Official Title:	A Pilot Randomized Trial of Video-based Family Therapy for Depressed Home Visited Mothers
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Study Protocol

Study Purpose: Assess the feasibility, acceptability, tolerability, safety, and preliminary effectiveness of a video-based family therapy intervention (Resilience Enhancement Skills Training, REST) in home visited mothers (pregnant and postpartum) with moderate to severe depressive symptoms and moderate to high family conflict.

Study Design: Effectiveness-implementation hybrid type 1 design with a pilot randomized trial.

Sample Size: We aimed to enroll 80 home visited mothers and their family members (N=160) in the study.

Characteristics of Subject Population: Mothers, at least 15 years old, in any trimester of pregnancy through 18 months postpartum, enrolled in participating home visiting (HV) agencies with moderate to severe depressive symptoms on the Beck Depression Inventory-Second Edition [BDI-II] scores of ≥ 20 and moderate to high family conflict with their family members on the Perceived Hostility Survey (Ages 18+) raw scores of at least 16 or Perceived Hostility Survey (Ages 8-17) raw scores of at least 14. *Family member* is defined as the mother's adult relative or her current intimate partner with whom she either lives with in the same home or has at least weekly contact. *Family* is defined as a dyad that includes the mother and her family member.

Scheme. The mother was the unit of randomization in the study. Block randomization with block size of 4 using R package "Blockrand" was used to randomize the mothers to the study groups. Mothers were randomized with equal probability to one of two study groups: 1) video-based family therapy (Resilience Enhancement Skills Training, REST), or 2) the active comparison condition standard of care (Video-delivered individual Problem Solving Therapy, V-PST). The family received REST. Although only the mother received V-PST, the mother and her family member were asked to complete outcome measures.

Process and blinding. The Statistician used Blockrand to randomize the mothers, by unique study IDs, to the study groups. The PI communicated with Statistician to obtain the study group assignments by unique study ID. The PI called the therapist and family to communicate the study group assignment on the same day the mother and her family member completed the baseline interview. The Research Assistants remained blind to study group assignment, and study participants (mothers and their family members) were instructed by the PI not to discuss their study group assignment with the Research Assistant who administered the study questionnaires to them. In addition, the PI instructed the Research Assistants to remind each study participant not to disclose the study group assignment prior to administering each study questionnaire. Research assistants were regularly supervised by the PI.

Outcomes: The primary outcomes included maternal depressive symptoms (measured using the Beck Depression Inventory-Second Edition), family conflict (measured using the Perceived Hostility Survey Ages 18+ and Ages 8-17 years old), and family cohesion (measured using the Multidimensional Scale of Perceived Social Support – Family subscale). The secondary outcome included maternal job attainment/school enrollment measured using an adapted ABCD study item. Outcomes were assessed from baseline through post-intervention (within one week of the final therapy session), three months later, and six months later.

Monitoring Trial Performance. The PI developed and utilized structured processes for ensuring intervention fidelity and fidelity to the study protocol. For this study, the PI 1) developed initial trainings and refresher trainings for data collection procedures and adherence to safety protocols for research staff; 2) supervised the research staff to ensure adherence to recruitment, data collection, and retention procedures; 3) held weekly meetings with lead staff at participating home visiting agencies to discuss recruitment, home visitor study responsibilities, and any issues related to reallocation of home visitor study responsibilities due to home visitor turnover. In addition, the study included data entry software that minimized missing data by flagging missed items before questionnaires were submitted. The secure, password protected database was regularly maintained and monitored throughout the study.

Fidelity monitoring for the interventions occurred in two phases. In phase one, the PI and Problem Solving Therapy (PST) expert assessed fidelity on a weekly basis in all 10 audio-recorded sessions for the first 2 families who are assigned to each REST therapist. They continued to assess fidelity on a weekly basis in all 10 audio-recorded sessions for the first two mothers who were assigned to each V-PST therapist. The PI and PST expert discussed and resolved any discrepancies in these fidelity assessments. The PI immediately provided any corrective feedback to REST therapists in weekly supervision. For the V-PST therapists, the PI immediately communicated any corrective feedback to the V-PST supervisor to address with the therapists in weekly supervision.

In phase two, the PST expert assessed fidelity in 10% of randomly selected audio-recorded REST sessions, originally assessed by the PI, and 10% of randomly selected audio-recorded V-PST sessions, originally assessed by the PI. The PST expert and the PI discussed and resolved any discrepancies in the fidelity assessments throughout Years 1 and 2 of the proposed study. These fidelity assessments occurred on an ongoing basis in order to provide immediate corrective feedback to REST therapists and V-PST therapists to ensure high fidelity.

Data and Safety Monitoring Board Procedures (DSMB). The DSMB has established procedures of operation and guidelines for determining the methods and frequency for review of Departmental studies. Table 1, below, guides the risk assessment for the study. Based on the DSMB's established guidelines, the study's total score of 6 on the 10-point scoring system indicates that it poses greater than minimal risk to human subjects. Tasks related to participant safety included the PI's assessment of potential risks associated with study recruitment and participation, and the design and implementation of procedures to minimize these risks should they arise. According to the Departmental DSMB policy, studies in this risk category will be independently monitored by a group of knowledgeable faculty members and an independent statistician. The DSMB met twice per year to monitor the study, which included data analysis by the independent statistician.

Table 1. Study Risk Assessment *				**ENTER SCORE**
I. Experimental Treatment				
Low Risk	No experimental treatment in study	1 point		
Moderate Risk	Treatment effects documented from studies with similar and/or	2 points		2

	different populations and/or settings. No serious adverse events expected. Specific plans to monitor adverse events (AE's) detailed in DSM plan.			
High Risk	Experimental treatment is being regulated by the FDA (e.g., investigational drug, device, or biologic)	4 points		
II. Procedures, Measurement, and Data Collection Methods				
Low Risk	Minimally invasive with low degree of emotional and/or physical discomfort. Probability of adverse events is low. Severity (magnitude) of adverse events is low. (Procedure may be rated as low if probability of AE is moderate to high as long as the severity is low, as in the case of a bruise from phlebotomy.) Procedures that meet IRB criteria for expedited review are commonly rated as low.	1 point		
Moderate Risk	Moderate degree of emotional and/or physical discomfort. Probability of adverse events is low. Severity of adverse events is moderate to high (e.g., PET scan, lumbar puncture, arterial lines).	2 points		2
High Risk	Moderate to high degree of emotional and/or physical discomfort. Probability of adverse events is moderate to high. Severity of adverse events is high (e.g., heart muscle biopsy, insulin infusion).	4 points		
III. Decision-Making Capability				
Non-vulnerable	Adult who (1) demonstrates decision-making capacity and (2) demonstrates no perception of undue influence or coercion to participate.	1 point		

Vulnerable	Any minor. Adult who (1) demonstrates limitations in decision-making capacity and/or (2) is prone to perception of undue influence or coercion to participate.	2 points	Minors ages 15-17 years old	2
			TOTAL	**6**

*****Adapted with permission from Slimmer et al., Western Journal of Nursing Research, 2004, 26(7), 797-803. [170]

Details on the family recruitment procedures, consent procedures, safety monitoring procedures, and the results on feasibility, acceptability, safety and tolerability have been published (please see Cluxton-Keller F, Hegel MT. A video-delivered family therapeutic intervention for perinatal women with clinically significant depressive symptoms and family conflict: Indicators of feasibility and acceptability. JMIR Form Res. 2022;6(10):e41697. doi: 10.2196/41697. PMID: 36194458; and Cluxton-Keller F, Hegel MT, Donnelly CL, Bruce ML. Video-delivered family therapy for perinatal women with depressive symptoms and family conflict: Feasibility, acceptability, safety, and tolerability results from a pilot randomized trial. JMIR Form Res. 2023;7:e51824. doi: 10.2196/51824. PMID: 37921846).

Statistical Analysis Plan

Generalized linear mixed-effects models (GLMM) were used to analyze changes in mothers and family members, separately, with fixed effects for time (baseline, post-intervention, three-month, six-month follow-up), study group (Resilience Enhancement Skills Training, Standard of Care), and study group*time interaction. An intervention effect is indicated by a significant study group*time interaction with greater improvement in the Resilience Enhancement Skills Training group. Individual-level random intercept and slope terms were included to account for correlations from repeated measures. Significance of change from baseline to the six month follow-up was tested for mothers and family members, separately. GLMM was used that accommodates intermittent missing data and attrition, and estimate is not biased assuming missing data mechanism is missing at random (MAR) [1]. The distinction between MAR and missing not at random is not verifiable using observed data [2]. However, we did not empirically observe systematic patterns of missing in the data for this study. While MAR is a plausible assumption in many cases, minor departures from MAR typically do not invalidate the results of an MAR-based analysis. [3-4].

References

1. Fitzmaurice GM, Laird NM, Ware JH. *Applied longitudinal analysis (2nd ed.).* John Wiley & Sons, Inc. 2011.
2. Hedeker D, Gibbons R. *Longitudinal Data Analysis*. 2006. Wiley-Interscience.
3. Collins L, Schafer J, Kam CM. A comparison of inclusive and restrictive strategies in modern missing-data procedures. Psychol Methods. 2001;(6):330-351.
4. Schafer JL, Graham JW. Missing data: Our view of the state of the art. Psychol Methods. 2002;7(2):147-177.