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Running Head: PERINATAL LOSS

Study Protocol: Randomized controlled trial of interpersonal psychotherapy (IPT) for major depression following perinatal loss

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Abstract

Introduction. This protocol describes a study testing the efficacy of interpersonal psychotherapy (IPT) for major depressive disorder following perinatal loss (early and late fetal death and early neonatal death). Perinatal loss is associated with elevated risk of major depressive disorder and posttraumatic stress disorder (PTSD). Perinatal loss conveys specific treatment needs. The trial will be the first fully-powered randomized trial of treatment for any psychiatric disorder following perinatal loss.

Methods and analysis. A sample of 274 women in Flint and Detroit areas in Michigan who experience a major depressive episode following a perinatal loss will be randomized to group IPT for perinatal loss or to group Coping with Depression (CWD). We anticipate that 50% of the sample will have co-occurring PTSD. Assessments occur at baseline, mid-treatment (8 weeks), post-treatment (16 weeks), and follow-up (28 weeks). Clinical outcomes include time to recovery from major depressive episode (primary), depressive symptoms, PTSD symptoms, and time to recovery from PTSD. Additional outcomes include social support, social role functioning (including parental functioning for those with living children), well-being, grief (including complicated grief and fault beliefs), and fear of subsequent pregnancies. Social support and grief are hypothesized mediators of the effects of IPT on time to recovery from major depressive episode.

Ethics and dissemination. The trial has Institutional Review Board approval, has a Data and Safety Monitoring Board, and has been submitted for voluntary Community Ethics Review Board review. Written operating procedures outline methods for protecting confidentiality, monitoring and recording adverse events, and safeguarding participants. In addition to dissemination to research and clinical communities, we will share results with community organizations through which we recruited, and will offer to share final study results with study participants. De-identified

datasets will be available through the National Institute of Mental Health Data Archive and to qualified investigators upon request.

Clinical trials registration. The trial was registered at clinicaltrials.gov (NCT04629599).

Key words: Miscarriage, stillbirth, fetal death, perinatal death, major depressive disorder, posttraumatic stress disorder, interpersonal psychotherapy.

Word count: 4,000

Article Summary: Strengths and limitations of this study

- This study addresses a clinical need, and will provide an evidence base for treating a vulnerable and understudied population whose distress has historically been minimized.
- The trial will have strong representation from disparities populations (African American women and socioeconomically disadvantaged women) who experience higher rates of perinatal loss, increasing its significance.
- Rigor and reproducibility are ensured by the randomized design, clear inclusion criteria, use of well-established research, recruitment, and retention methods, and transparent power and statistical analyses.
- Assessment strengths include the use of reliable and valid measures, the use of raters blinded to treatment condition at follow-up, and strong interrater reliability training and monitoring.
- Intervention strengths include clearly distinct treatment conditions, use of manualized treatment protocols and fidelity assessments, and team members with decades of experience responding to perinatal loss.

Introduction

About 650,000 women in the United States experience perinatal loss each year (including early and late fetal death and the death of a liveborn neonate within the first 28 days).[1 2] Rates of major depressive disorder (MDD) after perinatal loss are higher than after giving birth to a living infant, and are 3 times the rates among matched samples of community women.[3-20] Rates of posttraumatic stress disorder (PTSD) after perinatal loss are up to 7 times the rates of PTSD among mothers of living infants,[13] and elevated PTSD symptoms can occur for years after the loss.[21] Fetal or neonatal death triples rates of suicide and of hospitalization for suicide attempts.[22 23]

Not only do women with perinatal loss have higher rates of MDD and PTSD than mothers of living infants, their needs also differ from needs following many other kinds of bereavement. In perinatal loss, the fact of bereavement is compounded by the physical experience of miscarriage or of delivering a baby that has already died.[24] PTSD rates (25% overall and 66% for women with MDD) are higher after perinatal loss than after most other kinds of bereavement.[24] Many women experiencing perinatal loss grieve in secret, as others may not know about the loss. Even if others do know, there are few social norms that guide how others can or should support the bereaved, making support less likely and often less helpful (e.g., "you can just have another one").[12 25] They are sometimes considered "illegitimate mourners."[12 26-28] Reasons for loss are often unclear and many women blame themselves.

Despite recognition that MDD (with or without co-occurring PTSD) following perinatal loss causes significant impairment and that treatment as usual is often inadequate,[29-33] our previous pilot work[34] created and tested the first manual for treating any psychiatric disorder after perinatal loss. The manual is structured and applies interpersonal psychotherapy (IPT) principles to perinatal loss in a group format. Previous IPT and other treatment manuals for perinatal depression[35-38] focus

on helping women adjust their relationships, identity, roles, and routines to the demands of a new baby. This is inappropriate in the context of perinatal loss. Our manual applies IPT social support and communication principles to issues such as resolving conflicts over how to respond to the loss, grieving and requesting support in the absence of social norms about how to do so, and resolving questions of fault and role competence. It can be used by providers who do not know IPT. A randomized pilot study found results favoring the new IPT manual for PTSD recovery, treatment satisfaction, depressive symptoms, grief, and social support relative to Coping with Depression (CWD), a cognitive-behavioral based intervention that does not focus on perinatal loss, interpersonal issues, or social support.[34]

Based on those promising results, the current study will be the first fully-powered randomized trial of treatment for any psychiatric disorder following perinatal loss. We will compare our group IPT manual to a standard group depression treatment (CWD) in a sample of 274 women experiencing MDD in the context of perinatal loss. The trial will test the hypotheses that:

1. IPT for perinatal loss will result in reduced time to recovery from MDD (primary), depressive symptoms, and PTSD symptoms, relative to CWD. Among women meeting criteria for PTSD, IPT will result in reduced time to recovery from PTSD relative to CWD.
2. IPT for perinatal loss will result in increased social support, social role functioning (including parental functioning for women with living children), and well-being, and decreased grief and fear of subsequent pregnancies, relative to CWD.
3. Social support and grief will mediate the effects of IPT on time to MDD recovery.

This trial will provide an evidence base for treating a vulnerable and understudied population whose distress has historically been minimized. Given that poverty increases risk of perinatal

loss,[39-41] and doubles the risk of perinatal depression,[42-50] and that rates of perinatal loss for African-American women are double those for white women,[51-53] the location of the trial in Southeast Michigan, which includes Flint and Detroit (minority-majority cities with high rates of poverty), increases the trial's significance.

Methods and analysis

Rationale for design

Given that no other treatment exists for women who experience perinatal-loss related MDD that could be used as a comparator condition, we chose to use a general depression treatment, the Coping With Depression (CWD) course, as a control condition. We chose CWD over other standard depression treatments because it is the group treatment with the most empirical support for treating MDD[54 55] and because it is distinct from IPT. IPT addresses MDD through emotional exploration, work on relationships, communication, grief, and social support. CWD addresses MDD by changing thinking and behavior; it focuses on skills for reducing depression in general and does not have perinatal-loss specific components. Our IPT treatment differs from CWD in its focus on exploring reactions to the loss, addressing loss-related interpersonal challenges, and improving loss-related social support and grief-specific coping. The trial's secondary outcomes (social support, social functioning, grief) assess hypothesized differences between treatments. As desired, our pilot study found differences between conditions in the hypothesized mechanisms of social support and grief and in terms of in-session activities.[34]

Treatments

Manualized treatments are attention-matched (12 90-minute groups, 1 individual pre-group session, and 1 booster session). Both treatments allow new women to enter the group every 4 weeks of the 12-week group.

Interpersonal psychotherapy (IPT). Participants in the IPT condition receive 12 group sessions and 2 individual (pre-group and 1-month booster) sessions as outlined in the structured manual (see Table 1). The individual sessions prepare patients to use the group effectively, to keep group members focused on their treatment goals, and to maintain treatment gains. In addition, 3 of the 12 group sessions invite women to include their partners or other support people to bolster the woman's social support system and to reduce conflicts over how to react to the loss. Relationship distress is common following perinatal loss.[12 56]

Group sessions are semi-structured, and each woman covers the four group topics listed in Table 1 three times, approaching each topic from a different stage in the mourning process. We found that entering new women into the groups every four weeks allows remaining women to see their own progress and encourages new women through example and peer counseling.

Coping with Depression (CWD). CWD is a structured, manualized[57] psycho-educational group treatment for MDD. The CWD course is cognitive-behavioral. The problems shown by depressed individuals are viewed as behavioral, with cognitive patterns that can be unlearned or relearned. Its effectiveness is comparable to other forms of psychotherapy in depression.[55] The course content teaches skills including relaxation, cognitive skills, and behavioral activation. The CWD pre-group and booster sessions are the pre-group and booster sessions from the published CWD manual[57]. To ensure that the CWD intervention was distinct from IPT, we excluded the 2 sessions on social skills and emphasized pleasant activities that were individual rather that social. Consistent with standard CWD, we focused on addressing depression rather than discussing grief or perinatal loss. We expanded other CWD material (e.g., relaxation practice) to replace sessions on social skills. In our studies, the 12 CWD sessions covered: an introduction to social learning rationale of depression; learning to relax; relaxation in everyday situations; pleasant activities and

depression; formulating a pleasant activities plan; constructive thinking; planning for constructive thinking; and maintaining gains.

Participants

Participants will be 274 women who are experiencing MDD in the context of perinatal loss who (1) meet DSM-5[58] criteria for MDD; (2) have experienced a perinatal loss (including early and late fetal death, death of a liveborn neonate within the first 28 days, and medically recommended termination) within the last 1-12 months; (3) are 18 to 50 years old; (4) speak and understand English well enough to understand questionnaires when they are read aloud; (5) can provide the name and contact information of at least two locator persons; and (6) have access to a telephone. Exclusion criteria are: (1) onset of *current* major depressive episode prior to news of difficulties with the pregnancy or health risk to the infant (women with prior episodes are included); (3) current or past diagnosis of bipolar disorder, schizophrenia or other psychotic disorder; (4) primary diagnosis of current substance use disorder; (5) acute suicidal or homicidal risk; (6) beginning or changing dose of antidepressant medication or psychotherapy in the previous 12 weeks); (7) any IPT or cognitive-behavioral treatment in the previous 12 weeks. Women in stable concurrent psychotherapy who are included are asked to suspend this treatment during the active study treatment phase. PTSD is not an inclusion criterion for the study. However, based on our pilot,[34] we anticipate that slightly more than half the sample will meet criteria for PTSD at study enrollment.

Therapist training and supervision

We trained 8 study therapists (4 in IPT and 4 in CWD) who are MSWs or clinical or counseling psychologists. Therapists are recruited from their respective communities to moonlight as clinicians in this proposed study. Therapists are provided with the detailed treatment manuals.

Training for both conditions includes education and role plays. Therapists in both conditions will be monitored for adherence/competence throughout the study and retrained as needed.

Supervision involves review of therapists' audiotaped sessions and a weekly one-hour small-group telephone meeting for feedback and case discussion. Treatment sessions are audio recorded using digital audio recorders or a HIPAA-compliant version of Zoom. Study therapists remotely upload the recordings to the study's secure research server, where the supervisors can access the recordings to listen to them (remotely).

Randomization

Women are randomly assigned to IPT or CWD in a 1:1 ratio. We stratify randomization on whether women (1) have been taking antidepressant medications or attending other psychotherapy (stability of dose is an inclusion criterion); and (2) have experienced each type of perinatal loss (miscarriage, stillbirth, early neonatal death). Randomization sequences were created by the study statistician. Assignment is concealed in an envelope that research assistants open at the time of randomization.

Recruitment

Participants are recruited from counties in Southeast Michigan using a broad outreach strategy. We are partnering with regional health systems, community-based organizations in Flint and Detroit, and a regional Medicaid system to assist with study recruitment. Recruitment also includes flyers and referrals from: (1) local birthing centers, emergency departments, OBGYN offices, and federally qualified health centers; (2) hotlines, support groups, family nurse partnerships; (3) funeral homes, (4) churches, daycare centers, other places where women and mothers congregate (WIC offices, Medicaid offices, etc.), (5) bus ads, and (6) online venues.

Research sites

The study team is embedded in Flint and Detroit. We had planned to offer baseline assessments at women's homes or our offices, group sessions in community locations convenient for participants, and to conduct follow-up assessments by telephone. However, due to the COVID-19 pandemic, we are currently conducting all assessments and treatment sessions by Zoom, with an option to switch to holding groups in person in the future.

Retention

We employ techniques we have found helpful in achieving low attrition rates in previous studies.[59-65] These include study staff's strong relationships with participants, efforts to value and appreciate the women's participation in the study, and frequent personal contact. We are flexible about follow-up appointment scheduling and train research staff to be culturally sensitive. Follow-up assessments take place by Zoom or phone, with well-established safety procedures for emergencies.[65] We maintain a list of two other people who know where the participant resides. A cellular phone is used to contact women who have blocked calls. We conduct treatment groups at different times and locations to make attendance easier. If a woman misses a treatment appointment, the therapist calls her to check in and help problem-solve barriers to attendance. Finally, participant fees for follow-up assessments helps facilitate retention.

Assessments

Assessments take place at baseline, mid-treatment (8 weeks), post-treatment (16 weeks), and follow-up (28 weeks; see Table 2). Assessments are conducted by research assistants (RAs) trained in interviewer administered instruments and blind to treatment assignment. RAs are certified interviewer-rated instruments prior to beginning interviews. Interviewers and senior staff meet regularly to review assessment tapes, address questions, and monitor inter-rater reliability. Data quality is maintained through clerical and clinical checks after data are entered and through

regular examination of distributions, missing data, and outliers.

Diagnosis/screening. The Structured Clinical Interview for DSM-5 (SCID-5)[66] is used to establish study eligibility. During follow-up, the Longitudinal Interval Follow-up Examination (LIFE),[67 68] a standardized retrospective calendar-based interview, is used to assess MDD and PTSD recovery. The LIFE uses Psychiatric Status Ratings (PSRs) to measure severity of DSM-5 symptoms on a scale of 1 (asymptomatic) to 6 (incapacitated) for each week. Recovery is defined as 8 consecutive weeks of a PSR of 1-2.[69] The LIFE is the gold-standard way of determining onset and offset of psychiatric disorder.[68 70-73] We also use the LIFE to track participation in psychotherapeutic and psychopharmacologic treatment at baseline and follow-up. We assess partner violence using the Women's Experience with Battering screen.[74] Battered women (scores of 20+) are included in the study and provided with partner violence resources.

Depression severity is assessed using the Quick Inventory of Depressive Symptoms (QIDS), Self-Report version.[75]

PTSD symptom severity is assessed using the Life Events Checklist and PTSD Checklist for DSM-5 (LEC-PCL).[76-79] We also assess whether PTSD symptoms are related to the perinatal loss.

Social support and social functioning. We use the 12-item Multidimensional Scale for Perceived Social Support (MSPSS)[80] to assess overall social support. We use a validated adaptation of the Relationship Assessment Scale[81] to assess satisfaction with an important significant other (partner or other support person of the woman's choosing) relationship. We assess social functioning using the Short version of the Social Adjustment Scale – Self-Report (SAS-SR).[82] Because depression can affect parenting, we will analyze the SAS-SR total score as well as its parental functioning subscale.

Well-being (including life satisfaction, purpose and meaning) is measured by using the 23-item Neuro-QoL scale for positive affect and well-being.[83]

Grief symptoms are measured using the Perinatal Bereavement Grief Scale (PBGS).[4 84] Complicated grief is measured using the Inventory of Complicated Grief (ICG).[85] A few items on the ICG were reworded to refer to perinatal loss. Given that many women present with unwarranted beliefs about what caused the loss, we assess deservingness and guilt as grief outcomes using a 7-item scale about loss beliefs (the Loss Beliefs Scale). This scale includes items such as "I think what happened was my fault" and "The miscarriage, stillbirth, or baby's death was caused by something about me." This perinatal loss specific scale was created after reviewing the literature on beliefs about deserved bad outcomes (e.g.,[86-88]).

Fear of subsequent pregnancies is assessed by 7-point Likert items (from 1 = Strongly Disagree" to 7 = "Strongly Agree"): (1) "I am afraid to become pregnant again"; (2) "I look forward to becoming pregnant again"; (3) "I plan to become pregnant again"; (4) "I worry about what might happen if I get pregnant again," (5) "I do not want to be pregnant again."

Treatment acceptability is measured using the Client Satisfaction Questionnaire-Revised (CSQ-8-R).[89 90]

Treatment integrity. We will use the IPT and CWD adherence and competence scales developed in the pilot trial[34] to rate fidelity using audio recordings. As in the pilot trial, raters will also assess the percent of time in each group session spent discussing the perinatal loss and discussing loss-related communication strategies.[34]

Analysis

Primary analyses will be intent-to-treat. We will examine dose-response effects in secondary analyses. Primary tests will be two-sided with p=0.05. Descriptive statistics will include

effect sizes and measures of clinical significance.[91] Primary and secondary outcomes and all hypotheses are stated a priori, therefore 0.05 level of significance will be used. Per Kraemer,[92] we will not test for differences between conditions due to randomization as those differences are due to chance alone, rendering p-values meaningless. Covariates for analyses are specified a priori based on subject matter expertise. No interim analyses are planned.

Attrition analysis and missing data. We will compare characteristics of those who drop out by trial arm and compare those who complete the study with those who did not to inform the generalizability of findings. For the primary outcome of time to MDD recovery, unobserved time to MDD resolution for the drop-outs will be treated as censored. For secondary outcomes, the regression techniques below allow for missing at random (MAR) mechanism.[93] If patterns of missing data indicate potential not missing at random (NMAR) mechanisms, then models describing missing mechanisms will be considered (e.g., pattern-mixture models),[94] [95] and sensitivity analyses will be employed to investigate robustness of the results.

General approaches. For survival analyses, the proportional hazard (PH) assumption will be evaluated. If it holds, then survival analyses will use Cox regression. If not, time-varying effects will be investigated, and the model will be modified to include an interaction of relevant covariates with a function of time variable. Stratified models will also be considered.

Linear mixed effects (LME) models will be used to test differences between trial arms for continuous outcomes. All participants with at least one completed post-baseline assessment will be included. We expect these scores to follow normal distributions. However, generalized linear mixed effects (GLME) modeling will be used if outcome is not normally distributed and cannot be normalized using transformations.

Aim 1. (1) Using survival analysis, with initial QIDS score as a covariate, we will test the

hypothesis that IPT, relative to CWD, will result in reduced time to recovery from the major depressive episode (primary). (2) Using LME or GLME with baseline QIDS score as a covariate, we will test the hypothesis that IPT, relative to CWD, will result in reduced depressive symptoms (QIDS scores) across post-baseline assessments. (3) Using LME or GLME with baseline PCL score as a covariate, we will test the hypothesis that IPT, relative to CWD, will result in reduced PTSD symptoms (PCL score) across post-baseline assessments. (4) Using survival analysis, with initial PCL score as a covariate, we will test the hypothesis that IPT, relative to CWD, will result in reduced time to recovery from PTSD.

Aim 2. Using baseline scores as covariates, we will separately test the hypotheses that IPT for perinatal loss will result in increased social support, social role functioning, and well-being, and decreased grief and fear of subsequent pregnancies, relative to CWD, using the LME or GLME modeling described above. Specifically, controlling for baseline values, we will use separate analyses to test the effects of IPT vs. CWD on MSPSS, Relationship Assessment Scale, SAS-SR total, SAS-SR parenting subscale, Neuro-QoL, Perinatal Bereavement Grief Scale, Inventory of Complicated Grief, Loss Belief Scale, and Fear of Subsequent Pregnancy scores. We will also compare conditions on CSQ-8-R Treatment Acceptability.

Aim 3. We will test the hypotheses that social support (MSPSS scores) and grief (PBGS scores) will mediate the effects of IPT on time to MDD recovery. To test for mediation, trial arm will be treated as the independent variable and each potential mediator (one at a time) will be tested for their effect on the outcome variable at weeks 8, 16, and 28, with the baseline value of that outcome treated as a covariate. We will use a bias corrected bootstrapping analytic strategy[96 97] based on 5000 bootstrap samples to estimate confidence intervals (CIs) around the indirect effect of study group on the outcome variable, through the mediator.

Moderators. We will calculate differential effect estimates and test the interactions between several participant characteristics and the intervention effect in predicting time to recovery from MDD. Characteristics to be examined include race, ethnicity, having living children, type of perinatal loss, stable use of other antidepressant or psychosocial treatment at baseline, having PTSD at baseline, having a partner, number of past depressive episodes, and time since loss. Given our emphasis on meeting the needs of minority women, we will also evaluate whether mediation relationships or intervention effects on secondary outcomes differ by race.

Sample size

Recovery outcomes. For the primary outcome of time to MDD recovery (censored at 28 weeks), assuming 1:1 allocation, power 0.80, two-sided tests at 0.05 level of significance, and observed estimated hazard ratio=1.79, the required number of events is 94 (number of MDEs resolved). By week 28, there were 17 events in the preliminary data (17 women had MDD resolved, 11 in the IPT condition, and 6 in the CWD condition) out of 45 participants, so the rate of events was .38. Thus to have 94 events, total N=246 is required. Given that we obtained at least one follow-up assessment on 90% of participants in the pilot trial,[34] we increased the sample size to 274. Given the observed hazard ratio of 5.85 for PTSD in the pilot trial, power for PTSD recovery should be greater than 80%. Tests of mediation in Aim 3 will have greater power than the primary outcome because of reduction in error variance when controlling for the mediator.

Continuous (secondary) outcomes. Assuming an unadjusted d = .32 and a correlation of 0.6 between follow-up measures and 0.3 with baseline (as observed in the preliminary data), the adjusted effect size would be 0.40, and only n = 200 participants would be needed before attrition. If study attrition is higher, the study still has > 80% power for secondary outcomes (Table 3).

Ethics and Dissemination

The trial was approved by Michigan State University's Biomedical Institutional Review Board (FWA 00004556). It has been submitted for voluntary review by the Community Based Organization Partners Community Ethics Review Board.[98] A three-member external Data and Safety Monitoring Board reviews data and safety of study participants. Trial safety procedures are codified through checklists and a written manual of operating procedures.

Informed consent and confidentiality

When potential participants contact the study, study RAs meet with them privately (electronically or in person). RAs explain risks, benefits, and the voluntary nature of the study and obtain participants' signed informed consent.

Confidentiality is protected by having all information collected and handled by research staff trained to deal appropriately with sensitive clinical issues. Participants are informed about the limits of confidentiality concerning suicidal intent, homicidal intent, and suspected child or elder abuse. Computer files are available only to authorized personnel, with no names or obvious identifying information stored in data files. Confidentiality of recordings of study assessments and treatment sessions is protected through: (1) use of encrypted audio recorders and HIPAA-compliant videoconferencing; (2) labeling recordings with study IDs rather than names; (3) storing recordings on a secured computer server designed to hold and protect research data; and (4) limiting access to recordings.

Participant safety

Adverse events. Participant safety is monitored during study assessments and during study treatment sessions. Pre-specified adverse events are recorded and monitored using a structured system created within REDCap with alerts for follow-up actions.[65]

Suicide risk. During assessments, participants who score 2 or above (any active suicide ideation) on the QIDS suicide item are transferred via warm handoff to a national suicide hotline contracted for this trial. The suicide hotline assesses suicidality and emergent treatment needs, provides appropriate follow-up, and securely transmits a written disposition. This procedure has worked well in previous trials.[65]

Clinical deterioration. If a participant develops manic or psychotic symptoms, or if her QIDS score increases by 5+ points from baseline, she is evaluated by an independent clinician to see if she needs to be referred for other treatment and/or removed from the trial.

Treatment nonresponse. Women in either condition whose MDD has not remitted by the end of the study (week 28) are referred for other treatment.

Dissemination policy and access to data

In addition to dissemination through academic papers and presentation to clinical communities, we will also share results with community organizations through which we recruited through written reports and community talks and will offer to share final study results with study participants. De-identified datasets will be available to qualified investigators upon request.

Conclusion

This will be the first fully-powered RCT evaluating treatment for any psychiatric disorder following perinatal loss, a population whose distress has historically been minimized. Given the more than 160 requests for the IPT manual fulfilled to date worldwide, results have high potential for dissemination and uptake.

Author statement. Johnson: Conceptualization (lead), funding acquisition (lead), investigation (lead), intervention development (equal), safety protocols (lead), writing – original draft preparation (lead), writing – review and editing (lead). **Zlotnick:** Conceptualization (supporting), funding acquisition (supporting), clinical supervision (equal), safety protocols (supporting), writing – review and editing (supporting). **Price:** Funding acquisition (supporting), intervention development (equal), clinical supervision (equal). **Sikorskii:** Conceptualization (supporting), funding acquisition (supporting), data curation, formal analysis. **Key:** Funding acquisition (supporting), recruitment strategy (supporting). **Lamphere, Taylor, Huff, and Cinader:** Recruitment strategies (lead), development of operating procedures (supporting), choice of measures (supporting).

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Competing interests statement. The authors have no competing interests.

Table 1

Outline of IPT for major depressive disorder following perinatal loss

Session name	Session activities
1: Emotions of grief	Each woman tells her perinatal loss story and: expresses her feelings at the time of her loss, feels and expresses her current feelings about her loss, elicits support from and supports the other group members. Each woman is guided to: identify current supportive people, select one person to ask for grief support, role-play how to ask for support.
2: Understanding what happened	Each woman: explores her understanding of what happened to her pregnancy/baby, explores her thoughts/feelings about fault or blame, explores what the loss means to her, begins to explore who she has talked to about the loss and how she talks to them about her needs, identifies who she will invite to Session 3, role-plays how to communicate this invitation. The therapist: helps each woman unpack and examine whether there was anything she could have done to change the outcome, with support from the group, guides the women to seek information from their OBGYN providers about what does and does not contribute to perinatal loss, guides women to identify additional questions for their providers, helps each woman explore how she makes sense of her loss.
3: Grieving with others	Each woman is encouraged to invite a support person to the group. The therapist provides psychoeducation about: depression, grieving styles, ways to manage grieving differences, how IPT helps women recover and how partner/family/friend support can help women recover. Next the therapist guides each woman and her support person to: complete a written communication exercise about both partners' loss-related emotional needs, discuss their written answers privately for 20 minutes, discuss as a group what they learned from each other about support, discuss how each pair will manage communication with others in their social network, develop communication homework to improve each pair's support of each other regarding the loss.
4: Holding the memory and moving forward	Each woman discusses how she: holds the memory/meaning of her loss experience, can re-engage in life roles, seeks support and communication with key people, reflects on her grief process and her recovery from depression. The therapist guides the group by: reminding them that new members are added next week and discussing ways to welcome them, eliciting and role-modeling how to offer well-wishes to and from women completing their group treatment in this session.

Table 2

Schedule of Assessments

Measure	Baseline	Week 8	Week 16	Week 28
Diagnosis and safety				
SCID-5	X			
Women's Experience with Battering screener	X			
Longitudinal Interval Follow-up Examination	X	X	X	X
Psychiatric symptoms				
Quick Inventory of Depressive Symptoms	X	X	X	X
Life Events Checklist and PTSD Checklist	X	X	X	X
Hypothesized mediators				
Multidim. Scale of Perceived Social Support	X	X	X	X
Relationship Assessment Scale	X	X	X	X
Social Adjustment Scale total score	X	X	X	X
Social Adjustment Scale parental functioning	X	X	X	X
Other outcomes (grief, well-being, fear)				
NIH Neuro-Quality of Life scale	X	X	X	X
Perinatal Bereavement Grief Scale	X	X	X	X
Inventory of Complicated Grief	X	X	X	X
Loss Beliefs Scale	X	X	X	X
Fear of subsequent pregnancies	X	X	X	X
Treatment acceptability of IPT and CWD				
Client Satisfaction Scale – Revised			X	

Table 3

Power for n = 274 for secondary outcomes

	d = .29	*d* = .32	*d* = .35
10% attrition	.81	**.88**	.93
15% attrition	.74	.83	.88
20% attrition	.72	.80	.86
25% attrition	.69	.78	.84

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Pages
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**3**
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	**NA**
Funding	4	Sources and types of financial, material, and other support	**18**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**1, 18**
	5b	Name and contact information for the trial sponsor	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**4-6**
	6b	Explanation for choice of comparators	**6**
Objectives	7	Specific objectives or hypotheses	**5**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	**9**
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**9-10**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**8-9**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**6-8**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	**17**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	**10**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**8**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	**10-12**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**20**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**15**

Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	**9-10**
Methods: Assignment of interventions (for controlled trials)			
Allocation:			**9**
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**9**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**9**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**9**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**10**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**NA**
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**10-12**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**10**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**16**

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**12-15**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**12-15**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**12-15**
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**NA**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**13**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**16-17**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**NA**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**16**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**NA**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**16**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**NA**

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**16**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**18**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**17**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**17**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**17**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**NA**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**17**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**NA**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**NA**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol for the Healing After Loss (HeAL) Study: A randomized controlled trial of interpersonal psychotherapy (IPT) for major depression following perinatal loss

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Keywords:	Depression & mood disorders < PSYCHIATRY, Adult psychiatry < PSYCHIATRY, Maternal medicine < OBSTETRICS

Running Head: PERINATAL LOSS

Protocol for the Healing After Loss (HeAL) Study: A randomized controlled trial of interpersonal psychotherapy (IPT) for major depression following perinatal loss

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Abstract

Introduction. This protocol describes a study testing the efficacy of interpersonal psychotherapy (IPT) for major depressive disorder following perinatal loss (early and late fetal death and early neonatal death). Perinatal loss is associated with elevated risk of major depressive disorder and posttraumatic stress disorder (PTSD). Perinatal loss conveys specific treatment needs. The trial will be the first fully-powered randomized trial of treatment for any psychiatric disorder following perinatal loss.

Methods and analysis. A sample of 274 women in Flint and Detroit areas in Michigan who experience a major depressive episode following a perinatal loss will be randomized to group IPT for perinatal loss or to group Coping with Depression (CWD). We anticipate that 50% of the sample will have co-occurring PTSD. Assessments occur at baseline, mid-treatment (8 weeks), post-treatment (16 weeks), and follow-up (28 weeks). Clinical outcomes include time to recovery from major depressive episode (primary), depressive symptoms, PTSD symptoms, and time to recovery from PTSD. Additional outcomes include social support, social role functioning (including parental functioning for those with living children), well-being, grief (including complicated grief and fault beliefs), and fear of subsequent pregnancies. Social support and grief are hypothesized mediators of IPT effects on time to recovery from major depressive episode.

Ethics and dissemination. The trial was approved by Michigan State University's Biomedical Institutional Review Board. It has a Data and Safety Monitoring Board and has been submitted to the Community Based Organization Partners Community Ethics Review Board. Written operating procedures outline methods for protecting confidentiality, monitoring and recording adverse events, and safeguarding participants. We will share study results with research and clinical communities, community organizations through which we recruited, and will offer results to study

participants. De-identified datasets will be available through the National Institute of Mental Health Data Archive and to qualified investigators upon request.

Clinical trials registration. The trial was registered at clinicaltrials.gov (NCT04629599).

Key words: Miscarriage, stillbirth, fetal death, perinatal death, major depressive disorder, posttraumatic stress disorder, interpersonal psychotherapy.

Word count: 4,000

Article Summary: Strengths and limitations of this study

- This study addresses a clinical need, and will provide an evidence base for treating a n understudied population whose distress has historically been minimized.
- The trial will have strong representation from disparities populations (especially African American women and socioeconomically disadvantaged women) who experience higher rates of perinatal loss, increasing its significance.
- Rigor and reproducibility are ensured by the randomized design, clear inclusion criteria, use of well-established research, recruitment, and retention methods, use of reliable and valid measures, the use of raters blinded to treatment condition, and transparent power and statistical analyses.
- Intervention strengths include clearly distinct treatment conditions, use of manualized treatment protocols and fidelity assessments, and team members with decades of clinical experience responding to perinatal loss.
- Challenges may include recruitment during a global pandemic in communities with a higher levels of research mistrust and more mental health stigma than in the pilot trial.

Introduction

About 650,000 women in the United States experience perinatal loss each year (including early and late fetal death and the death of a liveborn neonate within the first 28 days).[1 2] Rates of major depressive disorder (MDD) after perinatal loss are higher than after giving birth to a living infant, and are 3 times the rates among matched samples of community women.[3-20] Rates of posttraumatic stress disorder (PTSD) after perinatal loss are up to 7 times the rates of PTSD among mothers of living infants,[13] and elevated PTSD symptoms can occur for years after the loss.[21] Fetal or neonatal death triples rates of suicide and of hospitalization for suicide attempts.[22 23]

Not only do women with perinatal loss have higher rates of MDD and PTSD than mothers of living infants, their needs also differ from needs following many other kinds of bereavement. In perinatal loss, the fact of bereavement is compounded by the physical experience of miscarriage or of delivering a baby that has already died.[24] Many women experiencing perinatal loss grieve in secret, as others may not know about the loss. Even if others do know, there are few social norms that guide how others can or should support the bereaved, making support less likely and often less helpful (e.g., "you can just have another one").[12 25] Reasons for loss are often unclear and many women blame themselves.

Despite recognition that MDD (with or without co-occurring PTSD) following perinatal loss causes impairment and that treatment as usual is often inadequate,[26-30] our previous pilot work[31] created and tested the first manual for treating any psychiatric disorder after perinatal loss. The manual is structured and applies interpersonal psychotherapy (IPT) principles to MDD following perinatal loss in a group format. Previous IPT and other treatment manuals for perinatal depression[32-35] focus on helping women adjust their relationships, identity, roles, and routines to the demands of a new baby. This is inappropriate in the context of perinatal loss. Our manual

applies IPT social support and communication principles to issues such as resolving conflicts over how to respond to the loss, grieving and requesting support in the absence of social norms about how to do so, and resolving questions of fault and role competence. It can be used by providers who do not know IPT. A randomized pilot trial of women experiencing MDD following perinatal loss established acceptability of proposed study procedures and identified high rates of co-occurring PTSD (54%) among study participants.[31] Results favored the new IPT manual for PTSD recovery, treatment satisfaction, depressive symptoms, grief, and social support relative to Coping with Depression (CWD), a cognitive-behavioral based intervention that does not focus on perinatal loss, interpersonal issues, or social support.[31]

Based on those promising results, the current study will be the first fully-powered randomized trial of treatment for any psychiatric disorder following perinatal loss. We will compare our group IPT manual to a general group depression treatment (CWD) in a sample of 274 women experiencing MDD in the context of perinatal loss. The trial will test the hypotheses that:

1. IPT for perinatal loss will result in reduced time to recovery from MDD (primary), depressive symptoms, and PTSD symptoms, relative to CWD. Among women meeting criteria for PTSD, IPT will result in reduced time to recovery from PTSD relative to CWD.
2. IPT for perinatal loss will result in increased social support, social role functioning (including parental functioning for women with living children), and well-being, and decreased grief and fear of subsequent pregnancies, relative to CWD.
3. Social support and grief will mediate the effects of IPT on time to MDD recovery.

This trial will provide an evidence base for treating a vulnerable and understudied population whose distress has historically been minimized. Given that poverty increases risk of perinatal loss,[36-38] and doubles the risk of perinatal depression,[39-47] and that rates of perinatal loss for

African-American women are double those for white women,[48-50] the location of the trial in Southeast Michigan, which includes Flint and Detroit (minority-majority cities with high rates of poverty), increases the trial's significance.

Methods and analysis

Patient and public involvement

Research questions arose from a clinical need identified by provider colleagues. Patients provided feedback on treatments, measures, and study procedures in the pilot trial.[31] Local minority-led community-based organizations provided feedback on measures, procedures, and recruitment methods appropriate for the Flint and Detroit areas. The study team is embedded in Flint and Detroit. Team members have lived experience. The trial has been submitted for voluntary review by the Flint-based Community Based Organization Partners Community Ethics Review Board for additional community feedback.[51]

Rationale for design

Given that no other treatment exists for women who experience perinatal-loss related MDD that could be used as a comparator condition, we chose to use a general depression treatment, the Coping With Depression (CWD) course, as a control condition. We chose CWD because it is the group treatment with the most empirical support for treating MDD[52 53] and because it is distinct from IPT. IPT addresses MDD through emotional exploration, work on relationships, communication, grief, and social support. CWD addresses MDD by changing thinking and behavior; it focuses on skills for reducing depression in general and does not have perinatal-loss specific components. Our IPT treatment differs from CWD in its focus on exploring reactions to the loss, addressing loss-related interpersonal challenges, and improving loss-related social support and grief-specific coping. The trial's secondary outcomes (social support, social

functioning, grief) assess hypothesized differences between treatments. As desired, our pilot study found differences between conditions in the hypothesized mechanisms of social support and grief and in terms of in-session activities.[31]

Treatments

Manualized treatments are attention-matched (12 groups of 90 minutes each, 1 individual pre-group session, and 1 booster session). Every 4 weeks, both treatments allow new women to enter the group and women completing 12 weeks to leave the group.

Interpersonal psychotherapy (IPT). Participants in the IPT condition receive 12 group sessions and 2 individual (pre-group and 1-month booster) sessions as outlined in the structured manual (see Table 1 and pilot trial[31]). The individual sessions prepare patients to use the group effectively, to keep group members focused on their treatment goals, and to maintain treatment gains. In addition, 3 of the 12 group sessions invite women to include their partners or other support people to bolster the woman's social support system and to reduce conflicts over how to react to the loss. Relationship distress is common following perinatal loss.[12 54]

Group sessions are semi-structured, and each woman covers the four group topics listed in Table 1 three times over her 12 group sessions, approaching each topic from a different stage in the mourning process. New women are allowed to enter group every four sessions. This allows remaining women to see their own progress and encourages new women through example and peer counseling.

Coping with Depression (CWD). CWD is a structured, manualized[55] psycho-educational group treatment for MDD. The CWD course is cognitive-behavioral. The problems shown by depressed individuals are viewed as behavioral, with cognitive patterns that can be unlearned or relearned. Its effectiveness is comparable to other forms of psychotherapy in depression.[53] The

course content teaches skills including relaxation, cognitive skills, and behavioral activation. The CWD pre-group and booster sessions are the pre-group and booster sessions from the published CWD manual[55]. To ensure that the CWD intervention was distinct from IPT, we excluded the 2 sessions on social skills and emphasized pleasant activities that were individual rather than social. Consistent with standard CWD, we focused on addressing depression rather than discussing grief or perinatal loss. We expanded other CWD material (e.g., relaxation practice) to replace sessions on social skills. In our studies, the 12 CWD sessions covered: an introduction to social learning rationale of depression; learning to relax; relaxation in everyday situations; pleasant activities and depression; formulating a pleasant activities plan; constructive thinking; planning for constructive thinking; and maintaining gains (see published manual[55] and pilot trial[31] for additional details).

Participants

Participants will be 274 women who are experiencing MDD in the context of perinatal loss who (1) meet DSM-5[56] criteria for MDD; (2) have experienced a perinatal loss (including early and late fetal death, death of a liveborn neonate within the first 28 days, and medically recommended termination) within the last 1-12 months; (3) are 18 to 50 years old; (4) speak and understand English well enough to understand questionnaires when they are read aloud; (5) can provide the name and contact information of at least two locator persons; and (6) have access to a telephone. Exclusion criteria are: (1) onset of *current* major depressive episode prior to news of difficulties with the pregnancy or health risk to the infant (women with prior episodes are included); (2) current or past diagnosis of bipolar disorder, schizophrenia or other psychotic disorder; (3) primary diagnosis of current substance use disorder; (4) acute suicidal or homicidal risk; (5) beginning or changing dose of antidepressant medication or psychotherapy in the previous 12 weeks); (6) any IPT or cognitive-behavioral treatment in the previous 12 weeks. Women in stable

concurrent psychotherapy who are included are asked to suspend this treatment during the active study treatment phase. PTSD is not an inclusion criterion. However, based on our pilot,[31] we anticipate that slightly more than half the sample will meet criteria for PTSD at study enrollment.

Therapist training and supervision

We trained 8 study therapists (4 in IPT and 4 in CWD) who are MSWs or clinical or counseling psychologists. Therapists are recruited from their respective communities to moonlight as clinicians in this proposed study. Therapists are provided with the detailed treatment manuals. Training for both conditions includes education and role plays. Therapists in both conditions will be monitored for adherence/competence throughout the study and retrained as needed.

Supervision involves review of therapists' audiotaped sessions and a weekly one-hour small-group telephone meeting for feedback and case discussion. Treatment sessions are audio recorded using digital audio recorders or a HIPAA-compliant version of Zoom. Study therapists remotely upload the recordings to the study's secure research server, where the supervisors can remotely access them.

Randomization

Women are randomly assigned to IPT or CWD in a 1:1 ratio. We stratify randomization on (1) whether women have been taking antidepressant medications or attending other psychotherapy (stability of dose is an inclusion criterion); and (2) type of perinatal loss (miscarriage, stillbirth, neonatal death). Randomization sequences were created by the study statistician. Assignment is concealed in an envelope that research assistants open at randomization.

Recruitment

Participants are recruited from counties in Southeast Michigan using a broad outreach strategy. We partner with regional health systems, community-based organizations in Flint and

Detroit, and a regional Medicaid system in study recruitment. Recruitment also includes flyers and referrals from: (1) local birthing centers, emergency departments, OBGYN offices, and federally qualified health centers; (2) hotlines, support groups, family nurse partnerships; (3) funeral homes; (4) churches, daycare centers, other places where women and mothers congregate (WIC offices, Medicaid offices, etc.); (5) bus ads; and (6) online venues. We began recruitment on September 1, 2021 and plan to end on March 1, 2025.

Research sites

We had planned to offer baseline assessments at women's homes or our offices, group sessions in community locations convenient for participants (as we did in the pilot trial),[31] and to conduct follow-up assessments by telephone. However, due to the COVID-19 pandemic, we are currently conducting all assessments and treatment sessions by Zoom, with an option to go back to holding groups in person in the future.

Retention

We employ techniques we have found helpful in achieving low attrition rates in previous studies.[31 57-59] These include study staff's strong relationships with participants, efforts to value and appreciate the women's participation in the study, and frequent personal contact. We are flexible about follow-up appointment scheduling and train research staff to be culturally sensitive. Follow-up assessments take place by Zoom or phone, with well-established safety procedures for emergencies.[57] We maintain a list of two other people who know where the participant resides. We conduct treatment groups at different times and locations to make attendance easier. If a woman misses a treatment appointment, the therapist calls her to check in and problem-solve barriers to attendance. Finally, participant fees for follow-up assessments help facilitate retention.

Assessments

Assessments take place at baseline, mid-treatment (8 weeks), post-treatment (16 weeks), and follow-up (28 weeks; see Table 2). Assessments are conducted by research assistants (RAs) trained and certified in interviewer administered instruments and blind to treatment assignment. Interviewers and senior staff meet regularly to review assessment tapes, address questions, and monitor inter-rater reliability. Data quality is maintained through clerical and clinical checks after data are entered and through regular examination of distributions, missing data, and outliers.

Diagnosis/screening. The Structured Clinical Interview for DSM-5 (SCID-5)[60] is used to establish study eligibility. During follow-up, the Longitudinal Interval Follow-up Examination (LIFE),[61 62] a standardized retrospective calendar-based interview, is used to assess MDD and PTSD recovery. The LIFE uses Psychiatric Status Ratings (PSRs) to categorize DSM-5 symptoms on a scale of 1 (asymptomatic) to 6 (incapacitated) for each week. A PSR of 5 or 6 indicates the participant meets full diagnostic criteria, 3 or 4 indicates subthreshold disorder, and 1 or 2 indicates the participant is not in episode. Recovery is defined as 8 consecutive weeks of a PSR of 1-2.[63] The LIFE is the gold-standard way of determining onset and offset of psychiatric disorder.[63] We also use the LIFE to track participation in psychotherapeutic and psychopharmacologic treatment at baseline and follow-up. We assess partner violence using the Women's Experience with Battering screen.[64] Battered women (scores of 20+) are included in the study and provided with partner violence resources.

Depressive symptoms are assessed using the Quick Inventory of Depressive Symptoms (QIDS), Self-Report version.[65]

PTSD symptoms are assessed using the Life Events Checklist and PTSD Checklist for DSM-5 (LEC-PCL).[66-69] We also assess whether PTSD symptoms are related to the perinatal loss.

Social support and social functioning. We use the 12-item Multidimensional Scale for

Perceived Social Support (MSPSS)[70] to assess overall social support. We use a validated adaptation of the Relationship Assessment Scale[71] to assess satisfaction with an important significant other (partner or other support person of the woman's choosing) relationship. We assess social functioning using the Short version of the Social Adjustment Scale – Self-Report (SAS-SR).[72] Because depression can affect parenting, we will analyze the SAS-SR total score as well as its parental functioning subscale.

Well-being (including life satisfaction, purpose and meaning) is measured by using the 23-item Neuro-QoL scale for positive affect and well-being.[73]

Grief symptoms are measured using the Perinatal Bereavement Grief Scale (PBGS).[4 74] Complicated grief is measured using the Inventory of Complicated Grief (ICG).[75] A few items on the ICG were reworded to refer to perinatal loss. Given that many women present with unwarranted beliefs about what caused the loss, we assess deservingness and guilt as grief outcomes using a 7-item scale about loss beliefs (the Loss Beliefs Scale). This scale includes items such as "I think what happened was my fault" and "The miscarriage, stillbirth, or baby's death was caused by something about me." This perinatal loss specific scale was created after reviewing the literature on beliefs about deserved bad outcomes (e.g.,[76-78]).

Fear of subsequent pregnancies is assessed by 7-point Likert items (from 1 = Strongly Disagree" to 7 = "Strongly Agree"): (1) "I am afraid to become pregnant again"; (2) "I look forward to becoming pregnant again"; (3) "I plan to become pregnant again"; (4) "I worry about what might happen if I get pregnant again," (5) "I do not want to be pregnant again."

Treatment acceptability is measured using the Client Satisfaction Questionnaire-Revised (CSQ-8-R).[79]

Treatment integrity. We will use the IPT and CWD adherence and competence scales

developed in the pilot trial[31] to rate fidelity using audio recordings. As in the pilot trial, raters will also assess the percent of time in each group session spent discussing the perinatal loss and discussing loss-related communication strategies.[31]

Analysis

Primary analyses will be intent-to-treat. We will examine dose-response effects in secondary analyses. Primary tests will be two-sided with p=0.05. Descriptive statistics will include effect sizes and measures of clinical significance.[80] Primary and secondary outcomes and all hypotheses are stated a priori, therefore 0.05 level of significance will be used. Per Kraemer,[81] we will not test for differences between conditions due to randomization as those differences are due to chance alone, rendering p-values meaningless. Covariates for analyses are specified a priori based on subject matter expertise. No interim analyses are planned.

Attrition analysis and missing data. We will compare characteristics of those who drop out by trial arm and compare those who complete the study with those who do not to assess generalizability of findings. For the primary outcome of time to MDD recovery, unobserved time to MDD resolution for the drop-outs will be treated as censored. For secondary outcomes, regression techniques below allow for missing at random (MAR) mechanism.[82] If patterns of missing data indicate potential not missing at random (NMAR) mechanisms, then models describing missing mechanisms will be considered (e.g., pattern-mixture models),[83] [84] and sensitivity analyses will be employed.

General approaches. For survival analyses, the proportional hazard (PH) assumption will be evaluated. If it holds, then survival analyses will use Cox regression. If not, time-varying effects will be investigated, and the model will be modified to include an interaction of relevant covariates with a function of time variable. Stratified models will also be considered.

Linear mixed effects (LME) models will be used to test differences between trial arms for continuous outcomes. All participants with at least one completed post-baseline assessment will be included. We expect these scores to follow normal distributions. However, generalized linear mixed effects (GLME) modeling will be used if outcome is not normally distributed and cannot be normalized using transformations.

Aim 1. (1) Using survival analysis, with initial QIDS score as a covariate, we will test the hypothesis that IPT, relative to CWD, will result in reduced time to recovery from the major depressive episode (primary). (2) Using LME or GLME with baseline QIDS score as a covariate, we will test the hypothesis that IPT, relative to CWD, will result in reduced depressive symptoms (QIDS scores) across post-baseline assessments. (3) Using LME or GLME with baseline PCL score as a covariate, we will test the hypothesis that IPT, relative to CWD, will result in reduced PTSD symptoms (PCL score) across post-baseline assessments. (4) Using survival analysis, with initial PCL score as a covariate, we will test the hypothesis that IPT, relative to CWD, will result in reduced time to recovery from PTSD.

Aim 2. Using baseline scores as covariates, we will separately test the hypotheses that IPT for perinatal loss will result in increased social support, social role functioning, and well-being, and decreased grief and fear of subsequent pregnancies, relative to CWD, using the LME or GLME modeling described above. Specifically, controlling for baseline values, we will use separate analyses to test the effects of IPT vs. CWD on MSPSS, Relationship Assessment Scale, SAS-SR total, SAS-SR parenting subscale, Neuro-QoL, Perinatal Bereavement Grief Scale, Inventory of Complicated Grief, Loss Belief Scale, and Fear of Subsequent Pregnancy scores. We will also compare conditions on CSQ-8-R Treatment Acceptability.

Aim 3. We will test the hypotheses that social support (MSPSS scores) and grief (PBGS

scores) will mediate the effects of IPT on time to MDD recovery. To test for mediation, trial arm will be treated as the independent variable and each potential mediator (one at a time) will be tested for their effect on the outcome variable at weeks 8, 16, and 28, with the baseline value of that outcome treated as a covariate. We will use a bias corrected bootstrapping analytic strategy[85 86] based on 5000 bootstrap samples to estimate confidence intervals (CIs) around the indirect effect of study group on the outcome variable, through the mediator.

Moderators. We will calculate differential effect estimates and test the interactions between several participant characteristics and the intervention effect in predicting time to recovery from MDD. Characteristics to be examined include race, ethnicity, having living children, type of perinatal loss, stable use of other antidepressant or psychosocial treatment at baseline, having PTSD at baseline, having a partner, number of past depressive episodes, and time since loss. Given our emphasis on meeting the needs of minority women, we will also evaluate whether mediation relationships or intervention effects on secondary outcomes differ by race.

Sample size

Recovery outcomes. For the primary outcome of time to MDD recovery (censored at 28 weeks), assuming 1:1 allocation, power 0.80, two-sided tests at p=0.05, and observed estimated hazard ratio=1.79, the required number of events is 94 (number of MDEs resolved). By week 28, there were 17 events in the preliminary data (17 women had MDD resolved, 11 in the IPT condition, and 6 in the CWD condition) out of 45 participants, so the rate of events was .38. Thus to have 94 events, total N=246 is required. Given that 90% of pilot trial participants completed at least one follow-up assessment,[31] we increased the sample size to 274. Given the observed hazard ratio of 5.85 for PTSD in the pilot trial, power for PTSD recovery should be greater than 80%.

Tests of mediation in Aim 3 will have greater power than the primary outcome because of reduction in error variance when controlling for the mediator.

Continuous (secondary) outcomes. Assuming an unadjusted d = .32 and a correlation of 0.6 between follow-up measures and 0.3 with baseline (as observed in the preliminary data), the adjusted effect size would be 0.40, and only n = 200 participants would be needed before attrition. If study attrition is higher, the study still has > 80% power for secondary outcomes (Table 3).

Ethics and Dissemination

The trial was approved by Michigan State University's Biomedical Institutional Review Board (FWA 00004556). A three-member external Data and Safety Monitoring Board reviews data and safety of study participants. Trial safety procedures are codified through checklists and a written manual of operating procedures.

Informed consent and confidentiality

When potential participants contact the study, study RAs meet with them privately (electronically or in person). RAs explain risks, benefits, and the voluntary nature of the study and obtain participants' signed informed consent.

Confidentiality is protected by research staff trained to manage sensitive clinical issues. Participants are informed about the limits of confidentiality concerning suicidal intent, homicidal intent, and suspected child or elder abuse. Computer files are available only to authorized personnel, with no names or obvious identifying information stored in data files. Confidentiality of recordings of study assessments and treatment sessions is protected through: (1) use of encrypted audio recorders and HIPAA-compliant videoconferencing; (2) labeling recordings with study IDs rather than names; (3) storing recordings on a secured computer server designed to hold and protect research data; and (4) limiting access to recordings.

Participant safety

Adverse events. Participant safety is monitored during study assessments and during study treatment sessions. Pre-specified adverse events are recorded and monitored using a structured system created within REDCap with alerts for follow-up actions.[57]

Suicide risk. During assessments, participants who score 2 or above (any active suicide ideation) on the QIDS suicide item are transferred via warm handoff to a national suicide hotline contracted for this trial. The suicide hotline assesses suicidality and emergent treatment needs, provides follow-up, and securely transmits a written disposition. This procedure has worked well in previous trials.[57]

Clinical deterioration. If a participant develops manic or psychotic symptoms, or if her QIDS score increases by 5+ points from baseline, she is evaluated by an independent clinician to see if she needs to be referred for other treatment and/or removed from the trial.

Treatment nonresponse. Women in either condition whose MDD has not remitted by the end of the study (week 28) are referred for other treatment.

Dissemination policy and access to data

Dissemination activities will include academic papers, presentations to clinical communities, community reports and talks with organizations through which we recruited, and offering to share final study results with study participants. De-identified datasets will be available to qualified investigators upon request.

Author statement. Johnson: Conceptualization (lead), funding acquisition (lead), investigation (lead), intervention development (equal), safety protocols (lead), writing – original draft preparation (lead), writing – review and editing (lead). **Zlotnick:** Conceptualization (supporting), funding acquisition (supporting), clinical supervision (equal), safety protocols (supporting), writing – review and editing (supporting). **Price:** Funding acquisition (supporting), intervention development (equal), clinical supervision (equal). **Sikorskii:** Conceptualization (supporting), funding acquisition (supporting), data curation, formal analysis. **Key:** Funding acquisition (supporting), recruitment strategy (supporting). **Lamphere, Taylor, Huff, and Cinader:** Recruitment strategies (lead), development of operating procedures (supporting), choice of measures (supporting).

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Competing interests statement. The authors have no competing interests.

Table 1

Outline of IPT for major depressive disorder following perinatal loss

Session name	Session activities
1: Emotions of grief	Each woman tells her perinatal loss story and: expresses her feelings at the time of her loss, feels and expresses her current feelings about her loss, elicits support from and supports the other group members. Each woman is guided to: identify current supportive people, select one person to ask for grief support, role-play how to ask for support.
2: Understanding what happened	Each woman: explores her understanding of what happened to her pregnancy/baby, explores her thoughts/feelings about fault or blame, explores what the loss means to her, begins to explore who she has talked to about the loss and how she talks to them about her needs, identifies who she will invite to Session 3, role-plays how to communicate this invitation. The therapist: helps each woman unpack and examine whether there was anything she could have done to change the outcome, with support from the group, guides the women to seek information from their OBGYN providers about what does and does not contribute to perinatal loss, guides women to identify additional questions for their providers, helps each woman explore how she makes sense of her loss.
3: Grieving with others	Each woman is encouraged to invite a support person to the group. The therapist provides psychoeducation about: depression, grieving styles, ways to manage grieving differences, how IPT helps women recover and how partner/family/friend support can help women recover. Next the therapist guides each woman and her support person to: complete a written communication exercise about both partners' loss-related emotional needs, discuss their written answers privately for 20 minutes, discuss as a group what they learned from each other about support, discuss how each pair will manage communication with others in their social network, develop communication homework to improve each pair's support of each other regarding the loss.
4: Holding the memory and moving forward	Each woman discusses how she: holds the memory/meaning of her loss experience, can re-engage in life roles, seeks support and communication with key people, reflects on her grief process and her recovery from depression. The therapist guides the group by: reminding them that new members are added next week and discussing ways to welcome them, eliciting and role-modeling how to offer well-wishes to and from women completing their group treatment in this session.

Table 2

Schedule of Assessments

Measure	Baseline	Week 8	Week 16	Week 28
Diagnosis and safety				
SCID-5	X			
Women's Experience with Battering screener	X			
Longitudinal Interval Follow-up Examination	X	X	X	X
Psychiatric symptoms				
Quick Inventory of Depressive Symptoms	X	X	X	X
Life Events Checklist and PTSD Checklist	X	X	X	X
Hypothesized mediators				
Multidim. Scale of Perceived Social Support	X	X	X	X
Relationship Assessment Scale	X	X	X	X
Social Adjustment Scale total score	X	X	X	X
Social Adjustment Scale parental functioning	X	X	X	X
Other outcomes (grief, well-being, fear)				
NIH Neuro-Quality of Life scale	X	X	X	X
Perinatal Bereavement Grief Scale	X	X	X	X
Inventory of Complicated Grief	X	X	X	X
Loss Beliefs Scale	X	X	X	X
Fear of subsequent pregnancies	X	X	X	X
Treatment acceptability of IPT and CWD				
Client Satisfaction Scale – Revised			X	

Table 3

Power for n = 274 for secondary outcomes

	d = .29	*d* = .32	*d* = .35
10% attrition	.81	**.88**	.93
15% attrition	.74	.83	.88
20% attrition	.72	.80	.86
25% attrition	.69	.78	.84

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Pages
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**3**
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	**NA**
Funding	4	Sources and types of financial, material, and other support	**18**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**1, 18**
	5b	Name and contact information for the trial sponsor	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**4-6**
	6b	Explanation for choice of comparators	**6**
Objectives	7	Specific objectives or hypotheses	**5**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	**9**
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**10**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**8-9**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**6-8**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	**17**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	**10**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**8**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	**11-13**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**20**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**15-16**

Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	**9-10**
Methods: Assignment of interventions (for controlled trials)			
Allocation:			**9**
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**9**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**9**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**9**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**10**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**NA**
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**11-13**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**10**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**16**

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**13-15**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**13-15**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**13-15**
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**NA**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**13**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**17**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**NA**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**16**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**NA**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**16**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**NA**

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**16**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**18**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**17**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**17**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**17**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**NA**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**17**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**attached**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**NA**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol for the Healing After Loss (HeAL) Study: A randomized controlled trial of interpersonal psychotherapy (IPT) for major depression following perinatal loss

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Running Head: PERINATAL LOSS

Protocol for the Healing After Loss (HeAL) Study: A randomized controlled trial of interpersonal psychotherapy (IPT) for major depression following perinatal loss

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Abstract

Introduction. This protocol describes a study testing the efficacy of interpersonal psychotherapy (IPT) for major depressive disorder following perinatal loss (early and late fetal death and early neonatal death). Perinatal loss is associated with elevated risk of major depressive disorder and posttraumatic stress disorder (PTSD). Perinatal loss conveys specific treatment needs. The trial will be the first fully-powered randomized trial of treatment for any psychiatric disorder following perinatal loss.

Methods and analysis. A sample of 274 women in Flint and Detroit areas in Michigan who experience a major depressive episode following a perinatal loss will be randomized to group IPT for perinatal loss or to group Coping with Depression (CWD). We anticipate that 50% of the sample will have co-occurring PTSD. Assessments occur at baseline, mid-treatment (8 weeks), post-treatment (16 weeks), and follow-up (28 weeks). Clinical outcomes include time to recovery from major depressive episode (primary), depressive symptoms, PTSD symptoms, and time to recovery from PTSD. Additional outcomes include social support, social role functioning (including parental functioning for those with living children), well-being, grief (including complicated grief and fault beliefs), and fear of subsequent pregnancies. Social support and grief are hypothesized mediators of IPT effects on time to recovery from major depressive episode.

Ethics and dissemination. The trial was approved by Michigan State University's Biomedical Institutional Review Board. It has a Data and Safety Monitoring Board and has been submitted to the Community Based Organization Partners Community Ethics Review Board. Written operating procedures outline methods for protecting confidentiality, monitoring and recording adverse events, and safeguarding participants. We will share study results with research and clinical communities, community organizations through which we recruited, and will offer results to study

participants. De-identified datasets will be available through the National Institute of Mental Health Data Archive and to qualified investigators upon request.

Clinical trials registration. The trial was registered at clinicaltrials.gov (NCT04629599).

Key words: Miscarriage, stillbirth, fetal death, perinatal death, major depressive disorder, posttraumatic stress disorder, interpersonal psychotherapy.

Word count: 4,000

Article Summary: Strengths and limitations of this study

- This study addresses a clinical need, and will provide an evidence base for treating a n understudied population whose distress has historically been minimized.
- The trial will have strong representation from disparities populations (especially African American women and socioeconomically disadvantaged women) who experience higher rates of perinatal loss, increasing its significance.
- Rigor and reproducibility are ensured by the randomized design, clear inclusion criteria, use of well-established research, recruitment, and retention methods, use of reliable and valid measures, the use of raters blinded to treatment condition, and transparent power and statistical analyses.
- Intervention strengths include clearly distinct treatment conditions, use of manualized treatment protocols and fidelity assessments, and team members with decades of clinical experience responding to perinatal loss.
- Challenges may include recruitment during a global pandemic in communities with a higher levels of research mistrust and more mental health stigma than in the pilot trial.

Introduction

About 650,000 women in the United States experience perinatal loss each year (including early and late fetal death and the death of a liveborn neonate within the first 28 days).[1 2] Rates of major depressive disorder (MDD) after perinatal loss are higher than after giving birth to a living infant, and are 3 times the rates among matched samples of community women.[3-20] Rates of posttraumatic stress disorder (PTSD) after perinatal loss are up to 7 times the rates of PTSD among mothers of living infants,[13] and elevated PTSD symptoms can occur for years after the loss.[21] Fetal or neonatal death triples rates of suicide and of hospitalization for suicide attempts.[22 23]

Not only do women with perinatal loss have higher rates of MDD and PTSD than mothers of living infants, their needs also differ from needs following many other kinds of bereavement. In perinatal loss, the fact of bereavement is compounded by the physical experience of miscarriage or of delivering a baby that has already died.[24] Many women experiencing perinatal loss grieve in secret, as others may not know about the loss. Even if others do know, there are few social norms that guide how others can or should support the bereaved, making support less likely and often less helpful (e.g., "you can just have another one").[12 25] Reasons for loss are often unclear and many women blame themselves.

Despite recognition that MDD (with or without co-occurring PTSD) following perinatal loss causes impairment and that treatment as usual is often inadequate,[26-30] our previous pilot work[31] created and tested the first manual for treating any psychiatric disorder after perinatal loss. The manual is structured and applies interpersonal psychotherapy (IPT) principles to MDD following perinatal loss in a group format. Previous IPT and other treatment manuals for perinatal depression[32-35] focus on helping women adjust their relationships, identity, roles, and routines to the demands of a new baby. This is inappropriate in the context of perinatal loss. Our manual

applies IPT social support and communication principles to issues such as resolving conflicts over how to respond to the loss, grieving and requesting support in the absence of social norms about how to do so, and resolving questions of fault and role competence. It can be used by providers who do not know IPT. A randomized pilot trial of women experiencing MDD following perinatal loss established acceptability of proposed study procedures and identified high rates of co-occurring PTSD (54%) among study participants.[31] Results favored the new IPT manual for PTSD recovery, treatment satisfaction, depressive symptoms, grief, and social support relative to Coping with Depression (CWD), a cognitive-behavioral based intervention that does not focus on perinatal loss, interpersonal issues, or social support.[31]

Based on those promising results, the current study will be the first fully-powered randomized trial of treatment for any psychiatric disorder following perinatal loss. We will compare our group IPT manual to a general group depression treatment (CWD) in a sample of 274 women experiencing MDD in the context of perinatal loss. The trial will test the hypotheses that:

1. IPT for perinatal loss will result in reduced time to recovery from MDD (primary), depressive symptoms, and PTSD symptoms, relative to CWD. Among women meeting criteria for PTSD, IPT will result in reduced time to recovery from PTSD relative to CWD.
2. IPT for perinatal loss will result in increased social support, social role functioning (including parental functioning for women with living children), and well-being, and decreased grief and fear of subsequent pregnancies, relative to CWD.
3. Social support and grief will mediate the effects of IPT on time to MDD recovery.

This trial will provide an evidence base for treating a vulnerable and understudied population whose distress has historically been minimized. Given that poverty increases risk of perinatal loss,[36-38] and doubles the risk of perinatal depression,[39-47] and that rates of perinatal loss for

African-American women are double those for white women,[48-50] the location of the trial in Southeast Michigan, which includes Flint and Detroit (minority-majority cities with high rates of poverty), increases the trial's significance.

Methods and analysis

Patient and public involvement

Research questions arose from a clinical need identified by provider colleagues. Patients provided feedback on treatments, measures, and study procedures in the pilot trial.[31] Local minority-led community-based organizations provided feedback on measures, procedures, and recruitment methods appropriate for the Flint and Detroit areas. The study team is embedded in Flint and Detroit. Team members have lived experience. The trial has been submitted for voluntary review by the Flint-based Community Based Organization Partners Community Ethics Review Board for additional community feedback.[51]

Rationale for design

Given that no other treatment exists for women who experience perinatal-loss related MDD that could be used as a comparator condition, we chose to use a general depression treatment, the Coping With Depression (CWD) course, as a control condition. We chose CWD because it is the group treatment with the most empirical support for treating MDD[52 53] and because it is distinct from IPT. IPT addresses MDD through emotional exploration, work on relationships, communication, grief, and social support. CWD addresses MDD by changing thinking and behavior; it focuses on skills for reducing depression in general and does not have perinatal-loss specific components. Our IPT treatment differs from CWD in its focus on exploring reactions to the loss, addressing loss-related interpersonal challenges, and improving loss-related social support and grief-specific coping. The trial's secondary outcomes (social support, social

functioning, grief) assess hypothesized differences between treatments. As desired, our pilot study found differences between conditions in the hypothesized mechanisms of social support and grief and in terms of in-session activities.[31]

Treatments

Manualized treatments are attention-matched (12 groups of 90 minutes each, 1 individual pre-group session, and 1 booster session). Every 4 weeks, both treatments allow new women to enter the group and women completing 12 weeks to leave the group.

Interpersonal psychotherapy (IPT). Participants in the IPT condition receive 12 group sessions and 2 individual (pre-group and 1-month booster) sessions as outlined in the structured manual (see Table 1 and pilot trial[31]). The individual sessions prepare patients to use the group effectively, to keep group members focused on their treatment goals, and to maintain treatment gains. In addition, 3 of the 12 group sessions invite women to include their partners or other support people to bolster the woman's social support system and to reduce conflicts over how to react to the loss. Relationship distress is common following perinatal loss.[12 54]

Group sessions are semi-structured, and each woman covers the four group topics listed in Table 1 three times over her 12 group sessions, approaching each topic from a different stage in the mourning process. New women are allowed to enter group every four sessions. This allows remaining women to see their own progress and encourages new women through example and peer counseling.

Coping with Depression (CWD). CWD is a structured, manualized[55] psycho-educational group treatment for MDD. The CWD course is cognitive-behavioral. The problems shown by depressed individuals are viewed as behavioral, with cognitive patterns that can be unlearned or relearned. Its effectiveness is comparable to other forms of psychotherapy in depression.[53] The

course content teaches skills including relaxation, cognitive skills, and behavioral activation. The CWD pre-group and booster sessions are the pre-group and booster sessions from the published CWD manual[55]. To ensure that the CWD intervention was distinct from IPT, we excluded the 2 sessions on social skills and emphasized pleasant activities that were individual rather than social. Consistent with standard CWD, we focused on addressing depression rather than discussing grief or perinatal loss. We expanded other CWD material (e.g., relaxation practice) to replace sessions on social skills. In our studies, the 12 CWD sessions covered: an introduction to social learning rationale of depression; learning to relax; relaxation in everyday situations; pleasant activities and depression; formulating a pleasant activities plan; constructive thinking; planning for constructive thinking; and maintaining gains (see published manual[55] and pilot trial[31] for additional details).

Participants

Participants will be 274 women who are experiencing MDD in the context of perinatal loss who (1) meet DSM-5[56] criteria for MDD; (2) have experienced a perinatal loss (including early and late fetal death, death of a liveborn neonate within the first 28 days, and medically recommended termination) within the last 1-12 months; (3) are 18 to 50 years old; (4) speak and understand English well enough to understand questionnaires when they are read aloud; (5) can provide the name and contact information of at least two locator persons; and (6) have access to a telephone. Exclusion criteria are: (1) onset of *current* major depressive episode prior to news of difficulties with the pregnancy or health risk to the infant (women with prior episodes are included); (2) current or past diagnosis of bipolar disorder, schizophrenia or other psychotic disorder; (3) primary diagnosis of current substance use disorder; (4) acute suicidal or homicidal risk; (5) beginning or changing dose of antidepressant medication or psychotherapy in the previous 12 weeks); (6) any IPT or cognitive-behavioral treatment in the previous 12 weeks. Women in stable

concurrent psychotherapy who are included are asked to suspend this treatment during the active study treatment phase. PTSD is not an inclusion criterion. However, based on our pilot,[31] we anticipate that slightly more than half the sample will meet criteria for PTSD at study enrollment.

Therapist training and supervision

We trained 8 study therapists (4 in IPT and 4 in CWD) who are MSWs or clinical or counseling psychologists. Therapists are recruited from their respective communities to moonlight as clinicians in this proposed study. Therapists are provided with the detailed treatment manuals. Training for both conditions includes education and role plays. Therapists in both conditions will be monitored for adherence/competence throughout the study and retrained as needed.

Supervision involves review of therapists' audiotaped sessions and a weekly one-hour small-group telephone meeting for feedback and case discussion. Treatment sessions are audio recorded using digital audio recorders or a HIPAA-compliant version of Zoom. Study therapists remotely upload the recordings to the study's secure research server, where the supervisors can remotely access them.

Randomization

Women are randomly assigned to IPT or CWD in a 1:1 ratio. We stratify randomization on (1) whether women have been taking antidepressant medications or attending other psychotherapy (stability of dose is an inclusion criterion); and (2) type of perinatal loss (miscarriage, stillbirth, neonatal death). Randomization sequences were created by the study statistician. Assignment is concealed in an envelope that research assistants open at randomization.

Recruitment

Participants are recruited from counties in Southeast Michigan using a broad outreach strategy. We partner with regional health systems, community-based organizations in Flint and

Detroit, and a regional Medicaid system in study recruitment. Recruitment also includes flyers and referrals from: (1) local birthing centers, emergency departments, OBGYN offices, and federally qualified health centers; (2) hotlines, support groups, family nurse partnerships; (3) funeral homes; (4) churches, daycare centers, other places where women and mothers congregate (WIC offices, Medicaid offices, etc.); (5) bus ads; and (6) online venues. We began recruitment on September 1, 2021 and plan to end on March 1, 2025.

Research sites

We had planned to offer baseline assessments at women's homes or our offices, group sessions in community locations convenient for participants (as we did in the pilot trial),[31] and to conduct follow-up assessments by telephone. However, due to the COVID-19 pandemic, we are currently conducting all assessments and treatment sessions by Zoom, with an option to go back to holding groups in person in the future.

Retention

We employ techniques we have found helpful in achieving low attrition rates in previous studies.[31 57-59] These include study staff's strong relationships with participants, efforts to value and appreciate the women's participation in the study, and frequent personal contact. We are flexible about follow-up appointment scheduling and train research staff to be culturally sensitive. Follow-up assessments take place by Zoom or phone, with well-established safety procedures for emergencies.[57] We maintain a list of two other people who know where the participant resides. We conduct treatment groups at different times and locations to make attendance easier. If a woman misses a treatment appointment, the therapist calls her to check in and problem-solve barriers to attendance. Finally, participant fees for follow-up assessments help facilitate retention.

Assessments

Assessments take place at baseline, mid-treatment (8 weeks), post-treatment (16 weeks), and follow-up (28 weeks; see Table 2). Assessments are conducted by research assistants (RAs) trained and certified in interviewer administered instruments and blind to treatment assignment. Interviewers and senior staff meet regularly to review assessment tapes, address questions, and monitor inter-rater reliability. Data quality is maintained through clerical and clinical checks after data are entered and through regular examination of distributions, missing data, and outliers.

Diagnosis/screening. The Structured Clinical Interview for DSM-5 (SCID-5)[60] is used to establish study eligibility. During follow-up, the Longitudinal Interval Follow-up Examination (LIFE),[61 62] a standardized retrospective calendar-based interview, is used to assess MDD and PTSD recovery. The LIFE uses Psychiatric Status Ratings (PSRs) to categorize DSM-5 symptoms on a scale of 1 (asymptomatic) to 6 (incapacitated) for each week. A PSR of 5 or 6 indicates the participant meets full diagnostic criteria, 3 or 4 indicates subthreshold disorder, and 1 or 2 indicates the participant is not in episode. Recovery is defined as 8 consecutive weeks of a PSR of 1-2.[63] The LIFE is the gold-standard way of determining onset and offset of psychiatric disorder.[63] We also use the LIFE to track participation in psychotherapeutic and psychopharmacologic treatment at baseline and follow-up. We assess partner violence using the Women's Experience with Battering screen.[64] Battered women (scores of 20+) are included in the study and provided with partner violence resources.

Depressive symptoms are assessed using the Quick Inventory of Depressive Symptoms (QIDS), Self-Report version.[65]

PTSD symptoms are assessed using the Life Events Checklist and PTSD Checklist for DSM-5 (LEC-PCL).[66-69] We also assess whether PTSD symptoms are related to the perinatal loss.

Social support and social functioning. We use the 12-item Multidimensional Scale for

Perceived Social Support (MSPSS)[70] to assess overall social support. We use a validated adaptation of the Relationship Assessment Scale[71] to assess satisfaction with an important significant other (partner or other support person of the woman's choosing) relationship. We assess social functioning using the Short version of the Social Adjustment Scale – Self-Report (SAS-SR).[72] Because depression can affect parenting, we will analyze the SAS-SR total score as well as its parental functioning subscale.

Well-being (including life satisfaction, purpose and meaning) is measured by using the 23-item Neuro-QoL scale for positive affect and well-being.[73]

Grief symptoms are measured using the Perinatal Bereavement Grief Scale (PBGS).[4 74] Complicated grief is measured using the Inventory of Complicated Grief (ICG).[75] A few items on the ICG were reworded to refer to perinatal loss. Given that many women present with unwarranted beliefs about what caused the loss, we assess deservingness and guilt as grief outcomes using a 7-item scale about loss beliefs (the Loss Beliefs Scale). This scale includes items such as "I think what happened was my fault" and "The miscarriage, stillbirth, or baby's death was caused by something about me." This perinatal loss specific scale was created after reviewing the literature on beliefs about deserved bad outcomes (e.g.,[76-78]).

Fear of subsequent pregnancies is assessed by 7-point Likert items (from 1 = Strongly Disagree" to 7 = "Strongly Agree"): (1) "I am afraid to become pregnant again"; (2) "I look forward to becoming pregnant again"; (3) "I plan to become pregnant again"; (4) "I worry about what might happen if I get pregnant again," (5) "I do not want to be pregnant again."

Treatment acceptability is measured using the Client Satisfaction Questionnaire-Revised (CSQ-8-R).[79]

Treatment integrity. We will use the IPT and CWD adherence and competence scales

developed in the pilot trial[31] to rate fidelity using audio recordings. As in the pilot trial, raters will also assess the percent of time in each group session spent discussing the perinatal loss and discussing loss-related communication strategies.[31]

Analysis

Primary analyses will be intent-to-treat. We will examine dose-response effects in secondary analyses. Primary tests will be two-sided with p=0.05. Descriptive statistics will include effect sizes and measures of clinical significance.[80] Primary and secondary outcomes and all hypotheses are stated a priori, therefore 0.05 level of significance will be used. Per Kraemer,[81] we will not test for differences between conditions due to randomization as those differences are due to chance alone, rendering p-values meaningless. Covariates for analyses are specified a priori based on subject matter expertise. No interim analyses are planned.

Attrition analysis and missing data. We will compare characteristics of those who drop out by trial arm and compare those who complete the study with those who do not to assess generalizability of findings. For the primary outcome of time to MDD recovery, unobserved time to MDD resolution for the drop-outs will be treated as censored. For secondary outcomes, regression techniques below allow for missing at random (MAR) mechanism.[82] If patterns of missing data indicate potential not missing at random (NMAR) mechanisms, then models describing missing mechanisms will be considered (e.g., pattern-mixture models),[83] [84] and sensitivity analyses will be employed.

General approaches. For survival analyses, the proportional hazard (PH) assumption will be evaluated. If it holds, then survival analyses will use Cox regression. If not, time-varying effects will be investigated, and the model will be modified to include an interaction of relevant covariates with a function of time variable. Stratified models will also be considered.

Linear mixed effects (LME) models will be used to test differences between trial arms for continuous outcomes. All participants with at least one completed post-baseline assessment will be included. We expect these scores to follow normal distributions. However, generalized linear mixed effects (GLME) modeling will be used if outcome is not normally distributed and cannot be normalized using transformations.

Aim 1. (1) Using survival analysis, with initial QIDS score as a covariate, we will test the hypothesis that IPT, relative to CWD, will result in reduced time to recovery from the major depressive episode (primary). (2) Using LME or GLME with baseline QIDS score as a covariate, we will test the hypothesis that IPT, relative to CWD, will result in reduced depressive symptoms (QIDS scores) across post-baseline assessments. (3) Using LME or GLME with baseline PCL score as a covariate, we will test the hypothesis that IPT, relative to CWD, will result in reduced PTSD symptoms (PCL score) across post-baseline assessments. (4) Using survival analysis, with initial PCL score as a covariate, we will test the hypothesis that IPT, relative to CWD, will result in reduced time to recovery from PTSD.

Aim 2. Using baseline scores as covariates, we will separately test the hypotheses that IPT for perinatal loss will result in increased social support, social role functioning, and well-being, and decreased grief and fear of subsequent pregnancies, relative to CWD, using the LME or GLME modeling described above. Specifically, controlling for baseline values, we will use separate analyses to test the effects of IPT vs. CWD on MSPSS, Relationship Assessment Scale, SAS-SR total, SAS-SR parenting subscale, Neuro-QoL, Perinatal Bereavement Grief Scale, Inventory of Complicated Grief, Loss Belief Scale, and Fear of Subsequent Pregnancy scores. We will also compare conditions on CSQ-8-R Treatment Acceptability.

Aim 3. We will test the hypotheses that social support (MSPSS scores) and grief (PBGS

scores) will mediate the effects of IPT on time to MDD recovery. To test for mediation, trial arm will be treated as the independent variable and each potential mediator (one at a time) will be tested for their effect on the outcome variable at weeks 8, 16, and 28, with the baseline value of that outcome treated as a covariate. We will use a bias corrected bootstrapping analytic strategy[85 86] based on 5000 bootstrap samples to estimate confidence intervals (CIs) around the indirect effect of study group on the outcome variable, through the mediator.

Moderators. We will calculate differential effect estimates and test the interactions between several participant characteristics and the intervention effect in predicting time to recovery from MDD. Characteristics to be examined include race, ethnicity, having living children, type of perinatal loss, stable use of other antidepressant or psychosocial treatment at baseline, having PTSD at baseline, having a partner, number of past depressive episodes, and time since loss. Given our emphasis on meeting the needs of minority women, we will also evaluate whether mediation relationships or intervention effects on secondary outcomes differ by race.

Sample size

Recovery outcomes. For the primary outcome of time to MDD recovery (censored at 28 weeks), assuming 1:1 allocation, power 0.80, two-sided tests at p=0.05, and observed estimated hazard ratio=1.79, the required number of events is 94 (number of MDEs resolved). By week 28, there were 17 events in the preliminary data (17 women had MDD resolved, 11 in the IPT condition, and 6 in the CWD condition) out of 45 participants, so the rate of events was .38. Thus to have 94 events, total N=246 is required. Given that 90% of pilot trial participants completed at least one follow-up assessment,[31] we increased the sample size to 274. Given the observed hazard ratio of 5.85 for PTSD in the pilot trial, power for PTSD recovery should be greater than 80%.

Tests of mediation in Aim 3 will have greater power than the primary outcome because of reduction in error variance when controlling for the mediator.

Continuous (secondary) outcomes. Assuming an unadjusted d = .32 and a correlation of 0.6 between follow-up measures and 0.3 with baseline (as observed in the preliminary data), the adjusted effect size would be 0.40, and only n = 200 participants would be needed before attrition. If study attrition is higher, the study still has > 80% power for secondary outcomes (Table 3).

Ethics and Dissemination

The trial was approved by Michigan State University's Biomedical Institutional Review Board (FWA 00004556). A three-member external Data and Safety Monitoring Board reviews data and safety of study participants. Trial safety procedures are codified through checklists and a written manual of operating procedures.

Informed consent and confidentiality

When potential participants contact the study, study RAs meet with them privately (electronically or in person). RAs explain risks, benefits, and the voluntary nature of the study and obtain participants' signed informed consent.

Confidentiality is protected by research staff trained to manage sensitive clinical issues. Participants are informed about the limits of confidentiality concerning suicidal intent, homicidal intent, and suspected child or elder abuse. Computer files are available only to authorized personnel, with no names or obvious identifying information stored in data files. Confidentiality of recordings of study assessments and treatment sessions is protected through: (1) use of encrypted audio recorders and HIPAA-compliant videoconferencing; (2) labeling recordings with study IDs rather than names; (3) storing recordings on a secured computer server designed to hold and protect research data; and (4) limiting access to recordings.

Participant safety

Adverse events. Participant safety is monitored during study assessments and during study treatment sessions. Pre-specified adverse events are recorded and monitored using a structured system created within REDCap with alerts for follow-up actions.[57]

Suicide risk. During assessments, participants who score 2 or above (any active suicide ideation) on the QIDS suicide item are transferred via warm handoff to a national suicide hotline contracted for this trial. The suicide hotline assesses suicidality and emergent treatment needs, provides follow-up, and securely transmits a written disposition. This procedure has worked well in previous trials.[57]

Clinical deterioration. If a participant develops manic or psychotic symptoms, or if her QIDS score increases by 5+ points from baseline, she is evaluated by an independent clinician to see if she needs to be referred for other treatment and/or removed from the trial.

Treatment nonresponse. Women in either condition whose MDD has not remitted by the end of the study (week 28) are referred for other treatment.

Dissemination policy and access to data

Dissemination activities will include academic papers, presentations to clinical communities, community reports and talks with organizations through which we recruited, and offering to share final study results with study participants. De-identified datasets will be available to qualified investigators upon request.

Author statement. Johnson: Conceptualization (lead), funding acquisition (lead), investigation (lead), intervention development (equal), safety protocols (lead), writing – original draft preparation (lead), writing – review and editing (lead). **Zlotnick:** Conceptualization (supporting), funding acquisition (supporting), clinical supervision (equal), safety protocols (supporting), writing – review and editing (supporting). **Price:** Funding acquisition (supporting), intervention development (equal), clinical supervision (equal). **Sikorskii:** Conceptualization (supporting), funding acquisition (supporting), data curation, formal analysis. **Key:** Funding acquisition (supporting), recruitment strategy (supporting). **Lamphere, Taylor, Huff, and Cinader:** Recruitment strategies (lead), development of operating procedures (supporting), choice of measures (supporting).

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Competing interests statement. The authors have no competing interests.

Table 1

Outline of IPT for major depressive disorder following perinatal loss

Session name	Session activities
1: Emotions of grief	Each woman tells her perinatal loss story and: expresses her feelings at the time of her loss, feels and expresses her current feelings about her loss, elicits support from and supports the other group members. Each woman is guided to: identify current supportive people, select one person to ask for grief support, role-play how to ask for support.
2: Understanding what happened	Each woman: explores her understanding of what happened to her pregnancy/baby, explores her thoughts/feelings about fault or blame, explores what the loss means to her, begins to explore who she has talked to about the loss and how she talks to them about her needs, identifies who she will invite to Session 3, role-plays how to communicate this invitation. The therapist: helps each woman unpack and examine whether there was anything she could have done to change the outcome, with support from the group, guides the women to seek information from their OBGYN providers about what does and does not contribute to perinatal loss, guides women to identify additional questions for their providers, helps each woman explore how she makes sense of her loss.
3: Grieving with others	Each woman is encouraged to invite a support person to the group. The therapist provides psychoeducation about: depression, grieving styles, ways to manage grieving differences, how IPT helps women recover and how partner/family/friend support can help women recover. Next the therapist guides each woman and her support person to: complete a written communication exercise about both partners' loss-related emotional needs, discuss their written answers privately for 20 minutes, discuss as a group what they learned from each other about support, discuss how each pair will manage communication with others in their social network, develop communication homework to improve each pair's support of each other regarding the loss.
4: Holding the memory and moving forward	Each woman discusses how she: holds the memory/meaning of her loss experience, can re-engage in life roles, seeks support and communication with key people, reflects on her grief process and her recovery from depression. The therapist guides the group by: reminding them that new members are added next week and discussing ways to welcome them, eliciting and role-modeling how to offer well-wishes to and from women completing their group treatment in this session.

Table 2

Schedule of Assessments

Measure	Baseline	Week 8	Week 16	Week 28
Diagnosis and safety				
SCID-5	X			
Women's Experience with Battering screener	X			
Longitudinal Interval Follow-up Examination	X	X	X	X
Psychiatric symptoms				
Quick Inventory of Depressive Symptoms	X	X	X	X
Life Events Checklist and PTSD Checklist	X	X	X	X
Hypothesized mediators				
Multidim. Scale of Perceived Social Support	X	X	X	X
Relationship Assessment Scale	X	X	X	X
Social Adjustment Scale total score	X	X	X	X
Social Adjustment Scale parental functioning	X	X	X	X
Other outcomes (grief, well-being, fear)				
NIH Neuro-Quality of Life scale	X	X	X	X
Perinatal Bereavement Grief Scale	X	X	X	X
Inventory of Complicated Grief	X	X	X	X
Loss Beliefs Scale	X	X	X	X
Fear of subsequent pregnancies	X	X	X	X
Treatment acceptability of IPT and CWD				
Client Satisfaction Scale – Revised			X	

Table 3

Power for n = 274 for secondary outcomes

	d = .29	*d* = .32	*d* = .35
10% attrition	.81	**.88**	.93
15% attrition	.74	.83	.88
20% attrition	.72	.80	.86
25% attrition	.69	.78	.84

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Pages
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**3**
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	**NA**
Funding	4	Sources and types of financial, material, and other support	**18**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**1, 18**
	5b	Name and contact information for the trial sponsor	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**4-6**
	6b	Explanation for choice of comparators	**6**
Objectives	7	Specific objectives or hypotheses	**5**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	**9**
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**10**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**8-9**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**6-8**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	**17**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	**10**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**8**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	**11-13**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**20**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**15-16**

Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	**9-10**
Methods: Assignment of interventions (for controlled trials)			
Allocation:			**9**
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**9**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**9**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**9**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**10**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**NA**
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**11-13**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**10**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**16**

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**13-15**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**13-15**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**13-15**
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**NA**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**13**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**17**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**NA**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**16**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**NA**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**16**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**NA**

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**16**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**18**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**17**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**17**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**17**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**NA**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**17**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**attached**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**NA**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol for the Healing After Loss (HeAL) Study: A randomized controlled trial of interpersonal psychotherapy (IPT) for major depression following perinatal loss

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Running Head: PERINATAL LOSS

Protocol for the Healing After Loss (HeAL) Study: A randomized controlled trial of interpersonal psychotherapy (IPT) for major depression following perinatal loss

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Abstract

Introduction. This protocol describes a study testing the efficacy of interpersonal psychotherapy (IPT) for major depressive disorder following perinatal loss (early and late fetal death and early neonatal death). Perinatal loss is associated with elevated risk of major depressive disorder and posttraumatic stress disorder (PTSD). Perinatal loss conveys specific treatment needs. The trial will be the first fully-powered randomized trial of treatment for any psychiatric disorder following perinatal loss.

Methods and analysis. A sample of 274 women in Flint and Detroit areas in Michigan who experience a major depressive episode following a perinatal loss will be randomized to group IPT for perinatal loss or to group Coping with Depression (CWD). We anticipate that 50% of the sample will have co-occurring PTSD. Assessments occur at baseline, mid-treatment (8 weeks), post-treatment (16 weeks), and follow-up (28 weeks). Clinical outcomes include time to recovery from major depressive episode (primary), depressive symptoms, PTSD symptoms, and time to recovery from PTSD. Additional outcomes include social support, social role functioning (including parental functioning for those with living children), well-being, grief (including complicated grief and fault beliefs), and fear of subsequent pregnancies. Social support and grief are hypothesized mediators of IPT effects on time to recovery from major depressive episode.

Ethics and dissemination. The trial was approved by Michigan State University's Biomedical Institutional Review Board. It has a Data and Safety Monitoring Board and has been submitted to the Community Based Organization Partners Community Ethics Review Board. Written operating procedures outline methods for protecting confidentiality, monitoring and recording adverse events, and safeguarding participants. We will share study results with research and clinical communities, community organizations through which we recruited, and will offer results to study

participants. De-identified datasets will be available through the National Institute of Mental Health Data Archive and to qualified investigators upon request.

Clinical trials registration. The trial was registered at clinicaltrials.gov (NCT04629599).

Key words: Miscarriage, stillbirth, fetal death, perinatal death, major depressive disorder, posttraumatic stress disorder, interpersonal psychotherapy.

Word count: 4,034

Article Summary: Strengths and limitations of this study

- This study addresses a clinical need, and will provide an evidence base for treating a n understudied population whose distress has historically been minimized.
- The trial will have strong representation from disparities populations (especially African American women and socioeconomically disadvantaged women) who experience higher rates of perinatal loss, increasing its significance.
- Rigor and reproducibility are ensured by the randomized design, clear inclusion criteria, use of well-established research, recruitment, and retention methods, use of reliable and valid measures, the use of raters blinded to treatment condition, and transparent power and statistical analyses.
- Intervention strengths include clearly distinct treatment conditions, use of manualized treatment protocols and fidelity assessments, and team members with decades of clinical experience responding to perinatal loss.
- Challenges may include recruitment during a global pandemic in communities with a higher levels of research mistrust and more mental health stigma than in the pilot trial.

Introduction

About 650,000 women in the United States experience perinatal loss each year (including early and late fetal death and the death of a liveborn neonate within the first 28 days).[1 2] Rates of major depressive disorder (MDD) after perinatal loss are higher than after giving birth to a living infant, and are 3 times the rates among matched samples of community women.[3-20] Rates of posttraumatic stress disorder (PTSD) after perinatal loss are up to 7 times the rates of PTSD among mothers of living infants,[13] and elevated PTSD symptoms can occur for years after the loss.[21] Fetal or neonatal death triples rates of suicide and of hospitalization for suicide attempts.[22 23]

Not only do women with perinatal loss have higher rates of MDD and PTSD than mothers of living infants, their needs also differ from needs following many other kinds of bereavement. In perinatal loss, the fact of bereavement is compounded by the physical experience of miscarriage or of delivering a baby that has already died.[24] Many women experiencing perinatal loss grieve in secret, as others may not know about the loss. Even if others do know, there are few social norms that guide how others can or should support the bereaved, making support less likely and often less helpful (e.g., "you can just have another one").[12 25] Reasons for loss are often unclear and many women blame themselves.

Despite recognition that MDD (with or without co-occurring PTSD) following perinatal loss causes impairment and that treatment as usual is often inadequate,[26-30] our previous pilot work[31] created and tested the first manual for treating any psychiatric disorder after perinatal loss. The manual is structured and applies interpersonal psychotherapy (IPT) principles to MDD following perinatal loss in a group format. Previous IPT and other treatment manuals for perinatal depression[32-35] focus on helping women adjust their relationships, identity, roles, and routines to the demands of a new baby. This is inappropriate in the context of perinatal loss. Our manual

applies IPT social support and communication principles to issues such as resolving conflicts over how to respond to the loss, grieving and requesting support in the absence of social norms about how to do so, and resolving questions of fault and role competence. It can be used by providers who do not know IPT. A randomized pilot trial of women experiencing MDD following perinatal loss established acceptability of proposed study procedures and identified high rates of co-occurring PTSD (54%) among study participants.[31] Results favored the new IPT manual for PTSD recovery, treatment satisfaction, depressive symptoms, grief, and social support relative to Coping with Depression (CWD), a cognitive-behavioral based intervention that does not focus on perinatal loss, interpersonal issues, or social support.[31]

Based on those promising results, the current study will be the first fully-powered randomized trial of treatment for any psychiatric disorder following perinatal loss. We will compare our group IPT manual to a general group depression treatment (CWD) in a sample of 274 women experiencing MDD in the context of perinatal loss. The trial will test the hypotheses that:

1. IPT for perinatal loss will result in reduced time to recovery from MDD (primary), depressive symptoms, and PTSD symptoms, relative to CWD. Among women meeting criteria for PTSD, IPT will result in reduced time to recovery from PTSD relative to CWD.
2. IPT for perinatal loss will result in increased social support, social role functioning (including parental functioning for women with living children), and well-being, and decreased grief and fear of subsequent pregnancies, relative to CWD.
3. Social support and grief will mediate the effects of IPT on time to MDD recovery.

This trial will provide an evidence base for treating a vulnerable and understudied population whose distress has historically been minimized. Given that poverty increases risk of perinatal loss,[36-38] and doubles the risk of perinatal depression,[39-47] and that rates of perinatal loss for

African-American women are double those for white women,[48-50] the location of the trial in Southeast Michigan, which includes Flint and Detroit (minority-majority cities with high rates of poverty), increases the trial's significance.

Methods and analysis

Patient and public involvement

Research questions arose from a clinical need identified by provider colleagues. Patients provided feedback on treatments, measures, and study procedures in the pilot trial.[31] Local minority-led community-based organizations provided feedback on measures, procedures, and recruitment methods appropriate for the Flint and Detroit areas. The study team is embedded in Flint and Detroit. Team members have lived experience. The trial has been submitted for voluntary review by the Flint-based Community Based Organization Partners Community Ethics Review Board for additional community feedback.[51]

Rationale for design

Given that no other treatment exists for women who experience perinatal-loss related MDD that could be used as a comparator condition, we chose to use a general depression treatment, the Coping With Depression (CWD) course, as a control condition. We chose CWD because it is the group treatment with the most empirical support for treating MDD[52 53] and because it is distinct from IPT. IPT addresses MDD through emotional exploration, work on relationships, communication, grief, and social support. CWD addresses MDD by changing thinking and behavior; it focuses on skills for reducing depression in general and does not have perinatal-loss specific components. Our IPT treatment differs from CWD in its focus on exploring reactions to the loss, addressing loss-related interpersonal challenges, and improving loss-related social support and grief-specific coping. The trial's secondary outcomes (social support, social

functioning, grief) assess hypothesized differences between treatments. As desired, our pilot study found differences between conditions in the hypothesized mechanisms of social support and grief and in terms of in-session activities.[31]

Treatments

Manualized treatments are attention-matched (12 groups of 90 minutes each, 1 individual pre-group session, and 1 booster session). Every 4 weeks, both treatments allow new women to enter the group and women completing 12 weeks to leave the group.

Interpersonal psychotherapy (IPT). Participants in the IPT condition receive 12 group sessions and 2 individual (pre-group and 1-month booster) sessions as outlined in the structured manual (see Table 1 and pilot trial[31]). The individual sessions prepare patients to use the group effectively, to keep group members focused on their treatment goals, and to maintain treatment gains. In addition, 3 of the 12 group sessions invite women to include their partners or other support people to bolster the woman's social support system and to reduce conflicts over how to react to the loss. Relationship distress is common following perinatal loss.[12 54]

Group sessions are semi-structured, and each woman covers the four group topics listed in Table 1 three times over her 12 group sessions, approaching each topic from a different stage in the mourning process. New women are allowed to enter group every four sessions. This allows remaining women to see their own progress and encourages new women through example and peer counseling.

Coping with Depression (CWD). CWD is a structured, manualized[55] psycho-educational group treatment for MDD. The CWD course is cognitive-behavioral. The problems shown by depressed individuals are viewed as behavioral, with cognitive patterns that can be unlearned or relearned. Its effectiveness is comparable to other forms of psychotherapy in depression.[53] The

course content teaches skills including relaxation, cognitive skills, and behavioral activation. The CWD pre-group and booster sessions are the pre-group and booster sessions from the published CWD manual[55]. To ensure that the CWD intervention was distinct from IPT, we excluded the 2 sessions on social skills and emphasized pleasant activities that were individual rather than social. Consistent with standard CWD, we focused on addressing depression rather than discussing grief or perinatal loss. We expanded other CWD material (e.g., relaxation practice) to replace sessions on social skills. In our studies, the 12 CWD sessions covered: an introduction to social learning rationale of depression; learning to relax; relaxation in everyday situations; pleasant activities and depression; formulating a pleasant activities plan; constructive thinking; planning for constructive thinking; and maintaining gains (see published manual[55] and pilot trial[31] for additional details).

Participants

Participants will be 274 women who are experiencing MDD in the context of perinatal loss who (1) meet DSM-5[56] criteria for MDD; (2) have experienced a perinatal loss (including early and late fetal death, death of a liveborn neonate within the first 28 days, and medically recommended termination) within the last 1-12 months; (3) are 18 to 50 years old; (4) speak and understand English well enough to understand questionnaires when they are read aloud; (5) can provide the name and contact information of at least two locator persons; and (6) have access to a telephone. Exclusion criteria are: (1) onset of *current* major depressive episode prior to news of difficulties with the pregnancy or health risk to the infant (women with prior episodes are included); (2) current or past diagnosis of bipolar disorder, schizophrenia or other psychotic disorder; (3) primary diagnosis of current substance use disorder; (4) acute suicidal or homicidal risk; (5) beginning or changing dose of antidepressant medication or psychotherapy in the previous 12 weeks); (6) any IPT or cognitive-behavioral treatment in the previous 12 weeks. Women in stable

concurrent psychotherapy who are included are asked to suspend this treatment during the active study treatment phase. PTSD is not an inclusion criterion. However, based on our pilot,[31] we anticipate that slightly more than half the sample will meet criteria for PTSD at study enrollment.

Therapist training and supervision

We trained 8 study therapists (4 in IPT and 4 in CWD) who are MSWs or clinical or counseling psychologists. Therapists are recruited from their respective communities to moonlight as clinicians in this proposed study. Therapists are provided with the detailed treatment manuals. Training for both conditions includes education and role plays. Therapists in both conditions will be monitored for adherence/competence throughout the study and retrained as needed.

Supervision involves review of therapists' audiotaped sessions and a weekly one-hour small-group telephone meeting for feedback and case discussion. Treatment sessions are audio recorded using digital audio recorders or a HIPAA-compliant version of Zoom. Study therapists remotely upload the recordings to the study's secure research server, where the supervisors can remotely access them.

Randomization

Women are randomly assigned to IPT or CWD in a 1:1 ratio. We stratify randomization on (1) whether women have been taking antidepressant medications or attending other psychotherapy (stability of dose is an inclusion criterion); and (2) type of perinatal loss (miscarriage, stillbirth, neonatal death). Randomization sequences were created by the study statistician. Assignment is concealed in an envelope that research assistants open at randomization.

Recruitment

Participants are recruited from counties in Southeast Michigan using a broad outreach strategy. We partner with regional health systems, community-based organizations in Flint and

Detroit, and a regional Medicaid system in study recruitment. Recruitment also includes flyers and referrals from: (1) local birthing centers, emergency departments, OBGYN offices, and federally qualified health centers; (2) hotlines, support groups, family nurse partnerships; (3) funeral homes; (4) churches, daycare centers, other places where women and mothers congregate (WIC offices, Medicaid offices, etc.); (5) bus ads; and (6) online venues. We began recruitment on September 1, 2021 and plan to end on March 1, 2025.

Research sites

We had planned to offer baseline assessments at women's homes or our offices, group sessions in community locations convenient for participants (as we did in the pilot trial),[31] and to conduct follow-up assessments by telephone. However, due to the COVID-19 pandemic, we are currently conducting all assessments and treatment sessions by Zoom, with an option to go back to holding groups in person in the future.

Retention

We employ techniques we have found helpful in achieving low attrition rates in previous studies.[31 57-59] These include study staff's strong relationships with participants, efforts to value and appreciate the women's participation in the study, and frequent personal contact. We are flexible about follow-up appointment scheduling and train research staff to be culturally sensitive. Follow-up assessments take place by Zoom or phone, with well-established safety procedures for emergencies.[57] We maintain a list of two other people who know where the participant resides. We conduct treatment groups at different times and locations to make attendance easier. If a woman misses a treatment appointment, the therapist calls her to check in and problem-solve barriers to attendance. Finally, participant fees for follow-up assessments help facilitate retention.

Assessments

Assessments take place at baseline, mid-treatment (8 weeks), post-treatment (16 weeks), and follow-up (28 weeks; see Table 2). Assessments are conducted by research assistants (RAs) trained and certified in interviewer administered instruments and blind to treatment assignment. Interviewers and senior staff meet regularly to review assessment tapes, address questions, and monitor inter-rater reliability. Data quality is maintained through clerical and clinical checks after data are entered and through regular examination of distributions, missing data, and outliers.

Diagnosis/screening. The Structured Clinical Interview for DSM-5 (SCID-5)[60] is used to establish study eligibility. During follow-up, the Longitudinal Interval Follow-up Examination (LIFE),[61 62] a standardized retrospective calendar-based interview, is used to assess MDD and PTSD recovery. The LIFE uses Psychiatric Status Ratings (PSRs) to categorize DSM-5 symptoms on a scale of 1 (asymptomatic) to 6 (incapacitated) for each week. A PSR of 5 or 6 indicates the participant meets full diagnostic criteria, 3 or 4 indicates subthreshold disorder, and 1 or 2 indicates the participant is not in episode. For survival analyses, recovery is defined as 8 consecutive weeks of a PSR of 1-2[63] at any time between baseline and the 28 week follow-up. Women who do not have at least 8 consecutive weeks of PSR of 1-2 during this time are considered "not recovered." The LIFE is the gold-standard way of determining onset and offset of psychiatric disorder.[63] We also use the LIFE to track participation in psychotherapeutic and psychopharmacologic treatment at baseline and follow-up. We assess partner violence using the Women's Experience with Battering screen.[64] Battered women (scores of 20+) are included in the study and provided with partner violence resources.

Depressive symptoms are assessed using the Quick Inventory of Depressive Symptoms (QIDS), Self-Report version.[65]

PTSD symptoms are assessed using the Life Events Checklist and PTSD Checklist for

DSM-5 (LEC-PCL).[66-69] We also assess whether PTSD symptoms are related to the perinatal loss.

Social support and social functioning. We use the 12-item Multidimensional Scale for Perceived Social Support (MSPSS)[70] to assess overall social support. We use a validated adaptation of the Relationship Assessment Scale[71] to assess satisfaction with an important significant other (partner or other support person of the woman's choosing) relationship. We assess social functioning using the Short version of the Social Adjustment Scale – Self-Report (SAS-SR).[72] Because depression can affect parenting, we will analyze the SAS-SR total score as well as its parental functioning subscale.

Well-being (including life satisfaction, purpose and meaning) is measured by using the 23-item Neuro-QoL scale for positive affect and well-being.[73]

Grief symptoms are measured using the Perinatal Bereavement Grief Scale (PBGS).[4 74] Complicated grief is measured using the Inventory of Complicated Grief (ICG).[75] A few items on the ICG were reworded to refer to perinatal loss. Given that many women present with unwarranted beliefs about what caused the loss, we assess deservingness and guilt as grief outcomes using a 7-item scale about loss beliefs (the Loss Beliefs Scale). This scale includes items such as "I think what happened was my fault" and "The miscarriage, stillbirth, or baby's death was caused by something about me." This perinatal loss specific scale was created after reviewing the literature on beliefs about deserved bad outcomes (e.g.,[76-78]).

Fear of subsequent pregnancies is assessed by 7-point Likert items (from 1 = Strongly Disagree" to 7 = "Strongly Agree"): (1) "I am afraid to become pregnant again"; (2) "I look forward to becoming pregnant again"; (3) "I plan to become pregnant again"; (4) "I worry about what might happen if I get pregnant again," (5) "I do not want to be pregnant again."

Treatment acceptability is measured using the Client Satisfaction Questionnaire-Revised

(CSQ-8-R).[79]

Treatment integrity. We will use the IPT and CWD adherence and competence scales developed in the pilot trial[31] to rate fidelity using audio recordings. As in the pilot trial, raters will also assess the percent of time in each group session spent discussing the perinatal loss and discussing loss-related communication strategies.[31]

Analysis

Primary analyses will be intent-to-treat. We will examine dose-response effects in secondary analyses. Primary tests will be two-sided with p=0.05. Descriptive statistics will include effect sizes and measures of clinical significance.[80] Primary and secondary outcomes and all hypotheses are stated a priori, therefore 0.05 level of significance will be used. Per Kraemer,[81] we will not test for differences between conditions due to randomization as those differences are due to chance alone, rendering p-values meaningless. Covariates for analyses are specified a priori based on subject matter expertise. No interim analyses are planned.

Attrition analysis and missing data. We will compare characteristics of those who drop out by trial arm and compare those who complete the study with those who do not to assess generalizability of findings. For the primary outcome of time to MDD recovery, unobserved time to MDD resolution for the drop-outs will be treated as censored. For secondary outcomes, regression techniques below allow for missing at random (MAR) mechanism.[82] If patterns of missing data indicate potential not missing at random (NMAR) mechanisms, then models describing missing mechanisms will be considered (e.g., pattern-mixture models),[83] [84] and sensitivity analyses will be employed.

General approaches. For survival analyses, the proportional hazard (PH) assumption will be evaluated. If it holds, then survival analyses will use Cox regression. If not, time-varying

effects will be investigated, and the model will be modified to include an interaction of relevant covariates with a function of time variable. Stratified models will also be considered.

Linear mixed effects (LME) models will be used to test differences between trial arms for continuous outcomes. All participants with at least one completed post-baseline assessment will be included. We expect these scores to follow normal distributions. However, generalized linear mixed effects (GLME) modeling will be used if outcome is not normally distributed and cannot be normalized using transformations.

Aim 1. (1) Using survival analysis, with initial QIDS score as a covariate, we will test the hypothesis that IPT, relative to CWD, will result in reduced time to recovery from the major depressive episode (primary). (2) Using LME or GLME with baseline QIDS score as a covariate, we will test the hypothesis that IPT, relative to CWD, will result in reduced depressive symptoms (QIDS scores) across post-baseline assessments. (3) Using LME or GLME with baseline PCL score as a covariate, we will test the hypothesis that IPT, relative to CWD, will result in reduced PTSD symptoms (PCL score) across post-baseline assessments. (4) Using survival analysis, with initial PCL score as a covariate, we will test the hypothesis that IPT, relative to CWD, will result in reduced time to recovery from PTSD.

Aim 2. Using baseline scores as covariates, we will separately test the hypotheses that IPT for perinatal loss will result in increased social support, social role functioning, and well-being, and decreased grief and fear of subsequent pregnancies, relative to CWD, using the LME or GLME modeling described above. Specifically, controlling for baseline values, we will use separate analyses to test the effects of IPT vs. CWD on MSPSS, Relationship Assessment Scale, SAS-SR total, SAS-SR parenting subscale, Neuro-QoL, Perinatal Bereavement Grief Scale, Inventory of Complicated Grief, Loss Belief Scale, and Fear of Subsequent Pregnancy scores. We

will also compare conditions on CSQ-8-R Treatment Acceptability.

Aim 3. We will test the hypotheses that social support (MSPSS scores) and grief (PBGS scores) will mediate the effects of IPT on time to MDD recovery. To test for mediation, trial arm will be treated as the independent variable and each potential mediator (one at a time) will be tested for their effect on the outcome variable at weeks 8, 16, and 28, with the baseline value of that outcome treated as a covariate. We will use a bias corrected bootstrapping analytic strategy[85 86] based on 5000 bootstrap samples to estimate confidence intervals (CIs) around the indirect effect of study group on the outcome variable, through the mediator.

Moderators. We will calculate differential effect estimates and test the interactions between several participant characteristics and the intervention effect in predicting time to recovery from MDD. Characteristics to be examined include race, ethnicity, having living children, type of perinatal loss, stable use of other antidepressant or psychosocial treatment at baseline, having PTSD at baseline, having a partner, number of past depressive episodes, and time since loss. Given our emphasis on meeting the needs of minority women, we will also evaluate whether mediation relationships or intervention effects on secondary outcomes differ by race.

Sample size

Recovery outcomes. For the primary outcome of time to MDD recovery (censored at 28 weeks), assuming 1:1 allocation, power 0.80, two-sided tests at p=0.05, and observed estimated hazard ratio=1.79, the required number of events is 94 (number of MDEs resolved). By week 28, there were 17 events in the preliminary data (17 women had MDD resolved, 11 in the IPT condition, and 6 in the CWD condition) out of 45 participants, so the rate of events was .38. Thus to have 94 events, total N=246 is required. Given that 90% of pilot trial participants completed at least one follow-up assessment,[31] we increased the sample size to 274. Given the observed hazard

ratio of 5.85 for PTSD in the pilot trial, power for PTSD recovery should be greater than 80%. Tests of mediation in Aim 3 will have greater power than the primary outcome because of reduction in error variance when controlling for the mediator.

Continuous (secondary) outcomes. Assuming an unadjusted d = .32 and a correlation of 0.6 between follow-up measures and 0.3 with baseline (as observed in the preliminary data), the adjusted effect size would be 0.40, and only n = 200 participants would be needed before attrition. If study attrition is higher, the study still has > 80% power for secondary outcomes (Table 3).

Ethics and Dissemination

The trial was approved by Michigan State University's Biomedical Institutional Review Board (FWA 00004556). A three-member external Data and Safety Monitoring Board reviews data and safety of study participants. Trial safety procedures are codified through checklists and a written manual of operating procedures.

Informed consent and confidentiality

When potential participants contact the study, study RAs meet with them privately (electronically or in person). RAs explain risks, benefits, and the voluntary nature of the study and obtain participants' signed informed consent.

Confidentiality is protected by research staff trained to manage sensitive clinical issues. Participants are informed about the limits of confidentiality concerning suicidal intent, homicidal intent, and suspected child or elder abuse. Computer files are available only to authorized personnel, with no names or obvious identifying information stored in data files. Confidentiality of recordings of study assessments and treatment sessions is protected through: (1) use of encrypted audio recorders and HIPAA-compliant videoconferencing; (2) labeling recordings with

study IDs rather than names; (3) storing recordings on a secured computer server designed to hold and protect research data; and (4) limiting access to recordings.

Participant safety

Adverse events. Participant safety is monitored during study assessments and during study treatment sessions. Pre-specified adverse events are recorded and monitored using a structured system created within REDCap with alerts for follow-up actions.[57]

Suicide risk. During assessments, participants who score 2 or above (any active suicide ideation) on the QIDS suicide item are transferred via warm handoff to a national suicide hotline contracted for this trial. The suicide hotline assesses suicidality and emergent treatment needs, provides follow-up, and securely transmits a written disposition. This procedure has worked well in previous trials.[57]

Clinical deterioration. If a participant develops manic or psychotic symptoms, or if her QIDS score increases by 5+ points from baseline, she is evaluated by an independent clinician to see if she needs to be referred for other treatment and/or removed from the trial.

Treatment nonresponse. Women in either condition whose MDD has not remitted by the end of the study (week 28) are referred for other treatment.

Dissemination policy and access to data

Dissemination activities will include academic papers, presentations to clinical communities, community reports and talks with organizations through which we recruited, and offering to share final study results with study participants. De-identified datasets will be available to qualified investigators upon request.

Author statement. Johnson: Conceptualization (lead), funding acquisition (lead), investigation (lead), intervention development (equal), safety protocols (lead), writing – original draft preparation (lead), writing – review and editing (lead). **Zlotnick:** Conceptualization (supporting), funding acquisition (supporting), clinical supervision (equal), safety protocols (supporting), writing – review and editing (supporting). **Price:** Funding acquisition (supporting), intervention development (equal), clinical supervision (equal). **Sikorskii:** Conceptualization (supporting), funding acquisition (supporting), data curation, formal analysis. **Key:** Funding acquisition (supporting), recruitment strategy (supporting). **Lamphere, Taylor, Huff, and Cinader:** Recruitment strategies (lead), development of operating procedures (supporting), choice of measures (supporting).

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Competing interests statement. The authors have no competing interests.

Table 1

Outline of IPT for major depressive disorder following perinatal loss

Session name	Session activities
1: Emotions of grief	Each woman tells her perinatal loss story and: expresses her feelings at the time of her loss, feels and expresses her current feelings about her loss, elicits support from and supports the other group members. Each woman is guided to: identify current supportive people, select one person to ask for grief support, role-play how to ask for support.
2: Understanding what happened	Each woman: explores her understanding of what happened to her pregnancy/baby, explores her thoughts/feelings about fault or blame, explores what the loss means to her, begins to explore who she has talked to about the loss and how she talks to them about her needs, identifies who she will invite to Session 3, role-plays how to communicate this invitation. The therapist: helps each woman unpack and examine whether there was anything she could have done to change the outcome, with support from the group, guides the women to seek information from their OBGYN providers about what does and does not contribute to perinatal loss, guides women to identify additional questions for their providers, helps each woman explore how she makes sense of her loss.
3: Grieving with others	Each woman is encouraged to invite a support person to the group. The therapist provides psychoeducation about: depression, grieving styles, ways to manage grieving differences, how IPT helps women recover and how partner/family/friend support can help women recover. Next the therapist guides each woman and her support person to: complete a written communication exercise about both partners' loss-related emotional needs, discuss their written answers privately for 20 minutes, discuss as a group what they learned from each other about support, discuss how each pair will manage communication with others in their social network, develop communication homework to improve each pair's support of each other regarding the loss.
4: Holding the memory and moving forward	Each woman discusses how she: holds the memory/meaning of her loss experience, can re-engage in life roles, seeks support and communication with key people, reflects on her grief process and her recovery from depression. The therapist guides the group by: reminding them that new members are added next week and discussing ways to welcome them, eliciting and role-modeling how to offer well-wishes to and from women completing their group treatment in this session.

Table 2

Schedule of Assessments

Measure	Baseline	Week 8	Week 16	Week 28
Diagnosis and safety				
SCID-5	X			
Women's Experience with Battering screener	X			
Longitudinal Interval Follow-up Examination	X	X	X	X
Psychiatric symptoms				
Quick Inventory of Depressive Symptoms	X	X	X	X
Life Events Checklist and PTSD Checklist	X	X	X	X
Hypothesized mediators				
Multidim. Scale of Perceived Social Support	X	X	X	X
Relationship Assessment Scale	X	X	X	X
Social Adjustment Scale total score	X	X	X	X
Social Adjustment Scale parental functioning	X	X	X	X
Other outcomes (grief, well-being, fear)				
NIH Neuro-Quality of Life scale	X	X	X	X
Perinatal Bereavement Grief Scale	X	X	X	X
Inventory of Complicated Grief	X	X	X	X
Loss Beliefs Scale	X	X	X	X
Fear of subsequent pregnancies	X	X	X	X
Treatment acceptability of IPT and CWD				
Client Satisfaction Scale – Revised			X	

Table 3

Power for n = 274 for secondary outcomes

	d = .29	*d* = .32	*d* = .35
10% attrition	.81	**.88**	.93
15% attrition	.74	.83	.88
20% attrition	.72	.80	.86
25% attrition	.69	.78	.84

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CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
Michigan State University

Healing after Perinatal Loss

FUNDING

This study is paid for by a grant from the National Institute of Child Health and Human Development.

THE PROJECT

You are invited to participate in a research project. The goal of the research project is to find ways to help women cope after perinatal loss. You have been invited to participate because you have experienced a recent perinatal loss (miscarriage, stillbirth, or early death of an infant). Participation in the study will last up to 8 months.

To help you decide if you want to be part of this research study, we will tell you about the risks and benefits. This consent form gives you information about the research study. A member of the research team will also discuss this research. This will include the goal of the research and the questions you will be asked. It also tells about the treatment you may receive, any risks, possible benefits, and other possible treatments. Once you understand, you will be asked if you wish to participate. If you do, you will be asked to sign this form.

WHAT WILL BE DONE

If you decide to participate, here's what will happen:

1. **Initial interview.** A member of the study team will ask you questions about your life. This includes questions about your loss, your mood and stress levels, your relationships, and about stressful events which you may have experienced. We will also ask you for your contact information and for the contact information of people who can help us find you and who we can reach out to in case of emergency. This meeting will take about 90 minutes. We will use results from this meeting to decide if this study is a good match for you. If it doesn't seem to be a good match for your needs, this will be your last interview. We will give you a list of resources related to perinatal loss.

2. **Random assignment.** If you are eligible for the study, you will be randomly assigned to one of two study programs. You have ½ chance of being assigned to each program. The words "random assignment" mean that we will use a method similar to flipping a coin to find out which program you will be in.

3. **Study programs**. Both study programs involve 2 individual (60 minute) and 12 group (90 minute) counseling sessions. In either condition, you will meet once individually with a counselor, then you will meet weekly for 12 weeks with a group of other women who also recently had a perinatal loss. Finally, about a month after the group ends, you will meet individually again with the counselor.
   (a) In the **CWD program**, we will focus on ways to improve your mood and reduce stress.
   (b) In the **IPT program**, we will talk about perinatal loss and how to get support you need.

4. **Follow-up interviews.** Everyone in the study will also be interviewed over the phone 3 times: about 8 weeks from now, after your program is over (about 16 weeks from now), and then 3 months after that (about 28 weeks from now). These interviews will last about an hour each. You will be given a $60 gift card for your participation in each of these interviews.

5. **Audio recording.** During the study, we will audio record meetings with the counselor and parts of the interviews with study staff. We do this so we can supervise our research staff. We record the groups, but you can ask us not to audio record an individual meeting or interview and still participate in the study. You can also ask that a recording of an individual meeting be deleted. Audio recorders are passcode protected and encrypted and Zoom is HIPAA compliant, to protect your confidentiality.

BENEFITS

You may or may not benefit from being part of this study. For those who are enrolled in the study, you may learn better ways to manage your mood and adjust to your loss.

RISKS OR DISCOMFORTS

There are some risks associated with the study. The questionnaires and interviews ask about sensitive personal issues that may be uncomfortable to talk about. You will be able to skip or not answer any questions that bother you. All the questions will be asked by research staff who are trained to deal sensitively with these issues. You may experience some discomfort when asked questions about your personal life, your loss, and/or problems you may have experienced. You will be referred to someone who can help you if you feel very uncomfortable. You may also become uncomfortable due to the length of the interview process. If you attend groups over Zoom, we will ask that other adults not be present, but there is always a possibility that someone could pass by and overhear the group conversation.

You may also feel uncomfortable discussing personal issues in a group setting. If you feel this way during group, please tell the group leader. We strongly encourage confidentiality in the research groups. However, it is possible that someone may reveal information shared in the group. If this occurs, that person will be asked not to come back to the group.

CONFIDENTIALITY

We are committed to protecting your privacy. We have received a Certificate of Confidentiality from the National Institute of Child Health and Human Development (NICHD). This will protect the researchers from being forced, even by court order, to provide information about you. NICHD may see your research information in an audit. Also, the university research supervisors (from the MSU Human Research Protection Program) may see this information in an audit. If this happens, they will also keep the information confidential.

Our Certificate of Confidentiality states that the information we collect about you can only be used for research and no other purpose. However, according to the Certificate of Confidentiality, confidentiality can be broken without your consent if harm to you, harm to others, or child abuse becomes a concern. if you are in serious current danger of hurting yourself, we may need to tell others to help you stay safe. If you are in serious danger of hurting someone else, we may need to tell that person and/or the appropriate police departments. Also, if we hear that someone has abused or neglected a child or elderly person, we have to let the appropriate state agencies know. If you attend groups over Zoom, we will ask that other adults not be present, but there is always a possibility that someone could pass by and overhear the group conversation.

Information you tell us that is not listed above will be kept confidential. You will not be personally identified in any reports or publications that may come from this study. Your information will be labeled using a study ID number. Information about you will be protected in locked filing cabinets in locked university research offices and on secure computers. Only research staff who need the information will have access to it.

The permission you give us to use your information will not expire. The study data may be kept permanently. While the study is going on, you will not be allowed to see this information about you. You may have this information when the study is over.

Anonymous research information from this study may be shared with other researchers. In this anonymous information, all personal information about participants (like names, addresses, phone numbers) is removed and replaced with a code number. Sharing anonymous data can help researchers learn how to solve health problems for adults and children around the world more quickly than before.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

DECISION TO PARTICIPATE AND RIGHT TO QUIT AT ANY TIME

You are free to decide whether or not to participate in this study. You are also free to quit the study at any time by telling the researchers in person or in writing. Research information collected up to the time that you quit will remain as part of the study data.

POSSIBLE ALTERNATIVE PROCEDURES

The first 12 weeks of the research program, we will ask you to temporarily take a break from other counseling you may be receiving. If you do not agree to do this, you will not be enrolled in the study. After you have completed the 12 weeks of the research program, you are free to receive other treatments or services.

QUESTIONS

Please ask any questions you may have. Is there anything about this research that you do not understand?

WHO TO CALL

If you ever have more questions about this project or want to report a research-related injury, please contact us. You may call Dr. Jennifer Johnson of Michigan State University at 810-600-5669. You may also email us at Heal@msu.edu or use regular mail to reach us at: 200 East 1st St, Room 366, Flint, MI 48502. If you have questions or concerns about your role and rights as a research participant, would like to obtain information or offer input, or would like to register a complaint about this study, you may contact the Michigan State University's Human Research Protection Program at 517-355-2180, Fax 517432-4503, or email irb@msu.edu or regular mail at 4000 Collins Rd, Suite 136, Lansing, MI 48910. If you like, your comments can be anonymous.

AUTHORIZATION: BY SIGNING BELOW, YOU AGREE TO PARTICIPATE IN THE STUDY

I will participate in this study. I understand what the research is about and what will happen. I also understand any possible dangers and inconveniences. I have received a copy of this consent form.

_____	_____	_____	_____
First Name (please print)	Middle Name	Last Name	Date

_____

Signature

Approved by a Michigan State University Institutional Review Board effective 7/8/2021.
This version supersedes all previous versions. MSU Study ID STUDY00004174.

_____ _____

City or municipality of birth Date of birth (optional: this helps us distinguish you from someone else with the same name)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Pages
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**3**
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	**NA**
Funding	4	Sources and types of financial, material, and other support	**18**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**1, 18**
	5b	Name and contact information for the trial sponsor	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**4-6**
	6b	Explanation for choice of comparators	**6**
Objectives	7	Specific objectives or hypotheses	**5**

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	**9**
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**10**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**8-9**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**6-8**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	**17**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	**10**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**8**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	**11-13**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**20**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**15-16**

Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	**9-10**
Methods: Assignment of interventions (for controlled trials)			
Allocation:			**9**
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**9**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**9**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**9**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**10**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**NA**
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**11-13**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**10**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**16**

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**13-15**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**13-15**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**13-15**
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**NA**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**13**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**17**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**NA**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**16**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**NA**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**16**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**NA**

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**16**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**18**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**17**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**17**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**17**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**NA**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**17**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**attached**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**NA**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.