Cover Page for Protocol

Sponsor name: UNC Lineberger Comprehensive Cancer Center
NCT number NCT04092816
Sponsor trial ID: LCCC1920
Official title of study: The Fathers and Mothers Invested in Lives of their Youth (FAMILY) Study: A pilot intervention for families affected by parental cancer
Document date: 12-7-20

LCCC1920: The Fathers and Mothers Invested in Lives of their Youth (FAMILY) Study: A pilot intervention for families affected by parental cancer

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Sponsor: Lineberger Comprehensive Cancer Center

Funding Source: Lineberger Development Award Program M0332; K07 CA218167-02

Version Date: December 7th, 2020

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

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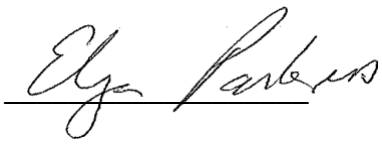
PI Signature: 

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1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

This is a single-arm pilot study to evaluate the feasibility and acceptability of a novel psychosocial intervention for parents with advanced cancer and their co-parents. In this single-center study, we will recruit ten mothers with metastatic breast cancer and their co-parents as dyads (N=20) to participate in the Fathers and Mothers Invested in the Lives of their Youth (FAMILY) intervention. The FAMILY intervention consists of manualized visits with a trained intervention facilitator and psychoeducation materials to help parents cope with cancer-related parenting concerns. The purpose of the intervention is to improve parenting concerns, emotional well-being, and end-of-life (EOL) preparation among participants. The primary hypothesis being tested is that a psychosocial intervention to reduce psychological distress and improve EOL preparation for mothers with metastatic breast cancer and their co-parents can be acceptable to the target population.

1.2 Background

Cancer is the leading disease-specific cause of early parental death in the United States (US),[1] and one in five cancer patients is between the ages of 21 and 55, the prime parenting years.[2] Among women, breast cancer is the leading cause of death from cancer globally, including women under age 50.[3]

Having dependent children worsens suffering for parents with advanced cancer and their families. In addition to the physical symptoms, functional limitations, and spiritual distress caused by the disease, parents with advanced cancer experience extraordinary psychological suffering related to parenting.[4,5] They have concerns about the impact of their illness and death on their children, as well as profound anticipatory grief about their inability to see their children into adulthood. Compared to advanced cancer patients without dependent children, parents are five times more likely to have anxiety.[6] Co-parents—spouses, grandparents, or other adults who will assume caregiving responsibilities if the patient is unavailable—must cope with their own grief and fears about solo parenting. Cross-sectional studies demonstrate that nearly 60% of parents[7] and co-parents[8] meet screening threshold criteria for anxiety and depression respectively. The consequences of bereaved co-parent maladjustment are compelling—they are four times more likely than other caregivers to meet diagnostic criteria for major depressive disorder and generalized anxiety disorder,[6] and their untreated depression is associated with worsened physical health[9] and psychiatric disorders in their children.[10] Children of seriously ill and dying cancer patients are twice as likely to experience clinically significant depressive symptoms[11] and remain at risk for other long-term psychological effects including anxiety, academic difficulties, and suicidal ideation.[12-15] The impact of terminal parental cancer and eventual death has lingering and long-term impact on the family.

For parents with advanced cancer, psychological distress and lack of EOL preparation are interlinked. In our research with bereaved fathers, reports of maternal worry about children were ubiquitous at the EOL and less than half of dying mothers were described as being at peace with dying. Many mothers were also inadequately prepared for the EOL—60% did not say

goodbye to their children prior to death and 50% did not die in the location of their choice.[16] These outcomes mirror results from the Coping with Cancer prospective cohort study. Compared to advanced cancer patients without dependent children, parents were half as likely to be peaceful, had worse quality of life (QOL) at the EOL, and were half as likely to complete advance care directives.[6] Together, these studies suggest that two defining features of the advanced cancer experience for parents are psychological suffering and inadequate EOL preparation.

No psychosocial interventions are proven to improve psychological distress for parents with advanced cancer. Much of the extant literature on cancer and parenting focuses on the effects of parental illness on children[14,17-20] and heavily relies upon samples of early-stage cancer patients with high 5-year survival rates.[21-25] Existing psychosocial interventions for parents with cancer are not specific to advanced cancer,[26-28] lack formal intervention testing with a control group,[13,27] or focus on pediatric, but not parental outcomes.[29,30] Despite strong evidence that parents with advanced cancer experience extreme suffering, no therapeutic interventions are proven to address their unique needs.

Parents with advanced cancer and their co-parents need tailored dyadic interventions. First, most parents' overarching goal—the well-being of their children—requires planning for future parenting, but is not addressed in standard advance care planning or psychosocial interventions for patients with advanced cancer. Second, our preliminary data on co-parent strain emphasize the need for interventions for both the co-parent and patient.[31] Third, the unique and high psychological distress in patients and co-parents may prevent their future EOL and childcare planning. Hence, they need customized strategies to reduce their distress. Fourth, interventions are more likely to be successful if patient and co-parent are targeted together by design due to the interdependence of experiences and psychological adjustment within dyads.[32-34]

Conceptual framework for the focus on dyads. Lewis' Integrated Framework for Communal Coping & Interdependences proposes that individual members of a dyad influence each other's motivation (interdependence) and decision-making (coping) for health-related behavior change.[35] A dyadic intervention should facilitate both greater intent and actual behavioral change for individuals by increasing the dyad's understanding of the mutuality of the problem. This model emphasizes interrelated psychological processes among dyads facing a health stressor by accounting for individual characteristics (e.g. demographic and illness factors), intrapersonal influences (e.g. individual appraisal and coping processes), and interpersonal characteristics (i.e. the simultaneous experiences of patient and co-parent and their influence on one another) on health outcomes. In this model, dyads experience a shared stressor (metastatic cancer), one parent's distress and readiness for EOL preparation will influence the other, and both parents will experience greater motivation to engage in EOL preparation by understanding their parenting concerns as mutual. In doing so, such a model facilitates more effective communication about their family's future care needs and reduces parental psychological distress (see Figure 1 for outcomes targeted by the intervention).

Rationale for focus on mothers with metastatic breast cancer and their co-parents. We focus on mothers with breast cancer due to high disease prevalence, evidence of willingness to

participate in psychosocial interventions,[36-38] and reduced variability in intervention efficacy due to gender or disease differences.

1.3 Purpose and Rationale

This study will evaluate whether a psychosocial intervention to reduce psychological distress and improve EOL preparation for mothers with metastatic breast cancer and their co-parents can be acceptable, feasible, and relevant to the target patient population.

This study is needed in order to generate critical data to: (1) refine the intervention in preparation for a pilot efficacy randomized controlled trial (RCT); and to generate preliminary data demonstrating the feasibility and acceptability of core intervention components. The preliminary data will support future grant applications for a full-scale efficacy RCT.

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

The primary objective of this study is to evaluate the acceptability of a pilot psychosocial intervention for mothers with metastatic breast cancer and their co-parents. Qualitative methods will evaluate acceptability based on patient and co-parent post-study satisfaction ratings and interviews.

2.2 Secondary Objectives

(1) A secondary objective of this study is to evaluate the feasibility of study procedures in preparation for a future RCT of the intervention. We will use interview data and descriptive statistics to evaluate and then refine screening, recruitment, retention, and intervention fidelity to optimally position us to conduct a RCT.

(2) A secondary objective of this study is to explore the impact of the intervention on target outcomes of emotional well-being and parenting concerns in women with metastatic breast cancer.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Participants who are patients must meet all of the inclusion criteria to participate in this study:

3.1.1. Be a woman with metastatic (stage IV) breast cancer who has current evidence of disease, and : (1) has previously received chemotherapy for metastatic disease, or (2) is unable to receive chemotherapy due to poor performance status
3.1.2. A mother of at least one dependent child, defined as a child <18 years of age who lives at least half-time in the home;
3.1.3. Be at least 18 years of age;

3.1.4. Adequate stamina to complete at least two study visits
3.1.5. Able to provide informed consent
3.1.6. Able to complete all study measures and visits in English;
3.1.7. Be willing to participate in study visits at the North Carolina Cancer Hospital (NCCH) if they live >75 miles away from NCCH or be willing to participate in study visits via virtual methods if UNC-CH COVID-19 precautions discourage in-person study visits;
3.1.8. Have an identified co-parent who is eligible and willing to participate in the study.

Eligible co-parent participants must meet all of the inclusion criteria to participate in the study:

3.1.9. Be an adult man or woman who is both a romantic partner or spouse of the patient and who would serve as the child(ren)'s primary caregiver if the patient were to become unavailable;
3.1.10. Able to provide informed consent;
3.1.11. Able to complete all study measures and visits in English;
3.1.12. Stated willingness to comply with all study procedures; and
3.1.13. Be at least 18 years of age.

3.2 Exclusion Criteria

All participants meeting any of the exclusion criteria at baseline will be excluded from study participation:

3.2.1. Unable to participate in study visits due to illiteracy, inability to speak English or other causes.
3.2.2. Live more than 75-miles away from the North Carolina Cancer Hospital (NCCH) and unable to attend study visits at NCCH or unwillingness to participate in virtual visits during UNC-CH mandated COVID-19 precautions *(participants who live more than 75-miles away and can attend study visits at NCCH or virtually remain eligible for participation).*
3.2.3. Unwilling to be audio-recorded during facilitated study visits and feedback interview.

4.0 STUDY PLAN

4.1 Schema

This is a non-randomized, single-arm psychosocial intervention pilot study of 10 patient-co-parent dyads (N=20). Dyads will participate in 2-3 study visits with an intervention facilitator and receive psychoeducation materials. Study visits will occur at NCCH, in participants' homes, or virtually via video conferencing when an in-person visit is not feasible. Home study visits will only be offered to participants who live within 75 miles of NCCH. We anticipate enrolling participants over a 18-month period (extended due to COVID-19) and that active participation will last for a three-month period.

4.2 Duration of Study

Expected duration of study participation is three months.

Baseline assessment (T0): We anticipate the pre-study visit assessment to last approximately 30 minutes.

Study visit 1 (T1): The first study visit consists of the first meeting with the intervention facilitator and the study visit assessments. The intervention facilitator meeting is expected to last 60-120 minutes. The study visit assessments are anticipated to take 30 minutes. If possible, visits will be scheduled two weeks apart; however, given the variable stamina of participants, participants will be given a seven-week period (five-week tolerance, from time of meeting with intervention facilitator to time of next study visit) to complete the study visit assessments.

Study visit 2 (T2): The second study visit consists of the second meeting with the intervention facilitator and the study visit assessments. The intervention facilitator meeting is expected to last 60-120 minutes. The study visit assessments are anticipated to take 30 minutes. If possible, visits will be scheduled two weeks apart; however, given the variable stamina of participants, participants will be given a seven-week period (five-week tolerance, from time of meeting with intervention facilitator to time of next study visit) to complete the study visit assessments.

Study visit 3 (T3): The optional third study visit consists of a third meeting with the intervention facilitator and the study visit assessments for participant dyads who elect to pursue a third study visit with the intervention facilitator. The intervention facilitator meeting is expected to last 60-120 minutes. The study visit assessments are anticipated to take 30 minutes. If possible, visits will be scheduled two weeks apart; however, given the variable stamina of participants, participants will be given a seven-week period (five-week tolerance) to complete the study visit assessments.

Post-intervention assessment (T4): The post-intervention assessment consists of a telephone or in-person interview with each participant to provide feedback on the intervention. The interview is expected to last 30-45 minutes. If possible, post-intervention assessments will be conducted within two weeks of the last intervention visit; however, given the variable stamina of participants, participants will be given a seven-week period (five-week tolerance) to complete the post-intervention interview.

Follow-up assessment 1 (T5): Chart abstraction will be performed by the study team 6 months after the dyad's most recent intervention study visit, with a two-week tolerance. Participants may choose to participate in an optional additional follow-up interview at this time.

Follow-up assessment 2 (T6): Chart abstraction will be performed by the study team 12 months after the dyad's most recent intervention study visit, with a two-week tolerance.

4.3 Study Details

Pre-study Assessments

Screening

The RA or PI will identify eligible patients through the UNC multidisciplinary breast conference and review of the outpatient five-day breast oncology clinic schedules. The study team will maintain a screening log that outlines whether screened patients meet eligibility criteria.

Screen failures

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. This may include participants whose physical or cognitive functioning worsens and interferes with their ability to engage in study activities; participants who die from their disease in the period between study enrollment and the first study visit; and participants who are lost to follow-up (i.e., do not respond to attempts to schedule first study visit).

Recruitment and informed consent:

The study team has conducted multiple prior studies with the target patient population and is highly experienced with respect to approaching eligible patients and clinic recruitment. Hundreds of advanced cancer patients who are parents have participated in the study team's prior research studies and the study team has demonstrated the ability to discuss sensitive topics such as parenting and advanced cancer in a manner that is acceptable to patients and their families.

UNC clinic recruitment will occur with the cooperation of the clinic attendings.
A member of the study team will confirm the patient's eligibility and receive permission from the patient's oncologist or advanced practice provider before approaching any eligible patient.

We will request that the patient's oncology provider first introduce the study purpose and study team member to potential participants using a brief recruitment script (see Appendix A). The study team member will then discuss the study with the eligible patient and provide information about the study (see Appendix B for recruitment brochure), allowing ample time for questions. The study team member will obtain written or verbal informed consent from all patients before enrollment. For patients receiving healthcare from the PI as their provider, the PI (instead of or in addition to an oncology provider) may pursue verbal confirmation of the patient's willingness to be contacted by other members of the study team for recruitment purposes.

This is a dyadic study and therefore requires both the patient and her co-parent to enroll for participation to occur. If the potential participant's co-parent is willing to participate in the study and is also present during initial recruitment then written informed consent will also be obtained at the same time as the patient. If the co-parent is not present at the time of patient enrollment then the study team will offer the following recruitment strategies for the co-parent of the consenting patient:

(1) Have the patient introduce the study to the co-parent with a study brochure and copy of the consent form for the co-parent followed by a phone call from the study team. If the co-parent is willing to participate in the study then the study team member will obtain verbal consent from him/her.

(2) If the co-parent is expected to attend a future oncology-related appointment with the patient, the study team will also offer to approach the co-parent in person at that visit.

In the event that a dyad would like to participate but the patient did not provide written consent at the time of initial in-person recruitment, both patient and co-parent may provide verbal consent over the phone. Both members of the dyad will sign additional written consents at the next available opportunity or meeting with study personnel. This will reduce participation burden in the event that a dyad or individual participant wishes to participate but wishes to discuss the study with their partner or family, would like additional time to consider participation, or for other reasons. This ensures that participants will not be caused unnecessary delay in scheduling study visits or collection of baseline measures.

All attempts will be made to recruit potential participants in person, and to obtain written informed consent. In circumstances where this is not feasible due to participant convenience, burden, or COVID-19 restrictions, potential participants may be recruited by email or telephone. This will only occur after the patient has verbally confirmed with the oncology provider that the study team may contact them. Participants who are unable to provide written consent for the above reasons may provide verbal consent to the study. In this circumstance, patient participants will provide electronic HIPAA consent via secure Qualtrics link, and all participants will provide additional written documentation of consent via Qualtrics link. All consent forms will be emailed to participants who wish to retain copies for their records. In the event that a participant consents verbally but

attends a study visit in person at a later date, additional written consents will be obtained at that time. Verbal consent is appropriate for the risk profile of this intervention.

Baseline study assessment
After receiving consent from both the patient and the co-parent, the study team member will obtain baseline assessment information from the participant dyad. Participants can complete the study forms online via a secure Qualtrics or RedCAP link, by pen and paper, or via telephone. The baseline study assessment consists of a demographic form and several patient/co-parent outcome measures (see Appendix C for copies of measures). See the study measures section for details about the measures and how they will be administered to the participants. Baseline assessments must be completed before the first study visit.

Study visits
During the study visits, the patient and co-parent participate together as a dyad with the intervention facilitator. The standard intervention will include Study Visits 1 and 2. Study Visit 3 is optional and will be offered to participant dyads who wish to have a third session with the intervention facilitator. Study visits will consist of two parts: (1) a face-to-face meeting with the intervention facilitator, and (2) data collection with the research assistant.

We will schedule study visits at the convenience of the participants. The participants will be provided with a choice regarding study visit location. The study visits will be conducted in either: (1) a clinical patient care area of the NCCH, (2) the participants' home (if they live within a 75-mile radius of NCCH), or (3) virtually via video conferencing if an in-person visit is not feasible. If participants request to participate in a home-based study visit then the intervention facilitator will travel with another member of the study team.

Participants will be provided a five-week interval to complete study visit assessments. The assessment window begins immediately after completing the face-to-face meeting with the intervention facilitator until five weeks after the study visit or immediately before participating in their next study visit – whichever time point occurs first. Participants can complete study assessments via an online Qualtrics link, via hard copy, or via telephone.

The intervention facilitator will be the PI or a trained licensed clinical social worker with experience providing clinical care to oncology and palliative medicine patient populations. The intervention facilitator will conduct the study visit in accordance with the study manual (see Appendix D for Intervention Facilitator manual) and patient education materials (see Appendix E for patient education materials) and will prepare a written memo after each study visit with participant dyads. The study visits with the intervention facilitator will be audio-recorded and professionally transcribed to aid with treatment fidelity monitoring and qualitative analyses.

Of note, the development of the intervention manual, training materials, and patient education materials have been extensively and iteratively reviewed by a panel of patient, caregiver, and healthcare provider stakeholders who have found the materials to be acceptable and emotionally sensitive. In addition, the intervention manual has several "branch" points in which questions and materials are offered to participants based on their stated willingness to acknowledge the severity of their illness and discuss sensitive topics. As such, the risk that the intervention content will cause undesired or unanticipated emotional distress to participants is reduced.

The intervention facilitator will be either the PI (a psychiatrist with expertise in psycho-oncology and 8 years of direct clinical experience with the target patient population) or a licensed clinical social worker supervised by the PI. The social worker will be a clinical member of the UNC Comprehensive Cancer Support Program and thus will have direct experience working with advanced cancer patients. He/she will undergo a minimum of two days of intervention training by the PI, involving self-study, role play, practice interviews, and demonstration of core competencies. In addition, the intervention will be supervised by the PI throughout the study and re-training to the social worker will be offered if large deviations from the intervention manual or other concerns arise during the course of the study. The PI has developed a comprehensive training manual to facilitate this.

Contact between or after study visits
Participants will be offered phone access to the intervention facilitator between or after study visits if they develop new or intervening concerns. The intervention facilitator will offer to connect participants with available resources and answer targeted questions but will not engage in formal psychotherapeutic counseling during these contacts. The number and reason for participants' contact with the intervention facilitator will be logged and evaluated at the end of the study.

Contact with bereaved participants
Patient participants in this study will all have a diagnosis of metastatic breast cancer and are therefore at risk of dying from their underlying disease during the study period. If a participant who is a breast cancer patient dies during the study period or up to six months following their participation in the study, the intervention facilitator will call the bereaved co-parent two weeks following the death of the patient (or within two weeks of the study team's notification of the death) to offer condolences and to provide brief psychosocial support to the participant. The intervention facilitator will follow a semi-structured telephone script that is included in the attachments.

Participant self-report study measures
Participants will complete several outcome measures. Each participant in the dyad will complete the study measures separately. Participants may complete some or all of the surveys and they can skip any questions they find distressing.

The measuring instruments, schedule of administration, and estimated duration are listed in Table 1 and include the following: Demographic and social history questions, the

Eastern Cooperative Oncology Group Performance status scale (modified for self-report), Parenting Concerns Questionnaire-Revised (PCQ-R), the Hospital Anxiety and Depression Scale (HADS), the Functional Assessment of Cancer Therapy – Palliative Care, FACIT-Pal, the Couples Illness Communication Scale (CICS) and several investigator-designed parental preparedness questions (see Appendix C for measures).

Table 1. Measuring instruments

Domain	Measure	Time (min)	Participant	Schedule
Demographic and baseline history forms	Demographic form Baseline history form	5	Patient Co-parent	Baseline
Acceptability	Study Visit Assessment form	5	Patient Co-parent	Visit 1 Visit 2 Visit 3 (if applicable)
Depression and anxiety	Hospital Anxiety and Depression Scale (HADS)	5	Patient Co-parent	Baseline Visit 1 Visit 2 Visit 3 (if applicable)
Parenting Concerns	Parenting Concerns Questionnaire-Revised (PCQ-R)	5	Patient Co-parent	Baseline Visit 1 Visit 2 Visit 3 (if applicable)
Parenting preparedness	Co-parenting and communication form	5	Patient Co-parent	Baseline Visit 1 Visit 2 Visit 3 (if applicable)
Health-related Quality of Life	Functional Assessment of Chronic Illness Therapy-Palliative Care (FACIT-Pal)	7	Patient	Baseline Visit 1 Visit 2 Visit 3 (if applicable)
Communication	Couples Illness Communication Scale (CICS)	2	Patient Co-parent	Baseline Visit 1 Visit 2 Visit 3 (if applicable)
Performance status	Eastern Cooperative Oncology Group Performance Status Scale (ECOG)	2	Patient	Baseline Visit 1 Visit 2 Visit 3 (if applicable)

Study team assessments

After each study visit, the PI and intervention facilitator will independently complete an intervention fidelity checklist.

Measures

Hospital Anxiety and Depression Scale (HADS)

The HADS is a 14-item self-administered rating scale to assess depression and anxiety symptoms in patients with physical illness (see Appendix D). The HADS has two 7-item sub-scales addressing depression and anxiety. It is graded on a 4-point scale with scores ranging from 0 to 42 (or 0-21 for each subscale) with higher scores representing greater

degrees of mood symptoms. The HADS is a well-validated instrument frequently used in oncology populations.[39,40] The average time to complete the HADS is 3-5 minutes.

Couples Illness Communication Scale (CICS)

The CICS is a brief self-report measure of illness-related couple communication. The CICS consists of 4 items measured on a 5-point Likert-type scale. It has demonstrated good acceptability, internal consistency, construct and convergent validity among couples in which one partner has cancer.[41] The average time to complete the CICS is 1-2 minutes.

Eastern Cooperative Oncology Group Performance Status Scale (ECOG)

The ECOG evaluates the severity of symptoms and amount of assistance the participant requires to complete "normal activities" using a 5-point scale. The ECOG is used to assess how the disease affects the daily living abilities of the patient and determine appropriate treatment and prognosis.[42] It has been modified for patient self-report and takes 1 minute to complete.

Parenting Concerns Questionnaire-Revised (PCQ-R)

The PCQ-R is a 21-item self-administered assessment of parenting concerns in advanced cancer patients. The PCQ-R is a modified version of the original Parenting Concerns Questionnaire – a general assessment of parenting concerns in cancer patients – with question items specifically addressing concerns of advanced cancer patients. The PCQ-R is measured on a 4-point scale and total score range for the PCQ is 0-63 with higher scores indicating greater distress. The original PCQ has demonstrated good internal consistency and face validity. The average time to complete the PCQ-R is 5 minutes.

Functional Assessment of Cancer Illness Therapy – Palliative Care (FACIT-Pal)

The FACIT-Pal is a 46-item self-administered assessment of general HRQOL in cancer patients. It has been validated in the literature and permits measurement of a number of symptoms including nausea, pain, and insomnia. It is graded on a five-point scale and has four sub-scales addressing emotional, social/family, physical and functional well-being.[43] The average time to complete the FACIT-Pal is 5-7 minutes.

Investigator-designed questions

Investigator-designed questions include items that are not found in validated scales or individual items from validated scales (to reduce participant response burden). Items on this form include questions about prior communication with children about illness, perceived social support, illness beliefs, and co-parenting support.[44,45] The estimated time to complete these items is 5-7 minutes.

Satisfaction assessment

The Lyon Satisfaction questionnaire is a validated 13-item assessment of acceptability and perceptions of visits in this population. One additional investigator-designed item asks participants to designate their overall satisfaction with their visit on a 5-point Likert-type scale. The estimated time to complete these items is 3-5 minutes.

<u>Post-intervention study interview</u>

Following completion of study visits with the intervention facilitator, participants will individually participate in a semi-structured interview with a member of the study team (PI or RA) to obtain feedback on the intervention (see Appendix F). If participants elect to withdraw from the study prior to completion of the scheduled intervention study visits, they will remain eligible to participate in this interview. The post-intervention interview will occur face-to-face in a private room of NCCH or via telephone and each member of the dyad will participate separately. The interview is expected to take 30-45 minutes. Participants are not required to answer questions they find emotionally distressing. All interviews will be audiotaped and then professionally transcribed. Interview audiofiles and transcriptions will be stored in a password-protected file within an electronic firewall-secured server maintained by the UNC School of Medicine.

Optional 6-month follow-up interview

If a participant is willing, the study team will follow up with them 6 months after finishing the study sessions. These participants will be asked to participate in an additional interview individually (separate from their partner). The interview is expected to take 20-30 minutes, and can be done in person or over the phone. This interview will also be audiotaped and transcribed. Participation in the 6-month follow-up interview is completely optional.

Medical record abstraction

The PI or RA will abstract demographic and medical history data from the patient participant charts including illness history and treatment, medical co-morbidities, and advance care planning documents.

Post-study Assessments

None. Participant dyads who participate in this study will not be eligible for the anticipated RCT that will formally test the efficacy of the intervention. If the participant with metastatic breast cancer dies from her disease up to six months after participating in the intervention then we will offer a bereavement phone call to her co-parent.

Participant compensation

Participants will receive up to $125 in incentives, pro-rated in installments over the study period. Participant dyads will receive a $25 gift card after data collection for each study visit is complete. They will receive an additional $50 after completing the post-intervention interview.

There is not additional compensation if participants choose to participate in the 6-month follow-up interview, but participation in this activity is completely optional.

Participant dyads who complete study visits at the hospital will be offered a parking voucher on the day of their study visit.

4.4 Expected Risks

Potential risks. The primary risks in this study are a loss of privacy, loss of patient confidentiality, and the risk of emotional distress elicited during the interviews, study measures, or study visits.

Loss of privacy. Approaching patients about enrollment in the clinic poses a risk to privacy. We expect this risk to be low. In the UNC Breast Clinic, RAs routinely approach patients for enrollment in clinical studies, and members of our team have completed prior psychosocial oncology studies with careful attention to patient privacy and high acceptability on the part of participants. For participants identified via discussions with patients (i.e., co-parents), the risk of loss of privacy is low as they will be able to review information about the study via review of study materials and telephone conversations with the PI or RA in the confidentiality of their home.

Loss of confidentiality. Loss of confidentiality could occur if the study database was breached. This risk will be minimized as a result of numerous steps to protect confidentiality (see Adequacy of Protection Against Risks, below). The alternative of not keeping identifiable information is not possible, because we will need to contact participants for follow-up. Increased risk to confidentiality is posed by unencrypted forms of communication (e.g. text message, unencrypted email), for those consenting to communicate with the study team via these methods.

Risk of emotional distress. All eligible patients for this study will have a diagnosis of metastatic breast cancer – an incurable illness frequently associated with intense emotional, physical and spiritual distress. All eligible co-parents for this study will have a loved one who has metastatic breast cancer. Both patients and co-parents may be at higher risk for temporary additional emotional discomfort or distress due to this study. Questions about quality of life, prognosis, parenting concerns, and EOL planning may be temporarily uncomfortable or distressing for some participants. We expect the risks of discomfort or distress to be moderate relative to the overall distress that the patients and their families experience due to their terminal illness. We have successfully conducted studies evaluating psychological distress, treatment decision-making, prognostic understanding, and supportive care needs with the patient and co-parent population described in the eligibility section above. Prior participants with a wide range of educational backgrounds, illness severity, and psychological adjustment have described our study practices as appropriate and acceptable. In addition, all intervention materials have previously undergone extensive review by a panel of patient, caregiver, and healthcare provider stakeholders (see LCCC1719 for details of this process) to enhance the relevance, acceptability, and emotional and cultural sensitivity of study materials.

In addition, the PI will continuously supervise the RA and intervention facilitator and conduct a 2-day training focused on how to recognize and address psychological distress or other concerns among participants that may occur during the course of the study. The training will consist of role plays and case examples, didactic and training manual materials, and review of the literature and available clinical resources. Training with the RA and intervention facilitator will be repeated as necessary throughout the study.

ADEQUACY OF PROTECTION AGAINST RISKS

Recruitment and informed consent. Eligible participants will be identified through conversation with oncology attendings and review of the outpatient five-day breast oncology clinic schedules. The RA or PI will receive permission from the patient's oncologist or advance practice provider before approaching any eligible patient. As such, participants for whom the treating oncology provider believes are at high risk of emotional distress from study participation will not be approached. The RA and PI will approach eligible patients about enrollment in the UNC Breast Clinic and we will ask each potential patient participant for consent. In the event that in-person recruitment is not feasible (such as COVID-19 restrictions), initial recruitment contacts may occur by email or telephone. Potential participants may only be contacted by email or telephone for recruitment after they have verbally confirmed with their oncology provider that they are willing to be contacted by the study team. For patients receiving healthcare from the PI as their provider, the PI (instead of or in addition to an oncology provider) may pursue verbal confirmation of the patient's willingness to be contacted by other members of the study team for recruitment purposes.

We will make all attempts to obtain written informed consent from participants when possible. Written informed consent will be obtained by the PI or other member of the study team for eligible participants who receive services at NC Cancer Hospital. Copies will be given to participants and kept locked in the study team's office. The PI or RA will obtain verbal consent from participants who do not receive services at NC Cancer Hospital before enrollment, or when in-person consent is not feasible (due to participant burden, convenience, or COVID-19 restrictions). Patient participants providing verbal consent will provide HIPAA consent electronically through a secure Qualtrics link, and will additionally provide documentation of adult consent via Qualtrics link. Participants will be emailed copies of all consent forms for their records if desired.

Participation in this study is voluntary. Patients who choose not to participate in this study will not be subject to prejudice in the delivery of health care by their physicians and clinical staff nor by the research institution. The informed consent discussion will occur with the RA or PI. The informed consent process will include review of the purpose of the research, procedures, risks, benefits, and participant's rights. Study participants can contact the PI to address all questions both prior to and after consenting to participate in the study. All participants will be specifically reminded that they may withdraw at any time without impacting their treatment or relationship with their clinical team and that they may choose not to answer any study question they would rather not answer.

Protections against risk. All members of the study team will undergo and maintain training in the responsible conduct of research. The RA will undergo training in enrollment of human subjects by the PI. The PI will bear responsibility in ensuring all study team members are up-to-date on required training and credentialing.

To protect against loss of privacy, all study-related interactions will be conducted in clinical patient care areas at UNC hospital or clinics, in the participant's home, virtually via HIPAA-compliant video conferencing, or via telephone after ascertaining with the participants that the location is private. Any phone messages will only state the name of the RA or PI and UNC, not the hospital, Cancer Center, or study name.

To protect against the risk of a loss of confidentiality, only the PI, the RA, intervention facilitator, and professional transcriber will have access to identifiable information or to the study database. The study database will be password-protected and housed on a secure server through the UNC Department of Psychiatry. The PI, intervention facilitator, and RA will only access the database through UNC-approved encrypted computers. Consent forms will be kept in a locked cabinet in the locked office of the PI and will be destroyed upon study completion. For analysis, identifiable information (such as patient, co-parent or children's names or schools or place of employment) will be removed from the analytic dataset, and participants will be assigned a unique study identifier. All interviews will be audiotaped and professionally transcribed for accuracy. All identifiers will be removed from the transcriptions. Audiotapes will be downloaded onto a secure, password-protected server and will be kept for up to two years following completion of the study and then destroyed.

To protect against the risk of emotional distress the RA will describe the nature of the study questions and their purposes during initial participant recruitment. We will also take the following additional measures to reduce the risk of emotional distress that may occur in some study participants. First, the RA or PI will receive permission from the patient's oncologist or nurse practitioner before approaching any eligible UNC patients. As such, participants who the treating oncology provider believes are at high risk of emotional distress from study participation will not be approached. Second, adverse events during or between study visits such as the unlikely eventuality of severe emotional distress (including suicidality) will be reported to the IRB by the PI—a board-certified psychiatrist with specialized training in psycho-oncology, and if the participant is a patient at UNC—her primary oncologist will be notified; if the participant such affected is the co-parent, then his/her primary care physician or practitioner (if available) will be notified by the PI. Should study staff observe emotional reactions necessitating clinical intervention, the study participant will be provided immediately support services in the form of psycho-oncology assessment by a trained member of the UNC Comprehensive Cancer Support Program (CCSP) psycho-oncology service (which the PI oversees). If the participant already receives CCSP services, we will also contact the participant's CCSP provider if severe emotional distress is noted during study visits.

POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO HUMAN SUBJECTS AND OTHERS

The benefit to participants in this study arises from the potential to help parents with advanced cancer to reduce their overall distress, to reduce their parenting concerns about their children's future care, and to improve their families' preparedness for and communication about the EOL of the mothers with cancer. Prior research has shown that parents with advanced cancer desire more psychosocial information and support for themselves and their family members. Patients participating in this pilot study may derive direct benefit from the opportunity to communicate

their parenting concerns with a trained intervention facilitator and co-parents and to identify ways to prepare their families for the EOL. Prior studies by members of our team in this type of research have had high response rates among the participants, particularly from mothers with breast cancer, suggesting that breast cancer patients are strongly motivated and interested in participating in clinical and psychosocial research studies.

4.5 Removal of Patients from Protocol

No significant adverse events are expected as a result of study participation. However, if an issue arises, the PI will be notified immediately. Members of the research team will meet regularly on a monthly basis to review study progress. Participants will be withdrawn from the study if any of the following conditions apply: (1) if exclusion criteria apply; (2) the participant requests to withdraw from the study; (3) the participant is unable to complete study visits due to death, physical or cognitive impairment, or is lost to follow-up. For any participants removed from the protocol, the PI will be notified and the reason for study removal as well as date of study removal will be documented.

5.0 TIME AND EVENTS TABLE

5.1 Time and Events Table

	Pre-study visit	**Baseline assessment (T0)**	**Study visit 1 (T1)** Day 7 ±35	**Study visit 2 (T2)** Day 14 ±35	**Study visit 3 (T3)** Day 28 ±35	**Post-intervention interview (T4)** Day 42 ±35	**Follow-up 1 (T5)** 6 months after last intervention visit ±14 days	**Follow-up 2 (T6)** 12 months after last intervention visit ±14 days
Medical record screening for eligibility	X							
Treating oncology provider approval	X							
Informed Consent (Patient)	X							
Informed Consent (Co-Parent)	X							
Baseline data		X						

collection								
Meeting with Intervention facilitator			X	X	X			
Participant patient-reported outcome data collection		X	X	X	X			
Semi-structured interview						X	X (optional)	
Non-direct assessments								
Medical chart abstraction		X	X	X	X	X	X	X
Adverse Events Reporting		X	X	X	X	X		

6.0 UNANTICIPATED PROBLEMS

6.1 Definition

As defined by UNC's IRB, unanticipated problems involving risks to study subjects or others (UPIRSO) refers to any incident, experience, or outcome that:

- Is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Is related or possibly related to a subject's participation in the research; and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

6.2 Reporting

Any UPIRSO that occurs during the conduct of this study and that meets all three criteria listed in 6.1 must be reported to the UNC IRB using the IRB's web-based reporting system.

7.0 STATISTICAL CONSIDERATIONS

7.1 Study Design

This study is the second phase of a three-phase project to develop and pilot test a psychosocial intervention tailored to parents with advanced cancer and their co-parents.

The first phase was an observational study with patient, caregiver, and healthcare provider stakeholders to obtain feedback on the intervention (see approved protocol LCCC1719). The second phase (currently proposed) is a pilot single-arm trial to assess the acceptability and feasibility of the newly developed intervention. The third phase will be a RCT to the test the preliminary efficacy of the intervention versus usual care.

In this single-center, single-arm interventional pilot study, we will recruit ten patients and their co-parent (n=20) to participate as dyads in a novel psychosocial intervention for parents with advanced cancer and their co-parents. This is a non-randomized study due to the need to preliminarily test the acceptability and feasibility of study procedures. Dyads will participate in two to three (third visit is optional) structured psychotherapeutic counseling visits addressing parenting concerns facilitated by the PI or a licensed clinical social worker (supervised by the PI). Participants will also receive psychoeducational materials targeted to their parenting concerns. Participant dyads will complete study assessments at baseline and after every study visit. At the end of the study they will participate in semi-structured interviews assessing their experiences with the study. Study investigators will then refine the study in preparation for a pilot RCT to test the efficacy of the intervention. The primary hypothesis being tested is that a psychosocial intervention to reduce psychological distress and improve end-of-life preparation for mothers with metastatic breast cancer and their co-parents can be acceptable to the target patient population.

7.2 Sample Size and Accrual

We will recruit 10 patient-co-parent dyads (n=20) for the proposed study. The sample size is adequate for qualitative analysis and consistent with psychosocial and behavioral intervention development.[46]

We are confident that we will have adequate access to the proposed sample during the study time frame. The 2015 UNC Tumor Registry records include 243 patients between the ages of 18-54 with a diagnosis of stage IV breast cancer who sought care at the outpatient facilities of the NC Cancer Hospital. Based on our prior studies, an estimated 75% of these patients identify themselves as parents.

7.3 Data Analysis Plans

Evaluate acceptability of the intervention

To evaluate acceptability of the intervention, we will administer a satisfaction assessment to each participant after each study visit and conduct post-intervention interviews with the patient and co-parent separately. We will seek input on: (1) the relevance of intervention components; (2)

format acceptability and tolerability (duration, number of sessions, settings); (3) language (tone and phrasing, tailoring); and (4) emotional and cultural sensitivity.

We will use thematic content analysis, a widely accepted qualitative analysis approach in health research, to identify major themes from interviews.[47] The RA and PI will review interview transcripts, coding and categorizing the data by expanding and collapsing categories until thematic saturation is reached.[48] We will use best practices for qualitative research such as triangulation of data from two sources (patients and co-parents), member checking, and creation of an audit trail.[49] We will use this feedback to refine the intervention prior to launching the RCT. We will use Atlas.ti qualitative analysis software to aid with analyses. Descriptive statistics from the quantitative rating scale and qualitative interview data will be collected concurrently, analyzed separately, and the two sets of findings converged.[50]

Evaluate feasibility of the intervention

To evaluate feasibility of intervention procedures, we will report the percentage of patient-co-parent dyads who enroll and complete the intervention as well as descriptive statistics on the demographic characteristics of patients and co-parents who enter, remain in, and drop out of the study. We will use descriptive statistics and qualitative analyses of post-intervention semi-structured interview data to explore barriers and facilitators to enrollment and retention, including reasons for enrollment, non-participation (e.g. fears of unintended outcomes, competing demands, etc.), ineligibility, or withdrawal and use this information to refine the intervention.

We will evaluate study procedure feasibility including the number of patients screened each month, the number of contacts necessary to enroll participants and schedule follow-up appointments, the duration of each study visit, the proportion of completed study measures at each visit, and the time it takes to complete these measures. Although adverse events are unlikely, we will examine the procedures for adverse event reporting and the study teams' response to such events.

To assess fidelity of the intervention—an aspect of feasibility critical to future implementation needs for the RCT—the PI will individually review audiotapes of each study visit to ascertain adherence to the protocol and underlying theory, and will rate each session according to an intervention checklist. The PI will provide re-training and feedback to the intervention facilitator if any problems in conducting sessions or adhering to protocol arise.

Explore impact of intervention on target outcomes

We will explore the impact of the intervention to improve emotional well-being (emotional well-being subscale of the FACIT-Pal) scores and parenting concerns (PCQ-R) scores among patient participants using paired t-tests. However, this pilot study is not designed nor powered to detect such differences as the primary objectives are to evaluate the feasibility and acceptability of the intervention.

7.4 Data Management/Audit

The PI and RA will coordinate and manage data for quality control assurance and integrity. The recorded interview data will be kept in a password-protected electronic file housed within a secure server within the UNC Department of Psychiatry. De-identified transcriptions will be entered into a qualitative analysis software program (Atlas.ti) which is accessed on password-protected, encrypted computers by the study team.

As an investigator initiated study, this trial will also be audited by the Lineberger Cancer Center audit committee every six or twelve months.

8.0 STUDY MANAGEMENT

8.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion. If the participant is not local and does not receive services at NC Cancer Hospital, or written consent is not feasible, he or she will be given verbal consent by the PI or RA.

8.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- A copy of the IRB-approved consent form

8.3 Registration Procedures

Once patients have consented to participate in this trial, they will be assigned a study ID number. This study ID number will be used throughout the study. Data will once again be stored on a password protected file and computer kept within a locked file cabinet and office.

All study participants will also be registered in Oncore™.

8.4 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

8.4.1 Emergency Modifications

UNC investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC IRB approval.

For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

8.4.2 Single Patient/Subject Exceptions

Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the UNC IRB.

8.4.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

Protocol Deviations: UNC personnel will record the deviation in OnCore® (or other appropriate database set up for the study), and report to any sponsor or data and safety monitoring committee

in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report UPIRSO.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO:
Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB (see section 6.1) must be reported by the Study Coordinator using the IRB's web-based reporting system.

8.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

8.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

8.7 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

9.0 REFERENCES

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10.0 **APPENDICES**

Appendix A: Recruitment script
Appendix B: Recruitment brochure
Appendix C: Self-report study measures
Appendix D: Study intervention manual
Appendix E: Patient education materials
Appendix F: Semi-structured interview guide