospital, 185 Cambridge St, Boston, MA 02114 (rvanderkruik@partners.org).

Suicidal ideation (SI) is not uncommon among individuals experiencing depression. A systematic review and meta-analysis on the prevalence of suicidality in major depressive disorder (MDD) found MDD patients to be at higher risk of lifetime and past year SI, suicide plan, and suicide attempt compared to non-MDD controls.[1] In a review of clinical trials conducted in patients with either MDD or bipolar disorder, 23% of participants reported active SI at some point during study participation.[2] It is thus concerning that many clinical trials systematically exclude suicidal patients from enrolling, as doing so limits generalizability and excludes this high-risk population warranting further study in treatment research.[3,4]

Barriers to enrolling suicidal patients in clinical trials include participant safety and research risks. A need for researchers to develop a plan to monitor and respond to suicide risk among study participants has been identified,[4] and a systematic review was conducted on practices for monitoring and responding to self-injurious thoughts and behaviors in longitudinal studies.[5] The review concluded that there were not clear common approaches to managing ethical and safety considerations for SI and suicidal behaviors across over 60 included studies[5]; the authors advocate for further research to evaluate optimal and feasible strategies for managing suicidal risk within research trials. Such safety protocols are particularly critical when conducting research on a national scale, as the procedures must appropriately address urgent and emergent situations remotely.

Although guidance regarding approaches and considerations for monitoring, assessing, and responding to suicide risk in clinical trials is available,[6,7] no empirical studies have explored the study participant's perspective on a given safety protocol in clinical research trials. Such insight would be valuable in assessing impact of safety protocol procedures, exploring possible unintended consequences, and improving procedures. In the Understanding and Preventing Women's Relapse of Depression (UPWARD) Supplemental Study of perinatal suicidality, a safety protocol was implemented and utilized to respond to participant SI and thoughts of self-harm reported during study interviews and self-report surveys. In this report, we describe participants' feedback regarding their experiences with the safety protocol and suggestions for improvements to the protocol.

METHODS

Study Methodology Overview

In a parent study of perinatal depression (UPWARD; National Institute of Mental Health [NIMH], NCT03623620),

Clinical Points

- Suicidal ideation is an exclusion criterion for most clinical studies of depression, highlighting a need for more robust participant safety protocols to allow for study of this at-risk population.
- Future safety protocols should emphasize the importance of transparency and the need for procedures that balance safety while also encouraging participants to answer risk assessments honestly.
- Safety protocols involving contact from study psychiatrists may help participants re-engage with their community providers and have the potential to positively impact the participant's mental health.

the researchers identified that a significant proportion of otherwise eligible candidates were excluded from participation based on an immediate risk of self-harm. Resultantly, an administrative supplement funded an observational prospective study with longitudinal follow-up of pregnant individuals with a history of recurrent depressive symptoms who endorsed suicidal ideation or thoughts of self-harm on the Patient Health Questionnaire-9[8] at screening, entitled UPWARD-S. This supplemental study aims to explore the phenomenology of suicidality in the perinatal time frame.

Eligible participants for the UPWARD-S study were 16 weeks gestation or earlier at baseline, were aged 18 years or older, had established and ongoing care with a community health care provider, and were willing to provide details for an emergency contact and at least 1 community health care provider. Participants were informed that the research team would contact these individuals in the context of the safety protocol. Subjects with a diagnosis of bipolar or psychotic disorder; with experience of mania, psychosis, or active substance abuse; or who were not comfortable completing surveys and interviews in English were not eligible for participation. After consenting, the participant was monitored via self-report questionnaires and telephone interviews from pregnancy at the baseline visit up to 6 months postpartum. At each study time point, the participant completed the Suicidal Ideation section of the Columbia-Suicide Severity Rating Scale (C-SSRS)[9] as a measure of the severity of any suicidal ideation and thoughts of self-harm. This measure was also used to guide the Suicidality Safety Protocol.

Suicidality Safety Protocol

Participants triggered the Suicidality Safety Protocol upon endorsing items 3, 4, or 5 on the Suicidal Ideation section of the C-SSRS during an interview or self-report online questionnaire. In both scenarios, participants were presented with information on emergency resources including the National Suicide Hotline, Postpartum Support International, and emergency services and were notified that a study psychiatrist would be in contact. Study staff then communicated relevant clinical details and contact information to the on-call study psychiatrist.

The study psychiatrist first contacted the participant via phone call, and then via text and/or email if the participant did not answer the phone. The study psychiatrist would contact the study subject as soon as possible, ideally within 2 hours, and was most often able to make contact within the hour. If the study psychiatrist was not able to reach the participant in a suitable time frame based on clinical judgment, the study psychiatrist contacted the emergency contact and/or the community provider to confirm the participant's whereabouts and safety. The study psychiatrist evaluated the severity of suicidality symptoms and current safety level once contact was made with the participant. The study psychiatrist involved local emergency resources as necessary. At the end of the call, the study psychiatrist documented the details of the communication with the participant, their emergency contact, and/or their health care provider.

Finally, study staff notified the participant's health care provider(s) of this suicidality alert and study staff response within 1 business day of the safety event. Provider(s) were also faxed an information packet including a privacy sheet, institutional review board (IRB)-approved letter explaining the context of the safety concern, the study psychiatrist's clinical safety note, and the participant's questionnaire responses (if relevant). See Supplementary Figure 1 for a summary of the safety protocol.

Participant Feedback Questionnaire

After the feedback questionnaire was approved by the IRB on October 17, 2021, all active participants who experienced safety protocol measures were given the opportunity to respond at the conclusion of their 6-month postpartum interview. The feedback survey, conducted over the phone, included 4 Likert-scale questions and 1 open response question. Participant comments during the safety protocol feedback survey were transcribed from audio recordings of the telephone interview. See Supplementary Appendix 1 for a copy of the survey.

Data Analytics

Quantitative measures were summarized with means and standard deviations. A qualitative content analysis approach was used for the open text question, with categories derived from the data.[10] One of the coauthors (K.A.D.) read all qualitative responses and drafted an initial codebook using inductive and deductive methods with guidance from an author with experience in qualitative research (R.V.). The 2 coders (K.A.D. and R.V.) met to review coding discrepancies, to establish operational definitions of codes, and to reach consensus on coding each qualitative response.

RESULTS

All eligible participants completed the Participant Feedback Survey (N = 16; 100% response rate; see Supplementary Figure 2). The average age of participants was 33.25 years (SD = 3.80), and all identified as non-Hispanic

Table 1. Categories of Safety Protocol Feedback (n = 13)

Category	Number of mentions	Example quotations
Experiences with the safety protocol		
1. Safety call led to improved treatment engagement/ mental health	6	"[The phone call with the study psychiatrist] was part of what convinced me to start Zoloft before I had my baby. […] Overall, it was reassuring that it was okay to start medications and to make these changes. It ended up being very positive for my overall mental health. I was very worried about my baby's safety with taking [medications], and she did wonderfully!" "Yes, I got on the medication, and I got into therapy from that call. To be honest, it was exactly what I needed, and I wouldn't change it. The speed with which [the study psychiatrist] called me and the compassion that she had for me and the information and just the legwork that she did for me was pivotal in my well-being. I'm just really, really grateful for that part of the program, because it really changed my outcomes a lot." "I think that, overall, it had a positive impact in a sense that it was helpful to know that someone was kind of looking out for me. I think from a standpoint of me having those thoughts, I think that it didn't really make those thoughts stop or go away, but it definitely helped to have that sort of support. […] I think that in general, it was helpful to kind of be a part of a study in a sense that I obviously wasn't alone in how I was feeling, especially at the beginning of my pregnancy."
2. Mixed experiences with emergency contact outreach	4	"My husband is my emergency contact, so he was a little alarmed when he got that call. But it wasn't a bad thing for him to become more aware of what was happening with me." "[The study psychiatrist] called at like 6:00 AM, and my husband was like, 'She's asleep, do you need to talk to her?' because I was passed out. And then he called my emergency contact, who was my husband, and he was like, 'She's asleep, I'm sure she's been up all night with the baby, do you really need me to wake her?' and he said 'Yes, I need you to wake her.' And so that was really annoying, I had literally just gotten to sleep and he woke me up, had a brief 5- to 10-minute conversation with me, and then I was awake and couldn't go back to sleep. And for somebody whose trigger for depression is lack of sleep ... [inaudible]. I wish he could have just talked to my husband and have him be able to verify that I was physically safe."
3. Safety call was unexpected	4	"I guess I wasn't really expecting to [receive the call], but I did know that you guys had this protocol, so I wasn't surprised when I got the call." "The first time you reached out, definitely no. I wasn't expecting a call at all, and I definitely didn't know it was a psychiatrist calling."
4. Discomfort or reluctance speaking about suicidal ideation	3	"I didn't really want to talk to anyone about how I felt at the time. […] I didn't really open up to my OB either, since I just didn't really feel comfortable." "I know the questions are already vetted and very specific, and they tend to follow what is already present in medical texts and whatnot. What I would say as somebody who suffers from depression and has suffered from severe needs, your brain wants to give you any way out when it can. So, when it says, 'Do you want to hurt yourself or feel weary?' and I can say no to one of them, I'm not going to answer yes to the question at all. The point being: my brain is looking for any way to not to tell people where I'm at."
5. Safety call led to decreased reporting of suicidal ideation	3	"I felt much less inclined to report any thoughts of suicide that I had after that because I know the nature of my thoughts are pretty innocuous. […] I honestly, like, there were times that I did have thoughts of suicide after that that I didn't report because I didn't want the attention, and I knew that I was fine and that I have things that I do to get me through those times, and they are pretty familiar to me. I kind of just stopped saying anything." "It actually made me less likely to answer genuinely."
Suggestions		
6. Modifications or alternative procedures	7	"I think you could just explain a bit more about the background of who it is that is contacting me. Like what do they want to talk about." "It just felt like a lot. I don't really know how much leeway you have as far as if people are reporting a lower intensity or a lower frequency. […] I had a lot of people calling me, and I was like, 'I'm fine, I'm going to be okay.' It was really intense and way more attention than I wanted." "I wish [the study psychiatrist] could have just talked to my husband and have him be able to verify that I was physically safe. And I could have called back, or you could have called back a little bit later."

and White. Most of the participants identified as married (75%) and employed for wages (69%), with at least a bachelor's degree (63%).

Most participants (75%; n = 12) reported that they were not expecting the safety call from a study psychiatrist, and the remaining 25% (n = 4) reported that they were expecting the call. Most participants (75%; n = 12) reported being at least "neutral" to "very comfortable," with an average score of 3.5 (SD = 1.21). The majority (69%; n = 11) of participants reported that the phone conversation with the study psychiatrist had a "positive impact" on their well-being, while 25% (n = 4) reported "no impact" and 1 participant (6%) reported that the call had a negative impact on their well-being. Half of the participants (n = 8) reported that they "increased engagement" with their depression care after the call with the study psychiatrist, and the remaining 50% reported no change in their engagement with depression care after the safety call.

Qualitative feedback was provided by 13 respondents (81%) in response to the question, "Your safety is of utmost importance to the UPWARD-S team. What recommendations do you have to modify or update the safety protocol, if any? Please also describe any other comments or feedback about your experiences with the UPWARD-S safety protocol." Coding of open text responses indicated key categories regarding experiences with the safety protocol as well as suggestions for protocol modification (see Table 1).

DISCUSSION

Our findings suggest that, despite mention of the safety protocol during the study consent procedures, most

participants were not expecting a call from the study psychiatrist when they triggered the protocol. Possible explanations for not expecting the call based on participants' comments include that participants did not have clear understanding of what the safety protocol involved or that some may have forgotten about the protocol. These findings indicate the importance of using clear and explicit descriptions of the safety protocol at the time a participant enrolls in the study, and future research might consider inclusion of periodic reminders regarding the safety protocol in longitudinal studies, although this raises the question of whether these reminders could further discourage honest answers from participants who wish to avoid receiving such outreach. Most participants reported having a positive experience with the study psychiatrist, and some reported that the safety protocol helped them to re-engage with their community provider and adjust their treatment. This is encouraging to hear from a patient safety and well-being perspective, and yet this finding should also be considered in the context of clinical effectiveness trials of a treatment for depression (ie, it may be possible that the safety protocol is influencing trajectory of depressive symptoms). It is possible that the calls also provide a source of social connection, which would be of interest to explore further as previous literature has found increased social connection to be an effective strategy for suicide prevention.[11]

Despite the majority reporting a positive or neutral experience with the safety protocol, some participants found the safety protocol procedures to be overwhelming or suggested that the protocol led to a decrease in subsequent reporting of suicidal ideation (Table 1, Category 5). Future research should take these unintended consequences into consideration, particularly in light of participant suggestions for modifications of the protocol. Specifically, participants suggested response based on factors that might more accurately indicate level of risk. In the context of remote and national clinical trials of depression, it is important to identify emergency contacts local to the participant who can be engaged as part of a given safety protocol. Furthermore, we suggest that future safety protocols consider the specific needs of this patient population; for example, researchers may want to determine an appropriate time frame for safety doctors to make calls in response to safety alerts as to avoid disrupting sleep of new mothers, as was suggested by one study participant who received a safety call in early morning hours.

The findings of this study should be interpreted within the context of several limitations including a small sample size, homogeneous sample with lack of racial and ethnic diversity, and partial assessment with the overall sample based on the timing of measurement. As this survey was administered at the 6-month follow-up, we did not capture the perspectives of participants who had been lost to follow-up or withdrawn from the study at this timepoint. Such limitations may limit the generalizability of our findings. This study is novel in the exploration of the patient perspective on experiences with a safety protocol in the context of a large-scale depression treatment study. We hope that future research will build on these findings to examine empirically how best to develop and implement safety protocols in the context of clinical trials for depression and suicidality that not only emphasize the importance of keeping patients safe but also respect the perspective and expertise of participants themselves.

Submitted: November 21, 2022; accepted April 6, 2023.

Published online: May 15, 2023.

Relevant financial relationships: **Dr Cohen**: *Research support:* Dr Cohen is an employee of Massachusetts General Hospital (MGH) and works with the MGH National Pregnancy Registry. *MGH National Pregnancy Registry:* Current sponsors: Alkermes, Inc. (2016–present); Eisai, Inc. (2022–present); Johnson & Johnson/Janssen Pharmaceuticals, Inc (2019–present); Otsuka America Pharmaceutical, Inc. (2008–present); Sage Therapeutics (2019–present); Sunovion Pharmaceuticals, Inc. (2011–Present); Supernus Pharmaceuticals (2021–present); and Teva Pharmaceutical Industries Ltd. (2018–present). Past sponsors: Forest/Actavis/Allergan (2016–2018, declined to sponsor: 2018–present), AstraZeneca Pharmaceuticals (2009–2014, declined to sponsor: 2014–present); AuroMedics Pharma LLC (2021–2022, declined to sponsor 2022–present); Aurobindo Pharma (2020–2022, declined to sponsor: 2022–present); Ortho-McNeil-Janssen Pharmaceuticals, Inc (2009–2014, declined to sponsor: 2015–present); and Pfizer, Inc. (2009–2011, declined to sponsor: 2012–present). As an employee of MGH, Dr Cohen works with the MGH CTNI, which has had research funding from multiple pharmaceutical companies and NIMH. *Other research support:* Brain & Behavior Research Foundation, National Institute on Aging, National Institutes of Health, and SAGE Therapeutics. *Advisory/consulting:* JDS Therapeutics LLC. *Speaking/honoraria:* None. *Royalty/patent, other income:* None. **Dr Freeman**: *Research support:* Dr Freeman is an employee of Massachusetts General Hospital and works with the MGH National Pregnancy Registry. *MGH National Pregnancy Registry:* Current sponsors: Alkermes, Inc. (2016–present); Eisai, Inc. (2022–present); Johnson & Johnson/Janssen Pharmaceuticals, Inc (2019–present); Otsuka America Pharmaceutical, Inc. (2008–present); Sage Therapeutics (2019–present); Sunovion Pharmaceuticals, Inc. (2011–present); Supernus Pharmaceuticals (2021–present); and Teva Pharmaceutical Industries Ltd. (2018–present). Past sponsors: Forest/Actavis/Allergan (2016–2018, declined to sponsor: 2018–present); AstraZeneca Pharmaceuticals (2009–2014, declined to sponsor: 2014–present); AuroMedics Pharma LLC (2021–2022, declined to sponsor: 2022–present); Aurobindo Pharma (2020–2022, declined to sponsor: 2022–present); Ortho-McNeil-Janssen Pharmaceuticals, Inc (2009–2014, declined to sponsor: 2015–present); Pfizer, Inc. (2009–2011, declined to sponsor: 2012–present). As an employee of MGH, Dr Freeman works with the MGH CTNI, which has had research funding from multiple pharmaceutical companies and NIMH. *Other research support:* SAGE Therapeutics and JayMac. *Advisory/consulting:* Janssen (Johnson & Johnson), Novartis, and Neurocrine; advisory boards, Eliem, Sage, Brainify, and Everly Health. *Speaking/honoraria:* WebMD, Medscape, Pri-Med, and Postpartum Support International. *Royalty/patent, other income:* scale royalties through MGH Scale, The Massachusetts General Hospital Female Reproductive Lifecycle and Hormones Questionnaire (Freeman et al 2013). **Dr Dimidjian** reports being a co-founder of Mindful Noggin, Inc. and receiving revenue from MindfulNoggin.com, royalties from Guilford Press and Wolters Kluwer, and funding from philanthropic foundations and the National Institutes of Health. **Drs Vanderkruik**, **Dunn**, and **Clifford** have nothing to disclose.

Funding/support: This research was supported by grant R01MH117253 from the National Institutes of Health.

Role of the sponsor: The funder has had no role in the conduct and publication of this study.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Mental Health.

Previous presentation: Presented at the 20th Annual Massachusetts General Hospital Clinical Research Day; October 13, 2022; Boston, MA.

Supplementary material: Available at Psychiatrist.com.

REFERENCES

1. Cai H, Xie X-M, Zhang Q, et al. Prevalence of suicidality in major depressive disorder: a systematic review and meta-analysis of comparative studies. *Front Psychiatry*. 2021;12:690130.
2. Ballard ED, Snider SL, Nugent AC, et al. Active suicidal ideation during clinical antidepressant trials. *Psychiatry Res*. 2017;257:303–308.
3. Courtet P, Nobile B. Inclusion of suicidal individuals in research studies. *J Clin Psychiatry*. 2020;81(3):20com13276.
4. Iltis AS, McCall WV, Deria R. Suicidality, depression, and the FDA: health inequities and the ethical conduct of research. *J Clin Psychiatry*. 2020;81(2):19m13050.
5. Bentley KH, Maimone JS, Kilbury EN, et al. Practices for monitoring and responding to incoming data on self-injurious thoughts and behaviors in intensive longitudinal studies: A systematic review. *Clin Psychol Rev*. 2021;90:102098.
6. Schatten HT, Gaudiano BA, Primack JM, et al. Monitoring, assessing, and responding to suicide risk in clinical research. *J Abnorm Psychol*. 2020;129(1):64–69.
7. Ali J, Morain SR, O'Rourke PP, et al. Responding to signals of mental and behavioral health risk in pragmatic clinical trials: ethical obligations in a healthcare ecosystem. *Contemp Clin Trials*. 2022;113:106651.
8. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606–613.
9. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168(12):1266–1277.
10. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Res*. 2005;15(9):1277–1288.
11. Motto JA, Bostrom AG. A randomized controlled trial of postcrisis suicide prevention. *Psychiatr Serv*. 2001;52(6):828–833.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Early Career Psychiatrists section. Please contact Joseph F. Goldberg, MD, at jgoldberg@psychiatrist.com.

See supplementary material for this article at PSYCHIATRIST.COM.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: The Challenge of Clinical Research and Suicidality: Participant Feedback on a Safety Protocol

Authors: Rachel Vanderkruik, PhD, MSc; Marlene P. Freeman, MD; Katherine A. Dunn, BS; Charlotte A. Clifford, BA; Sona Dimidjian, PhD; and Lee S. Cohen, MD

DOI Number: 10.4088/JCP.22m14737

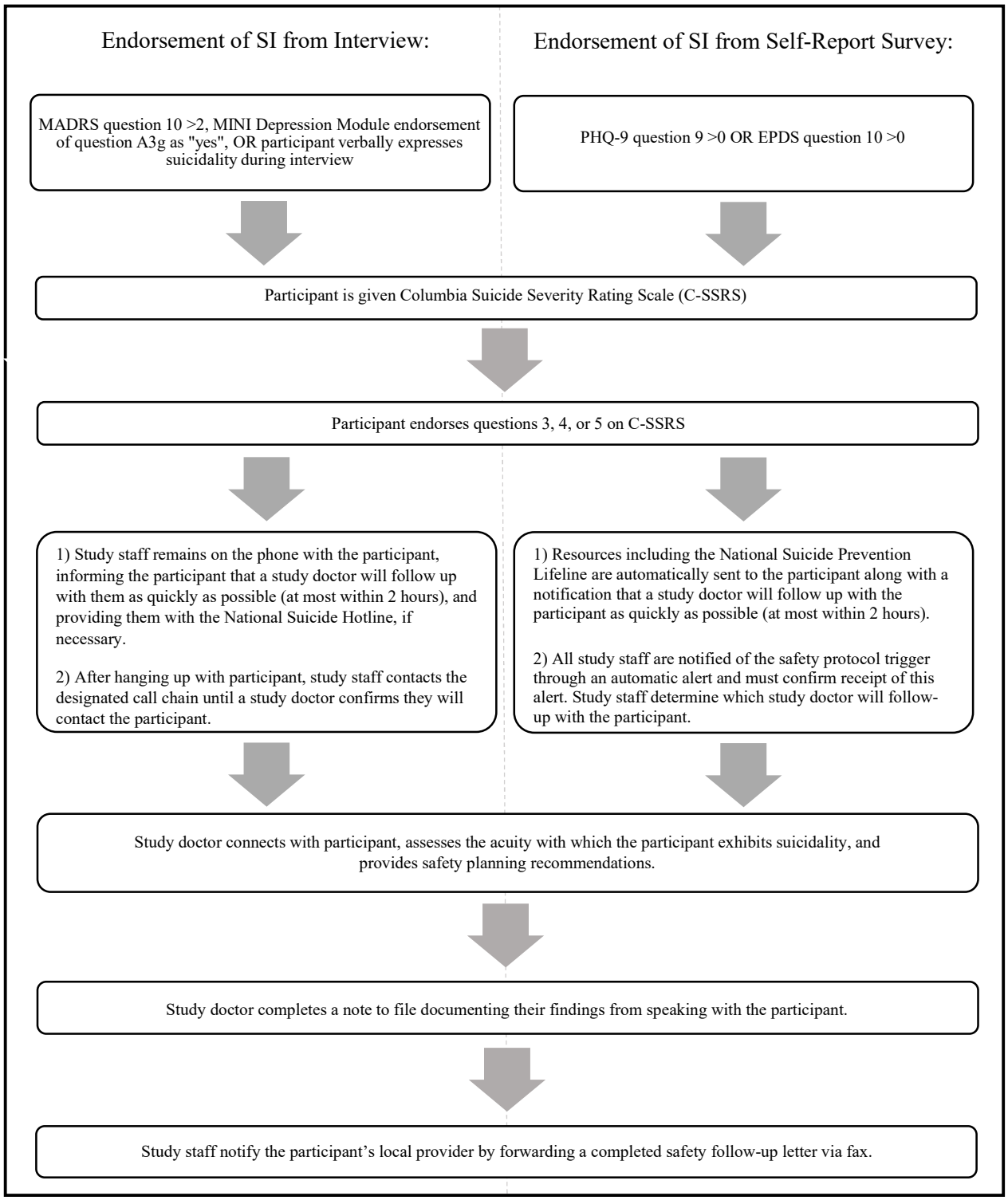
List of Supplementary Material for the article

1. Figure 1 Summary of UPWARD-S Safety Protocol
2. Appendix 1 Suicidality Safety Protocol Feedback Questionnaire
3. Figure 2 Participant Flow Diagram

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Figure 1. Summary of UPWARD-S Safety Protocol



Supplementary Appendix 1. Suicidality Safety Protocol Feedback Questionnaire

1. Were you expecting to receive this call from the study psychiatrist? *[Yes/No]*
2. Thinking about how you felt during and after the call, how comfortable were you with this call from the study psychiatrist? *[0: Not Comfortable to 5: Very Comfortable]*
3. Overall, did the phone conversation with the study psychiatrist have a positive impact, negative impact, or essentially no impact on your wellbeing? *[Positive Impact/Negative Impact/No Impact]*
4. After the call with the study psychiatrist, did you make any changes in your care for depression? For example, did you increase the frequency of seeing your caregiver or seek out additional treatment? *[Increased Engagement/Decreased Engagement/No Change in Engagement]*
5. Your safety is of utmost importance to the UPWARD-S team. What recommendations do you have to modify or update the safety protocol, if any? Please also describe any other comments or feedback about your experiences with the UPWARD-S safety protocol. *[open text]*

Supplementary Figure 2. Participant Flow Diagram