BMJ Open

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

Jennifer E Johnson ,[1,2] Ann B Price,[3] Alla Sikorskii,[4] Kent D Key,[2] Brandon Taylor,[2] Susan Lamphere,[2] Christine Huff,[2] Morgan Cinader,[2] Caron Zlotnick[3,5,6]

To cite: Johnson JE, Price AB, Sikorskii A, *et al*. Protocol for the Healing After Loss (HeAL) Study: a randomised controlled trial of interpersonal psychotherapy (IPT) for major depression following perinatal loss. *BMJ Open* 2022;**12**:e057747. doi:10.1136/bmjopen-2021-057747

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-057747).

Received 25 September 2021
Accepted 30 March 2022

For numbered affiliations see end of article.

Correspondence to
Jennifer E Johnson;
JJohns@msu.edu

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 post-traumatic stress disorder (PTSD). Perinatal loss conveys specific treatment needs. The trial will be the first fully powered randomised 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 randomised to group IPT for perinatal loss or to group coping with depression. 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 hypothesised 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 organisation 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 organisations through which we recruited, and will offer results to study participants. Deidentified datasets will be available through the National Institute of Mental Health Data Archive and to qualified investigators on request.

Trial registration number NCT04629599.

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 minimised.
- 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.
- Rigour and reproducibility are ensured by the randomised 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 manualised 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 USA 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 three times the rates among matched samples of community women.[3–20] Rates of post-traumatic stress disorder (PTSD) after perinatal loss are up to seven 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 hospitalisation 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 (eg, '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 randomised 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 favoured the new IPT manual for PTSD recovery, treatment satisfaction, depressive symptoms, grief and social support relative to coping with depression (CWD), a cognitive-behavioural-based intervention that does not focus on perinatal loss, interpersonal issues or social support.[31]

Based on those promising results, this study will be the first fully powered randomised 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 minimised. Given that poverty increases risk of perinatal loss,[36–38] and doubles the risk of perinatal depression,[39–46] and that rates of perinatal loss for African-American women are double those for white women,[47–49] 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 organisations 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 organisation partners community ethics review board for additional community feedback.[50]

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 CWD course, as a control condition. We chose CWD because it is the group treatment with the most empirical support for treating MDD[51 52] 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 behaviour; 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 hypothesised differences between treatments. As desired, our pilot study found differences between conditions in the hypothesised mechanisms of social support and grief and in terms of in-session activities.[31]

Treatments

Manualised treatments are attention-matched (12 groups of 90 min each, 1 individual pregroup session and 1 booster session). Every 4 weeks, both treatments allow

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 obstetric 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 min, discuss as a group what they learnt 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-modelling how to offer well-wishes to and from women completing their group treatment in this session.

IPT, interpersonal psychotherapy.

new women to enter the group and women completing 12 weeks to leave the group.

Interpersonal psychotherapy

Participants in the IPT condition receive 12 group sessions and 2 individual (pregroup 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 53]

Group sessions are semistructured, 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 counselling.

Coping with depression

CWD is a structured, manualised[54] psychoeducational group treatment for MDD. The CWD course is cognitive behavioural. The problems shown by depressed individuals are viewed as behavioural, with cognitive patterns that can be unlearned or relearned. Its effectiveness is comparable to other forms of psychotherapy in depression.[52] The course content teaches skills including relaxation, cognitive skills and behavioural activation. The CWD pregroup and booster sessions are the pregroup and booster sessions from the published CWD manual.[54] To ensure that the CWD intervention was distinct from IPT, we excluded the two sessions on social skills and emphasised 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 (eg, 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[54] 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 Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5[55]) 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 18–50 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) and (6) any IPT or cognitive-behavioural 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 enrolment.

Therapist training and supervision

We trained eight study therapists (four in IPT and four in CWD) who are MSWs or clinical or counselling 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 1-hour small-group telephone meeting for feedback and case discussion. Treatment sessions are audiorecorded using digital audio recorders or a Health Insurance Portability and Accountability Act (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.

Randomisation

Women are randomly assigned to IPT or CWD in a 1:1 ratio. We stratify randomisation 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). Randomisation sequences were created by the study statistician. Assignment is concealed in an envelope that research assistants (RAs) open at randomisation.

Recruitment

Participants are recruited from counties in Southeast Michigan using a broad outreach strategy. We partner with regional health systems, community-based organisations in Flint and Detroit, and a regional Medicaid system in study recruitment. Recruitment also includes flyers and referrals from: (1) local birthing centres, emergency departments, OBGYN offices and federally qualified health centres; (2) hotlines, support groups, family nurse partnerships; (3) funeral homes; (4) churches, daycare centres, other places where women and mothers congregate (WIC offices, Medicaid offices, etc); (5) bus ads and (6) online venues. We began recruitment on 1 September 2021 and plan to end on 1 March 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 56–58] 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.[56] 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 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[59] is used to establish study eligibility. During the follow-up, the Longitudinal Interval Follow-up Examination (LIFE),[60 61] a standardised retrospective calendar-based interview, is used to assess MDD and PTSD recovery. The LIFE uses Psychiatric Status Ratings to categorise 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

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
Hypothesised mediators				
Multidimensional 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	

CWD, coping with depression; IPT, interpersonal psychotherapy; PTSD, post-traumatic stress disorder; SCID-5, Structured Clinical Interview-5.

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 eight consecutive weeks of a PSR of 1–2[62] at any time between baseline and the 28-week follow-up. Women who do not have at least eight 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.[62] 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.[63] 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.[64]

PTSD symptoms are assessed using the Life Events Checklist and PTSD Checklist for DSM-5.[65–68] 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)[69] to assess overall social support. We use a validated adaptation of the Relationship Assessment Scale[70] 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).[71] Because depression can affect parenting, we will analyse 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 National Institutes of Health (NIH) Neuro-Quality of Life (Neuro-QoL) scale for positive affect and well-being.[72]

Grief symptoms are measured using the Perinatal Bereavement Grief Scale (PBGS).[4 73] Complicated grief is measured using the Inventory of Complicated Grief (ICG).[74] 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.[75–77]

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).[78]

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 intenon 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.[79] Primary and secondary outcomes and all hypotheses are stated a priori, therefore, 0.05 level of significance will be used. Per Kraemer,[80] we will not test for differences between conditions due to randomisation 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 generalisability 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.[81] If patterns of missing data indicate potential not MAR mechanisms, then models describing missing mechanisms will be considered (eg, pattern-mixture models),[82 83] and sensitivity analyses will be employed.

General approaches

For survival analyses, the proportional hazard 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 postbaseline assessment will be included. We expect these scores to follow normal distributions. However, generalised LME (GLME) modelling will be used if outcome is not normally distributed and cannot be normalised 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 postbaseline 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 modelling 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, PBGS, ICG, 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[84 85] based on 5000 bootstrap samples to estimate 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.

Table 3 Power for n=274 for secondary outcomes

	d=0.29	d=0.32	d=0.35
10% attrition	0.81	**0.88**	0.93
15% attrition	0.74	0.83	0.88
20% attrition	0.72	0.80	0.86
25% attrition	0.69	0.78	0.84

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 HR=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 0.38. 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 HR 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=0.32 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 authorised 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 audiorecorders and HIPAA-compliant videoconferencing; (2) labelling 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. Prespecified adverse events are recorded and monitored using a structured system created within Research Electronic Data Capture (REDCap) with alerts for follow-up actions.[56]

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.[56]

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 non-response

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 organisations through which we recruited, and offering to share final study results with study participants. De-identified datasets will be available to qualified investigators on request.

Author affiliations
[1]Department of Obstetrics, Gynecology, and Reproductive Biology, Michigan State University College of Human Medicine, Flint, Michigan, USA
[2]Division of Public Health, Michigan State University College of Human Medicine, Flint, Michigan, USA
[3]Department of Psychiatry, Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA
[4]Department of Psychiatry, Michigan State University College of Osteopathic Medicine, East Lansing, Michigan, USA
[5]Butler Hospital, Providence, Rhode Island, USA
[6]Women and Infants Hospital of Rhode Island, Providence, Rhode Island, USA

Twitter Jennifer E Johnson @JJohnsPhD

Contributors JEJ: conceptualisation (lead), funding acquisition (lead), investigation (lead), intervention development (equal), safety protocols (lead), writing—original draft preparation (lead), writing—review and editing (lead). CZ: conceptualisation

(supporting), funding acquisition (supporting), clinical supervision (equal), safety protocols (supporting), writing—review and editing (supporting). ABP: funding acquisition (supporting), intervention development (equal), clinical supervision (equal). AS: conceptualisation (supporting), funding acquisition (supporting), data curation, formal analysis. KDK: funding acquisition (supporting), recruitment strategy (supporting). SL, BT, CH and MC: recruitment strategies (lead), development of operating procedures (supporting), choice of measures (supporting).

Funding This work was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) grant number (R01 HD100471). NICHD had no role in the design of the study and will have no role in the implementation of the study, analysis of the data, or writing of the manuscript.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Jennifer E Johnson http://orcid.org/0000-0003-2540-7213

REFERENCES

1 Armstrong DS. Emotional distress and prenatal attachment in pregnancy after perinatal loss. *J Nurs Scholarsh* 2002;34:339–45.
2 AmericanPregnancy. AmericanPregnancy, 2008. Available: www.americanpregnancy.org/main/statistics.html [Accessed June 2008].
3 Gavin NI, Gaynes BN, Lohr KN, *et al*. Perinatal depression: a systematic review of prevalence and incidence. *Obstet Gynecol* 2005;106:1071–83.
4 Klier CM, Geller PA, Ritsher JB. Affective disorders in the aftermath of miscarriage: a comprehensive review. *Arch Womens Ment Health* 2002;5:129–49.
5 Neugebauer R, Kline J, Shrout P, *et al*. Major depressive disorder in the 6 months after miscarriage. *JAMA* 1997;277:383–8.
6 Lee DT, Wong CK, Cheung LP, *et al*. Psychiatric morbidity following miscarriage: a prevalence study of Chinese women in Hong Kong. *J Affect Disord* 1997;43:63–8.
7 Neugebauer R. Depressive symptoms at two months after miscarriage: interpreting study findings from an epidemiological versus clinical perspective. *Depress Anxiety* 2003;17:152–61.
8 Neugebauer R, Kline J, O'Connor P, *et al*. Determinants of depressive symptoms in the early weeks after miscarriage. *Am J Public Health* 1992a;82:1332–9.
9 Neugebauer R, Kline J, O'Connor P, O'Conner P, *et al*. Depressive symptoms in women in the six months after miscarriage. *Am J Obstet Gynecol* 1992;166:104–9.
10 Beutel M, Deckardt R, von Rad M, *et al*. Grief and depression after miscarriage: their separation, antecedents, and course. *Psychosom Med* 1995;57:517–26.
11 Thapar AK, Thapar A. Psychological sequelae of miscarriage: a controlled study using the general health questionnaire and the hospital anxiety and depression scale. *Br J Gen Pract* 1992;42:94–6.
12 Stirtzinger RM, Robinson GE, Stewart DE, *et al*. Parameters of grieving in spontaneous abortion. *Int J Psychiatry Med* 1999;29:235–49.
13 Gold KJ, Leon I, Boggs ME, *et al*. Depression and posttraumatic stress symptoms after perinatal loss in a population-based sample. *J Womens Health* 2016;25:263–9.
14 Boyle FM, Vance JC, Najman JM, *et al*. The mental health impact of stillbirth, neonatal death or SIDS: prevalence and patterns of distress among mothers. *Soc Sci Med* 1996;43:1273–82.
15 Vance JC, Boyle FM, Najman JM. Gender differences in parental psychological distress following perinatal death or sudden infant death syndrome. *British Journal of Psychiatry* 1995;167:806–11.
16 Clarke M, Williams AJ. Depression in women after perinatal death. *Lancet* 1979;1:916–7.
17 Carrera L, Díez-Domingo J, Montañana V, *et al*. Depression in women suffering perinatal loss. *Int J Gynaecol Obstet* 1998;62:149–53.
18 HJEM J, Cuisinier MCJ, Hoogduin KAL. Controlled prospective study on the mental health of women following pregnancy loss. *American Journal of Psychiatry* 1996;153:226–30.
19 Kulathilaka S, Hanwella R, de Silva VA. Depressive disorder and grief following spontaneous abortion. *BMC Psychiatry* 2016;16:100.
20 Wall-Wieler E, Roos LL, Bolton J. Duration of maternal mental health-related outcomes after an infant's death: a retrospective matched cohort study using linkable administrative data. *Depress Anxiety* 2018;35:305–12.
21 Gravensteen IK, Helgadóttir LB, Jacobsen E-M, *et al*. Women's experiences in relation to stillbirth and risk factors for long-term post-traumatic stress symptoms: a retrospective study. *BMJ Open* 2013;3:e003323.
22 Gissler M, Hemminki E, Lönnqvist J. Suicides after pregnancy in Finland, 1987-94: register linkage study. *BMJ* 1996;313:1431–4.
23 Schiff MA, Grossman DC. Adverse perinatal outcomes and risk for postpartum suicide attempt in Washington state, 1987-2001. *Pediatrics* 2006;118:e669–75.
24 Engelhard IM, van den Hout MA, Arntz A. Posttraumatic stress disorder after pregnancy loss. *Gen Hosp Psychiatry* 2001;23:62–6.
25 Nikčević AV. Development and evaluation of a miscarriage follow-up clinic. *J Reprod Infant Psychol* 2003;21:207–17.
26 DiMarco MA, Menke EM, McNamara T. Evaluating a support group for perinatal loss. *MCN Am J Matern Child Nurs* 2001;26:135–40.
27 McCreight BS. Perinatal loss: a qualitative study in Northern Ireland. *Omega* 2008;57:1–19.
28 Conway K. Miscarriage experience and the role of support systems: a pilot study. *Br J Med Psychol* 1995;68 (Pt 3:259–67.
29 Brier N. Understanding and managing the emotional reactions to a miscarriage. *Obstet Gynecol* 1999;93:151–5.
30 Cordle CJ, Prettyman RJ. A 2-year follow-up of women who have experienced early miscarriage. *J Reprod Infant Psychol* 1994;12:37–43.
31 Johnson JE, Price AB, Kao JC, *et al*. Interpersonal psychotherapy (ipt) for major depression following perinatal loss: a pilot randomized controlled trial. *Arch Womens Ment Health* 2016;19:845–59.
32 Crockett K, Zlotnick C, Davis M, *et al*. A depression preventive intervention for rural low-income African-American pregnant women at risk for postpartum depression. *Arch Womens Ment Health* 2008;11:319–25.
33 O'Hara MW, Stuart S, Gorman LL, *et al*. Efficacy of interpersonal psychotherapy for postpartum depression. *Arch Gen Psychiatry* 2000;57:1039–45.
34 Ramezani S, Khosravi A, Motaghi Z, *et al*. The effect of cognitive-behavioural and solution-focused counselling on prevention of postpartum depression in nulliparous pregnant women. *J Reprod Infant Psychol* 2017;35:172–82.
35 Milgrom J, Gemmill AW, Gemmill AW, B. G., Gemmill, *et al*. Internet cognitive behavioral therapy for women with postnatal depression: a randomized controlled trial of MumMoodBooster. *J Med Internet Res* 2016;18:e54.
36 Norsker FN, Espenhain L, A Rogvi S, *et al*. Socioeconomic position and the risk of spontaneous abortion: a study within the Danish national birth cohort. *BMJ Open* 2012;2:e001077.
37 Seaton SE, Field DJ, Draper ES, *et al*. Socioeconomic inequalities in the rate of stillbirths by cause: a population-based study. *BMJ Open* 2012;2:e001100.
38 Singh GK, Daus GP, Allender M, *et al*. Social determinants of health in the United States: addressing major health inequality trends for the nation, 1935-2016. *Int J MCH AIDS* 2017;6:139–64.
39 Hobfoll SE, Ritter C, Lavin J, *et al*. Depression prevalence and incidence among inner-city pregnant and postpartum women. *J Consult Clin Psychol* 1995;63:445–53.
40 Scholle SH, Haskett RF, Hanusa BH, *et al*. Addressing depression in obstetrics/gynecology practice. *Gen Hosp Psychiatry* 2003;25:83–90.
41 Davila M, McFall SL, Cheng D. Acculturation and depressive symptoms among pregnant and postpartum Latinas. *Matern Child Health J* 2009;13:318–25.
42 Chaudron LH, Kitzman HJ, Peifer KL, *et al*. Prevalence of maternal depressive symptoms in low-income Hispanic women. *J Clin Psychiatry* 2005;66:418–23.
43 Boury JM, Larkin KT, Krummel DA. Factors related to postpartum depressive symptoms in low-income women. *Women Health* 2004;39:19–34.
44 Price SK, Proctor EK. A rural perspective on perinatal depression: prevalence, correlates, and implications for help-seeking among low-income women. *J Rural Health* 2009;25:158–66.

45 Morris-Rush JK, Freda MC, Bernstein PS. Screening for postpartum depression in an inner-city population. *Am J Obstet Gynecol* 2003;188:1217–9.
46 Evans J, Heron J, Francomb H, *et al*. Cohort study of depressed mood during pregnancy and after childbirth. *BMJ* 2001;323:257–60.
47 Mukherjee S, Velez Edwards DR, Baird DD, *et al*. Risk of miscarriage among black women and white women in a U.S. prospective cohort study. *Am J Epidemiol* 2013;177:1271–8.
48 Willinger M, Ko C-W, Reddy UM. Racial disparities in stillbirth risk across gestation in the United States. *Am J Obstet Gynecol* 2009;201:469.e1–469.e8.
49 US_Department_of_Health_and_Human_Services. Infant Mortality and African Americans 2017, 2018. Available: https://minorityhealth.hhs.gov/omh/browse.aspx?lvl=4&lvlid=23 [Accessed 12-10-2018].
50 Community_Based_Organization_Partners. Community Based Organization Partners - Community Ethics Review Board (CBOP-CERB) 2021. Available: https://www.hfrcc.org/cerb/ [Accessed 17 September 2021].
51 Johnson JE. Wirksamkeit von gruppenbehandlungen bei majorer depression (efficacy of group treatments for major depressive disorder). *Gruppenpsychotherapie und Gruppendynamik* 2009;45:181–207.
52 Cuijpers P. A psychoeducational approach to the treatment of depression: A meta-analysis of lewinsohn's "coping with depression" course. *Behav Ther* 1998;29:521–33.
53 Gilbert K, Smart LS. *Coping with infant or fetal loss: The couple's healing process*. New York: Bruner/Mazel, 1992.
54 Lewinsohn P, Antonuccio DO, Breckenridge JS, *et al*. *The "Coping With Depression" course. Eugene*. OR: Castalia, 1984.
55 American_Psychiatric_Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. Washington DC: American Psychiatric Association, 2013.
56 Johnson JE, Jones R, Miller T, *et al*. Study protocol: a randomized controlled trial of suicide risk reduction in the year following jail release (the spirit trial). *Contemp Clin Trials* 2020;94:106003.
57 Johnson JE, Zlotnick C. Pilot study of treatment for major depression among women prisoners with substance use disorder. *J Psychiatr Res* 2012;46:1174–83.
58 Zlotnick C, Miller IW, Pearlstein T, *et al*. A preventive intervention for pregnant women on public assistance at risk for postpartum depression. *Am J Psychiatry* 2006;163:1443–5.
59 First M, Williams JBW, Karg RS, *et al*. *Structured clinical interview for DSM-5*. Arlington, VA: American Psychiatric Association, 2015.
60 Keller MB, Lavori PW, Friedman B, *et al*. The longitudinal interval follow-up evaluation. A comprehensive method for assessing outcome in prospective longitudinal studies. *Arch Gen Psychiatry* 1987a;44:540–8.
61 Warshaw MG, Keller MB, Stout RL. Reliability and validity of the longitudinal interval follow-up evaluation for assessing outcome of anxiety disorders. *J Psychiatr Res* 1994;28:531–45.
62 Keller MB. Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. *JAMA* 2003;289:3152-60.
63 Smith P, Earp JA, Devellis R. Measuring battering: Development of the Women's Experience with Battering (WEB) scale. *Women's Health: Research on gender, behavior, and policy* 1995;1:273–88.
64 Rush AJ, Trivedi MH, Ibrahim HM, *et al*. The 16-Item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry* 2003;54:573–83.
65 Weathers F, Litz BT, Keane TM. The PTSD checklist for DSM-5 (PCL-5): national center for PTSD, 2013. Available: www.ptsd.va.gov
66 Blevins CA, Weathers FW, Davis MT, *et al*. The posttraumatic stress disorder checklist for DSM-5 (PCL-5): development and initial psychometric evaluation. *J Trauma Stress* 2015;28:489–98.
67 Bovin MJ, Marx BP, Weathers FW, *et al*. Psychometric properties of the PTSD checklist for diagnostic and statistical manual of mental Disorders-Fifth edition (PCL-5) in veterans. *Psychol Assess* 2016;28:1379-–91..
68 Wortmann JH, Jordan AH, Weathers FW, *et al*. Psychometric analysis of the PTSD Checklist-5 (PCL-5) among treatment-seeking military service members. *Psychol Assess* 2016;28:1392–403.
69 Dahlem NW, Zimet GD, Walker RR. The multidimensional scale of perceived social support: a confirmation study. *J Clin Psychol* 1991;47:756–61.
70 Renshaw KD, McKnight P, Caska CM, *et al*. The utility of the relationship assessment scale in multiple types of relationships. *J Soc Pers Relat* 2011;28:435–47.
71 Gameroff MJ, Wickramaratne P, Weissman MM. Testing the short and screener versions of the social adjustment Scale-Self-report (SAS-SR). *Int J Methods Psychiatr Res* 2012;21:52–65.
72 Salsman JM, Victorson D, Choi SW, *et al*. Development and validation of the positive affect and well-being scale for the neurology quality of life (Neuro-QOL) measurement system. *Qual Life Res* 2013;22:2569–80.
73 Ritsher JB, Neugebauer R. Perinatal bereavement grief scale: distinguishing grief from depression following miscarriage. *Assessment* 2002;9:31–40.
74 Prigerson HG, Maciejewski PK, Reynolds CF, *et al*. Inventory of complicated grief: a scale to measure maladaptive symptoms of loss. *Psychiatry Res* 1995;59:65–79.
75 Callan MJ, Kay AC, Dawtry RJ. Making sense of misfortune: deservingness, self-esteem, and patterns of self-defeat. *J Pers Soc Psychol* 2014;107:142–62.
76 Lucas T, Alexander S, Firestone I, *et al*. Belief in a just world, social influence and illness attributions: evidence of a just world boomerang effect. *J Health Psychol* 2009;14:258–66.
77 Glinder JG, Compas BE. Self-blame attributions in women with newly diagnosed breast cancer: a prospective study of psychological adjustment. *Health Psychol* 1999;18:475–81.
78 Attkisson CC, Zwick R. The client satisfaction questionnaire. psychometric properties and correlations with service utilization and psychotherapy outcome. *Eval Program Plann* 1982;5:233–7.
79 Citrome L. Compelling or irrelevant? using number needed to treat can help decide. *Acta Psychiatr Scand* 2008;117:412–9.
80 Kraemer HC. A source of false findings in published research studies: adjusting for covariates. *JAMA Psychiatry* 2015;72:961–2.
81 Little R, Rubin M. *Statistical analysis with missing data*. New York: Wiley and Sons, 1987.
82 Hogan JW, Roy J, Korkontzelou C. Handling drop-out in longitudinal studies. *Stat Med* 2004;23:1455–97.
83 Shen C, Weissfeld L. Application of pattern-mixture models to outcomes that are potentially missing not at random using pseudo maximum likelihood estimation. *Biostatistics* 2005;6:333–47.
84 Preacher KJ, Selig JP. Advantages of Monte Carlo confidence intervals for indirect effects. *Commun Methods Meas* 2012;6:77–98.
85 Biesanz JC, Falk CF, Savalei V. Assessing mediational models: testing and interval estimation for indirect effects. *Multivariate Behav Res* 2010;45:661–701.