Protocol

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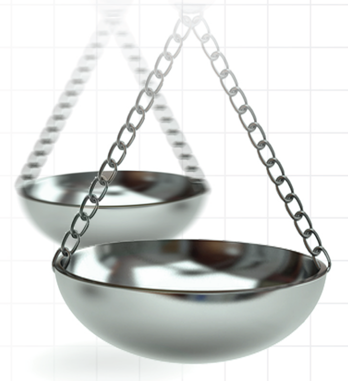

Journal of **Comparative Effectiveness Research**

Study Protocol for the Social Interventions for Support During Treatment for Endometrial Cancer and Recurrence (SISTER) study: a community engaged national randomized trial

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Aim: Social isolation in cancer patients is correlated with prognosis and is a potential mediator of treatment completion. Black women with endometrial cancer (EC) are at increased risk for social isolation when compared with White patients. We developed the Social Interventions for Support during Treatment for Endometrial Cancer and Recurrence (SISTER) study to compare and evaluate interventions to address social isolation among Black women with high-risk EC in USA. The primary objective of the SISTER study is to determine whether virtual support interventions improve treatment completion compared with Enhanced Usual Care. Secondary objectives include comparing effectiveness virtual evidence-based interventions and evaluating barriers and facilitators to social support delivery. **Patients & methods:** This is a multi-site prospective, open-label, community-engaged randomized controlled trial, consisting of three intervention arms: enhanced usual care, facilitated support group and one-to-one peer support. Primary outcome will be measured using relative dose. Qualitative semi-structured interviews will be conducted with a subset of participants to contextualize the relative degree or lack thereof of social isolation, over time. **Data analysis:** Primary analysis will be based on an intent-to-treat analysis. Multivariable analysis will be performed to determine the effect of the intervention on the primary and secondary outcomes of interest, relative dose and social isolation score. Semi-structured interviews will be qualitatively analyzed using inductive and deductive approaches of content analysis. **Discussion/conclusion:** Endometrial cancer mortality disproportionately affects Black women, and social isolation contributes to this disparity. The SISTER study aims to identify whether and to what extent differing social support vehicles improve key outcomes for Black women in the United States with high-risk EC.

Clinical Trial Registration: NCT04930159 (ClinicalTrials.gov)

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Keywords: Black women • disparities • endometrial cancer • social isolation • social support

Background

Endometrial cancer is the most common gynecologic malignancy in the US with increasing incidence and an estimated 28 cases per 100,000 females in 2021 [1–3]. National statistics for endometrial cancer do not include gender identity and thus include cisgender women and those of other genders born with a uterus. The most common type of endometrial cancer is low-grade endometrioid, often diagnosed in early stages with favorable prognoses requiring surgical treatment only [4]. In contrast, high risk endometrial cancer includes high grade endometrioid, serous, clear cell and carcinosarcoma types. These cancer types require adjuvant post-operative treatment and have higher risk of recurrence and death [5,6]. In the US, Black women are at significantly increased risk for these high-risk types compared with White women and over 50% of Black women with endometrial cancer will be diagnosed with high-risk disease [7]. In addition, Black women experience poorer overall 5-year survival rates relative to White women even after accounting for these racial differences in stage and histology subtype (63.1 vs 86.1%) [7]. Other critical factors which also drive uterine cancer disparities include geographic, economic and other social factors such as socioeconomic status and educational attainment [8,9].

Social isolation is the lack of social contacts, institutional connections and community engagement for a given individual [10,11]. Social isolation contributes to poor overall survival in patients with cancer. An association has been demonstrated between social isolation and cancer metastasis, chemoresistance, radiotherapy resistance, apoptosis evasion and immune suppression. The National Comprehensive Cancer Network (NCCN) classifies social isolation as a sub-issue within distress. Standard of care guidelines include care items such as support groups, individual counseling and spiritual support [12]. They are especially important for Black women with cancer, who are at increased risk for social isolation due to systemic and structural stressors including high risk of ineffective patient-provider communication, differences in quality of care received, and lower likelihood of receiving adequate health information [13,14]. Effective interventions to address social isolation among Black women with cancer include culturally relevant peer support groups, nurse navigation programs, and cognitive behavioral strategies to decrease social isolation, improve cancer-related knowledge, and help participants manage negative cancer-related stress and thoughts [13]. Described interventions have focused on women with breast cancer, and to date there have been no such studies among Black women with endometrial cancer.

Clinical trial eligibility requirements often function as systemic barriers to enrolling minorities. These criteria can include restrictions for medical comorbidities, exclusion of patients with limited English proficiency, location of available trials and other factors. Additionally, the majority of clinical trials do not report data on race. The combination of these factors negatively impacts minority accrual and access to potentially beneficial interventions and treatments, and hinders our understanding of potentially differential impacts/effects of studied interventions in diverse populations [15–17]. In an analysis of US clinical trials from 2003 to 2016, there were 55,689 total enrollees in 1012 clinical trials. Black people were significantly less likely to be enrolled in clinical trials compared with White people (enrollment fraction 0.7 vs 1.2%, $p < 0.001$) [18] Despite efforts from the NCI to increase diversity in clinical trials, including the NIH revitalization act and creation of the "Clinical Trials Screening and Accrual Log", there has been a downward trend in Black enrollment compared with the years 1996–2002, and again from 2003 to 2013 [15,17,19]. Previously cited patient-level barriers to participation, such as refusal to participate or lack of interest in clinical trials due to mistrust in the healthcare system, have not borne out in focused studies evaluating patient interest in clinical trials [17]. National organizations like the Food and Drug Administration and the American Society of Clinical Oncology urge researchers to reconsider clinical trial eligibility criteria in order to make clinical trials more representative of the intended treatment populations while also providing benefits to wider populations [20,21].

There is an urgent need for evidence-based guidance on the best method to provide social support to Black women with endometrial cancer due to the persistently marked racial inequities. In partnership with the Black endometrial cancer survivor network, The Endometrial Cancer Action Network for African Americans (ECANA), we designed the Social Interventions for Support during Treatment for Endometrial Cancer and Recurrence (SISTER) Study, a multi-site prospective, open label, randomized controlled trial assessing the effects of a social intervention on treatment completion and Social Provisions Scale-24 (SPS-24) scores in Black women with high risk and recurrent endometrial cancer. The primary objective of the SISTER study is to determine whether either of two virtual interventions (Facilitated Support Group; 1:1 Peer Support) improves recommended treatment completion compared with Enhanced Usual Care (written materials on support systems, side effects, healthy behaviors) among Black women with high-risk endometrial cancer. Our second objective is to compare the effectiveness of two virtual evidenced-based interventions on level of social isolation during cancer treatment among Black women with high-risk endometrial cancer (Table 3). The third objective is an implementation aim – to evaluate the barriers and facilitators to social support delivery among patients, providers and cancer center leaders.

Methods

Conceptual framework

The SISTER Study leverages the conceptual framework of the influence of social networks on cancer care and outcomes by Kroenke *et al.* [22]. The interventions are designed to directly impact the most upstream factor – social isolation – while the study design will measure and evaluate downstream factors of treatment completion, and the mediating factors in between. All items highlighted in yellow are measured in the SISTER study (Figure 1).

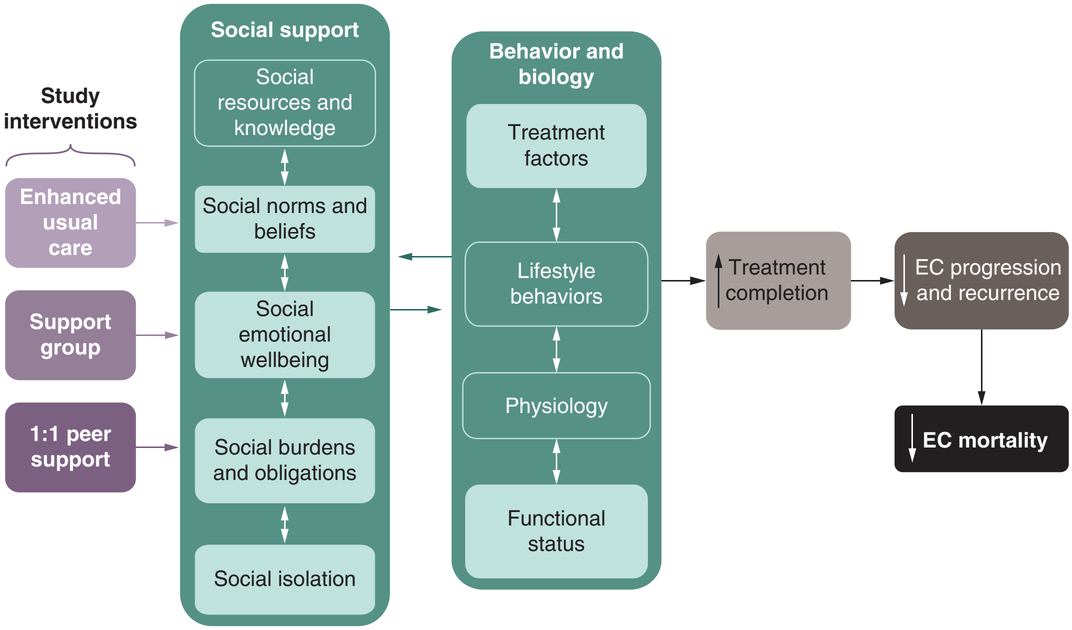

Figure 1. Conceptual framework for the SISTER study.
Light green boxes indicates measured by the SISTER Study.
EC: Endometrial cancer.

Organizational structure

This is a community-engaged study conducted and coordinated through the University of Washington School of Medicine, in close partnership with the Endometrial Cancer Action Network for African Americans (ECANA) [23]. Several departments within the University are responsible for coordinating and conducting the study. The organizational structure for the SISTER study can be found in Figure 2. The Intervention Coordinating Center (ICC), located within the Department of Obstetrics and Gynecology, is responsible for maintaining coordination for all aspects of the study, site training, periodically assessing protocol compliance and monitoring site performance. The Data Coordinating Center (DCC), located within the Center for Biomedical Statistics in the Department of Biostatistics, maintains the study data management system, facilitates primary data collection, and works closely with the ICC to maintain the public webpage. The Stakeholder Coordinating Center (SCC) includes an Advocate Advisory Board, comprising individuals with lived experience of EC including both survivors and close caregivers, and External Advisory Board, which are responsible for providing critical input into study-related issues. Details on the engagement process, from idea inception through funding and initiation of the SCC will be the focus of a separate publication.

The ICC, DCC and SCC report to the Executive Committee. The Executive Committee meets monthly and is responsible for ensuring successful study execution, adherence to the Patient-Centered Outcomes Research Institute's (PCORI) engagement principles, decision making, conflict resolution and dissemination of results. The Executive Committee is co-chaired by a researcher with experience in national multi-site studies and a cancer survivor with experience in managing a cancer support organization for Black women. Their complementary patient and researcher perspectives ensure mutually beneficial stakeholder engagement and patient-centered operations. Other members of the Executive Committee include co-Principal Investigators and stakeholder representatives covering expertise in clinical epidemiology, comparative effectiveness research, biostatistics and gynecologic oncology. The Executive Committee is ultimately accountable to the University of Washington Internal Review Board and the External and Advocate Advisory Boards.

Equally important to the organizational structure and conduct of the SISTER Study are peer supporters. Peer supporters are Black women endometrial cancer survivors, who undergo a robust peer support training for their roles. Briefly, a formal 2-day training completed via virtual sessions facilitated on zoom and included SISTER Study orientation, didactic sessions on research fundamentals, interactive sessions on active listening, communicating with empathy, self-disclosure and summarization; suicide warning signs awareness and referral process, and study

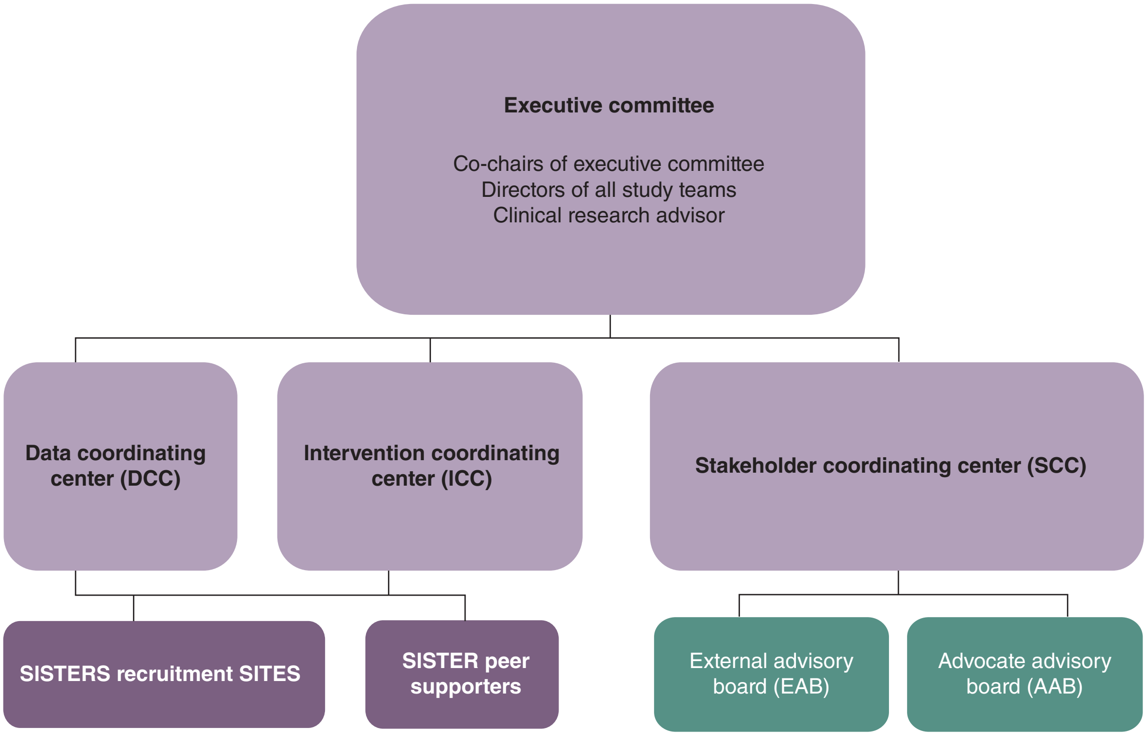

Figure 2. Organization structure of the SISTER Study.

documentation and data integrity procedures. Skills assessments and readiness testing were evaluated through group role-play exercises, repeated materials review, and a written quiz. Peer supporters are responsible for facilitating either group or 1:1 support for study participants in the interventional study arms. In addition, they provide operational feedback at quarterly meetings with the principal investigator and monthly meetings with the director of peer supporters.

Site selection

The study setting is academic gynecologic oncology practices in the US They span most regions in the US, with a focus on areas with the largest Black populations. A total of ten clinical sites were selected based on readiness of site infrastructure, staff engagement, patient population characteristics and the number of cases of Black women with high-risk endometrial cancer. Each site's staff and clinicians, who recruit participants into the study, are required to undergo training conducted by the ICC. Another requirement for each site is a quality management plan (QMP). The QMP allows for good practice and data quality through review of participant enrollment, reasons for exclusion, participant demographics and follow-up rates by site. The DCC will check data quality within the data entry system, and the ICC will review participant enrollment forms, patient reported outcomes data entry, electronic medical record data abstraction and adverse events. There are regular meetings between the ICC, DCC and research site leads at each site to discuss any concerns or troubleshoot unexpected challenges.

Outcomes

The primary outcome for the SISTER Study is treatment completion rate, using the measure of relative dose. Initially operationalized to evaluate drug delivery in phase III clinical trials, relative dose is the ratio of actual to expected total dose of a given treatment and ranges from 0 to 100% [24]. For this study, relative dose will be calculated over the 6-month study enrollment period. Information regarding both the actual total dose and expected total dose are abstracted from the electronic medical records at each study site, as appropriate for each treatment modality (Table 1). In the case of a range of cycles or fractions recorded as the official treatment plan, the minimum will be used as the expected dose. Table 1 details the most common and expected regimens. However, relative dose is amenable to any treatment combination. Non-standard regimens will undergo the same process of calculation for expected dose (at time of enrollment) and actual dose received (at 6-month review). For each study

Table 1. Standard treatment modalities and relative dose calculations.

Treatment	Components and frequency	Calculation of relative dose
Chemotherapy	Carboplatin AUC 6 and paclitaxel 175 mg/m^2 infusions every 21 days for 6 cycles	Actual number of chemotherapy cycles received for both drugs / expected total cycles received (12 cycles)
Pelvic radiation	4500 Gy of external beam radiation treatment delivered in 25 fractions over 5 weeks	Actual total radiation fractions received / expected radiation fractions received (25 fractions)
Vaginal radiation	3–5 High dose rate brachytherapy insertion treatments	Actual total radiation fractions from HDR received / expected radiation fractions from HDR received (3 fractions)
Immunotherapy	Mg infusion every 21 days for 6 cycles (dose varies by medication), n	Actual number of cycles / expected total cycles received (6)

AUC: Area under the curve.

Table 2. Secondary and exploratory outcome measures.

Secondary, or exploratory	Outcome name	SISTER study rationale	Specific measure to be used	Ref.
Secondary	Social isolation	Priority outcome for Black women with EC; Mediator of treatment completion	SPS-24; PROMIS social isolation 4a	[10,26]
Exploratory	Distress / anxiety	Improved distress is a common outcome of peer support interventions and known contributor to poor cancer outcomes	PROMIS emotional distress-anxiety short form 4a	[25,27–31]
Exploratory	Racial hypervigilance	Concerns / adaptations to avoid experiencing discrimination are associated with poor mental and physical health, and increased stress	Heightened Vigilance Scale	[32]
Exploratory	Financial toxicity	Financial need, worry, and bankruptcy are associated with poor quality of life & increased mortality among cancer patients	Comprehensive Score for financial Toxicity	[33]
Exploratory	Functional and physical well being	The effects of treatment toxicity on physical and functional status are strongly related to treatment completion and may be modified by social support	Trial Outcome Index of the FACT-En	[34–36]
Exploratory	Patient satisfaction with medical care	Patient satisfaction with medical care has been associated with treatment adherence	The Patient Satisfaction Questionnaire Short-Form (PSQ-18)	[37]

EC: Endometrial cancer.

participant, medical record abstraction will occur at three different time points – at time of enrollment to obtain planned treatment regimen, at 3-months to assess for any changes to treatment regimen, and at 6-months to assess the actual treatment received over the study course. If a participant dies, changes treatment regimens during the study period, or decides to discontinue treatment, the expected total dose will not change. Treatment completion rates will be calculated in three ways: for all intravenous-delivery (infused) chemotherapy, immunotherapy, and other systemic agents; for all radiation therapy; and as an average of infused and radiation therapy.

Secondary outcomes for the SISTER study include patient-reported social isolation, measured by the Social Provisions Scale – 24 (SPS-24) and the PROMIS Social Isolation 4a [25,26]. The SPS-24 is a validated twenty-four item questionnaire developed by Cutrona and Russell that measures several aspects of social support: attachment, social integration, reassurance of worth, reliable alliance, guidance and opportunity for nurturance. After a comprehensive review of measures of social isolation previously used among cancer populations, Black women and Black women with cancer, the SPS-24 was selected by ECANA members. This measure is also the most common scale administered in studies focused on Black women with cancer and the instrument used in translational research. The PROMIS Social Isolation 4a was additionally selected given its shorter form, ability to analyze results by individual question, and broader use in the larger cancer community.

The exploratory outcomes and the chosen measures for each are described in Table 2, representing the mediating factors from the SISTER Study conceptual framework and chosen in collaboration with ECANA. All measures will be collected at baseline, 1 month, 3 months and 6 months.

In addition to these quantitative measures, qualitative semi-structured interviews will be conducted with a subset of participants to contextualize the relative degree, or lack thereof, of social isolation over time. In addition, there is a component of social support that is critical among Black women with cancer, 'linked fate', which is the concept that an individual's life chances are inextricably tied to the fate of those within their own racial/ethnic group. Linked fate arises from lived experiences such as discrimination and invokes a consciousness for collective action for the common good of the whole group [38,39]. Currently, there is no validated survey to measure linked fate in a

Table 3. Nature, structure and delivery of SISTER study intervention arms.

	Enhanced usual care	Facilitated support group	1:1 Peer check-in	Ref.
Nature	Participants will receive information on local support groups as recommended by the NCCN with the addition of written ECANA informational materials about coping with side effects and establishing support structures and healthy behaviors during treatment.	Weekly group gatherings where content will alternate between group conversation and focused topics (e.g., treatment side effects, mental health, family dynamics, nutrition, financial hardship) with facilitated discussion by a trained professional in nutrition, psychotherapy, cognitive behavioral therapy, or medicine. Each group will cycle through the same order of topics.	1:1 peer support via telephone during or near a treatment visit. Call content will be focused on social support and driven by the needs of the participant.	[40]
Structure	Written materials in an appealing package	Group gathering led by trained ECANA peer supporter and co-facilitator. Each group limited in size per analytic plan.	Participants are paired with an ECANA peer supporter based on scheduling availability who will provide 1:1 support during/near treatment visits via phone call	
Delivery	Materials will be provided by mail.	Weekly virtual group gathering on an audio/visual platform (e.g., Zoom).	1:1 support call will be no more frequent than once a week and no less frequent than once every 3 weeks to allow for treatment schedule variation.	
Materials required	Home address	Smartphone, tablet, or computer and Wi-Fi / cellular network access†	Basic or smartphone†	
Tracking Engagement	Package tracking to confirm receipt; Series of 3 engagement questions in follow-up survey collections.	Participant attendance recorded at each group and data gathered for reporting by participant.	Number of successful connections recorded, tracked and organized by participant	

†Participants are screened during enrollment for access to a smart phone and/or tablet and consistent Wi-Fi. If they do not have access, they are sent a smartphone and Wi-Fi hotspot to be able to participate. This resource is funded by philanthropic support and ensures financial hardship does not preclude participation in the study.
ECANA: Endometrial Cancer Action Network for African–Americans; NCCN: National Comprehensive Cancer Network.

large sample. Thus, these qualitative interviews are also designed to capture this concept for a fully intersectional assessment of social support. The interview guide will be co-developed by the university and community-based research team via a collaborative process for which we have prior experience. Interviews will be approximately 1 h in length and conducted through a HIPAA-compliant teleconference platform at baseline and at 6-months. Interviews will be recorded, transcribed and de-identified.

Trial design

This is a multi-site prospective, open-label randomized controlled trial to determine the impact of social support interventions on treatment completion and patient-reported social isolation among Black women with high-risk endometrial cancer (Figure 3). The study consists of three intervention arms: enhanced usual care, facilitated support group and 1:1 peer support. Table 3 describes the nature, structure, and delivery of each intervention arm. Development of the three intervention arms was a multi-level process that included a systematic review of peer support literature and incorporated input and recommendations from multiple stakeholders. The specific stakeholders involved include the Steering Group of the ECANA, two focus groups of Black women with endometrial cancer and cancer center leadership at select study sites.

Inclusion & exclusion criteria

Careful and intentional inclusion and exclusion criteria for the SISTER Study were developed, (Box 1) enlisting multiple stakeholders. Gender identity is not a specific inclusion or exclusion factor, though all EC survivor community consultants are currently cisgender women.

Implementation evaluation

The SISTER Study incorporates an effectiveness-implementation hybrid design, reflected in the third objective. The Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework is an evidence-based evaluation framework and is used to assess impact of the intervention. Reach (the proportion of randomized patients that participated in the intervention) and Effectiveness (treatment completion) are captured through quantitative data collected by the DCC. Adoption, Implementation and Maintenance are assessed through a variety of stakeholder interviews. The Consolidated Framework for Implementation Research (CFIR) will guide the analysis of the qualitative interview data in order to proactively identify modifiable factors that can boost or

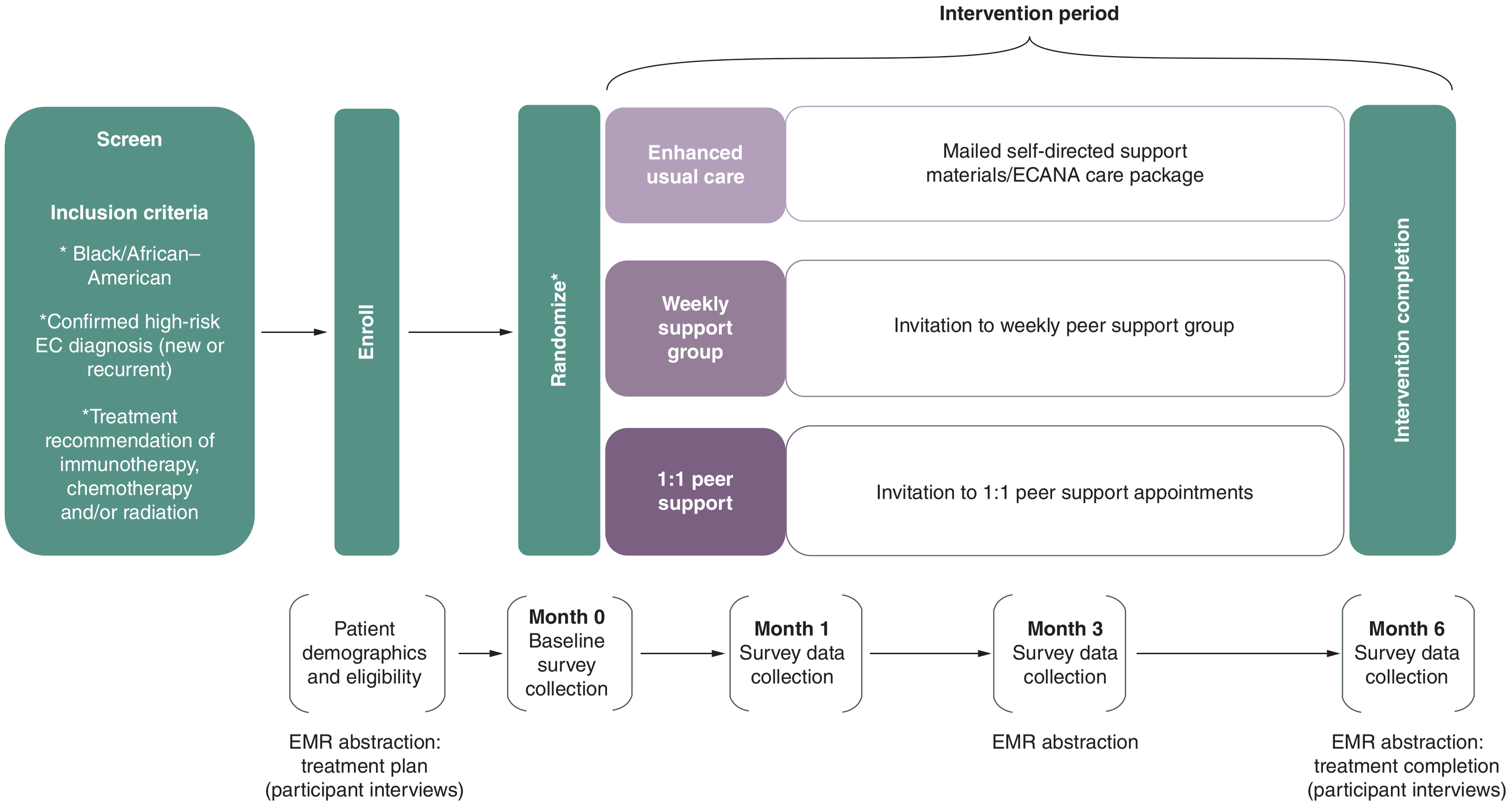

Figure 3. SISTER study design.

EC: Endometrial cancer; ECANA: Endometrial Cancer Action Network for African–Americans; EMR: Electronic Medical Record.

Box 1. SISTER study inclusion and exclusion criteria.

The inclusion criteria include:

1. Adult 18 years of age or older; and
2. Self-identify as Black/African–American
3. Presenting with high-risk EC established by anatomic pathology with tumor stage and grade classification by the following:
    a. Pathology documentation from any hospital/clinic/medical center, and
    b. FIGO Stage 1A with grade 2, grade 3, or grade 4 of any histology type [3] or
    c. FIGO Stage 1A with non-endometrioid (carcinosarcoma, serous, clear cell, undifferentiated or mixed) histology
    d. FIGO Stage 1B, 2, 3 or 4 of any grade or histology
    e. Recurrent endometrial cancer of any stage or grade
4. Documented provider recommendation to initiate adjuvant therapy with chemotherapy (infusion only), radiation and/or immunotherapy.
5. Patient planning on starting treatment

The exclusion criteria include:

1. New diagnosis of FIGO Stage IA grade 1 endometrioid adenocarcinoma
2. Has already started treatment for diagnosed high risk EC
3. History of other cancer diagnosis requiring chemotherapy, radiation therapy, or immunotherapy within the past 12 months;
4. Incarcerated in a detention facility or in police custody (patients wearing a monitoring device can be enrolled) at baseline/ screening;
5. Contraindication to all non-surgical therapy available for endometrial cancer (i.e., chemotherapy, radiation, and immunotherapy contraindicated);
6. Treatment plan consisting of only oral medications (chemotherapy, immunotherapy, or hormonal therapy) as only adjuvant treatment, with no infusion component;
7. Enrollment into hospice prior to randomization
8. Unable to provide written informed consent in English and requires a translator;
9. Unable to be contacted for research surveys;
10. Recent hospitalization for psychiatric illness in the past 6 months
11. Any diagnosis of dementia, Alzheimer's, or other clinically significant severe memory loss that would impact the ability to participate fully in the intervention (i.e., use of a healthcare proxy for decision-making, ability to remember and participate in clinical conversations)

impede Adoption, Implementation and Maintenance of the study interventions and, ultimately, to understand the interventions' success or failure.

Intervention evaluation is a dynamic aim evaluated at various time points: at baseline, at 25% targeted enrollment, at 50% targeted enrollment, at 100% targeted enrollment, and at the completion of the study. At each of these time points, Reach and Effectiveness quantitative metrics, as well as a subset of qualitative interview data, are evaluated. Peer supporter interviews (n = 8) are performed at baseline, 50% enrollment and 100% enrollment. Study recruiter interviews (n = 3) are performed at 25% enrollment. Participant interviews (n = 45) are conducted at entry and exit from the study and analyzed at 25, 50 and 100% enrollment, as well as at study completion. Healthcare staff interviews (one to two gynecologic oncologists and nurses at each site, n = 19) are performed at 50% enrollment. Finally, cancer center leadership interviews (n = 9) are performed at study completion.

Participant recruitment

Eligible participants are identified by clinicians, staff, and from the screening of EC care practice logs maintained by each site as part of routine care delivery. All participants agreeing to consider study participation are asked to consent via an informed process either in person or over the phone. Participants may withdraw from the study at any time. Participants receive remuneration consisting of $25 per data collection at baseline, 1 and 3 months, and an additional $30 for the final timepoint if all others are completed. To aid in retention, participants will receive a package at 4.5 months which contains tailored messages of encouragement from the peer supporters, as well as a study magnet and water tumbler. Participants also have access 24/7 to study coordinator contact information as well as an informational website.

Interview recruitment

A subset of 45 total participants (15 enhanced usual care, 15 facilitated support group, and 15 1:1 peer support) will be approached and asked to participate in the one-on-one interviews with study staff members. Participants receive an additional $90 for each interview participation.

Randomization

After obtaining consent, participants will be randomly assigned, in an unblinded fashion to one of three intervention arms. Research coordinators will use the DCC maintained web-portal to perform randomization based on generated assignments. Stratified block randomization with block sizes of 7 and 10 will be employed, ensuring a randomization probability of 0.30, 0.40 and 0.30 for enhanced usual care, facilitated support group, and 1:1 peer support, respectively.

Sample size

A study sample size of n = 252 was established to provide a minimum of 80% statistical power for the secondary outcome of SPS-24 social isolation, and >80% power for the primary outcome of treatment completion. Sample size estimation accounted for a type 1 error rate of 0.025 to accommodate a conservative Bonferroni correction for two statistical tests of the primary end point (enhanced usual care vs 1:1 peer support, enhanced usual care vs facilitated support group). We plan to use covariate adjustment for SPS-24 measured at baseline as one would do in a traditional analysis of covariance (ANCOVA) model and conservatively assumed a correlation between baseline and 6-month SPS-24 of 0.3. A minimum of n = 70 participants are required in each intervention arm to detect an effect size 4.0 points (standard deviation of 8.0) with 80% power, a change that represents the total absence or presence of one aspect of each of the subscales. Due to the group nature of the Facilitated Support Group intervention, outcomes among participants randomized to this intervention may be correlated with one another. We therefore increased the sample size for the Facilitated Support Group by 30% (variance inflation factor = 1.30), assuming an intraclass correlation coefficient of 0.12 and average anticipated group size of 4. Finally, we accounted for possible loss to follow-up and missing data of 7–8% [41]. These calculations resulted in a total sample size of 252 participants (76 enhanced usual care, 100 facilitated support group, and 76 1:1 peer support). With this sample size, the study has 84% power to detect an absolute improvement in relative dose of 6.5% or larger, which represents a small but meaningful improvement in treatment completion relative to improvements observed in other studies (8–16%) [30].

Data & safety monitoring

Overall, as a randomized trial of non-medical peer support interventions, this is a minimal risk study. In lieu of a Data Safety Monitoring Board, the study will operate with a data safety monitoring plan (DSMP) in which mental health adverse events (MHAE) will be captured by research staff via peer supporters, care providers, or patient report. MHAEs are defined as reportable abuse (elder, child) and scoring above 21 on the Suicidal Ideation Attributes Scale (SIDAS) [42]. The SIDAS is completed at baseline and at each survey point (1, 3 and 6 months). This definition was reached over several iterative discussions with the study team, Executive Committee, Advocate Advisory Board, and External Advisory Board. MHAEs will be monitored by the SISTER Executive Committee. The Executive Committee meets monthly and holds Quarterly meetings to review any data and adverse events and make recommendations for these events, with the aid of outside bioethics and/or psychiatric experts as needed. In addition to MHAEs, all traditionally defined serious adverse events (i.e., death during the period of protocol-defined surveillance; life-threatening event related to the treatment or significant disability/incapacity related to the treatment; inpatient hospitalization) will be captured and recorded by research staff but not subject to Executive Committee review. These events will be reported alongside primary outcomes for the study in initial publications.

Data analysis

Data will be analyzed using R statistical software [43]. The primary analysis will be based on an intent-to-treat analysis. Multivariable analysis using generalized linear mixed models will be performed to determine the effect of the intervention on the primary outcome of interest, treatment completion rate. Models will be adjusted for recruitment site, intervention arm assignment, and the clustering of subjects by lead intervention provider. Furthermore, if an association between the intervention and treatment completion is observed, we will conduct

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mediation analysis using regression models. This analysis will consider several variables (e.g., social isolation) that are part of the causal pathway to treatment completion.

A linear mixed effects model will be used to longitudinally model SPS-24 outcomes. Adjustments will be made for recruitment site, intervention arm assignment, baseline SPS-24, and follow-up assessment time (1, 3 and 6 months). A two-level linear mixed effects model will be used to model SPS-24 outcomes within participants over time and for the clustering of participants on lead intervention provider.

As the primary outcome will be obtained from the participant's chart, we do not anticipate any missing data on the primary outcome. For the SPS-24 outcomes, we will conduct sensitivity analyses using tenfold multiple imputation to assess the robustness of the results when missing data are imputed. Sensitivity analyses will also be conducted to assess intervention efficacy on primary and secondary outcome measures by first excluding individuals who did not adequately engage in the interventions.

Treatment effect heterogeneity will be assessed by adjusting the primary and secondary outcome models for interaction terms between the subgroup variable of interest (age, partnered status, or high financial need as identified in the enrollment assessment) and the intervention group indicator variable. These analyses are considered exploratory and hypothesis-generating, with the intention of examining demographic subgroups for whom virtual interventions could be modified to improve effectiveness.

For the qualitative analysis, we will develop a code book *a priori* but allow for revision with information from the baseline survey data. Each interview will be analyzed by 2 coders, case summaries generated, and group meetings used to evaluate interpretation, consistency of coding, and transparent reflexivity. We anticipate thematic saturation will occur in 12–13 interviews, and thus have budgeted up to 15. Cross-cutting themes will be identified with similarities and differences between intervention groups highlighted.

Discussion/conclusion

Endometrial cancer remains the most common gynecologic malignancy in US with higher mortality disproportionally affecting Black women [7]. Endometrial cancer disparities result from multifactorial processes including social factors such as social isolation [44]. Although it is known that social support interventions result in decreased social isolation, improved treatment adherence and improved health, to date, there have been no evidence-based approaches to address social isolation among Black women with high-risk endometrial cancer. Thus, the SISTER study is designed to identify the most effective social support intervention to support Black women undergoing treatment for high-risk endometrial cancer. Although SISTER was designed alongside US Black EC survivors and is thus specific to this context, by utilizing a broader conceptual model of social isolation and cancer outcomes, we hope this work will be adaptable to other contexts where marginalized status can create social isolation across populations.

The SISTER study uses a multi-site, randomized controlled trial of social interventions allowing for the highest quality of evidence to be observed. Uniquely, the study also uses an effectiveness-implementation hybrid design that allows the testing of a clinical intervention while simultaneously observing and gathering information on implementation [45]. In addition, a multi-stakeholder approach was integrated at every step of study design including idea conception. Integration of stakeholders into research design is important because it increases benefit to participants, creates efficiency in use of resources, and leads to accountability at all levels [46,47]. Our use of validated patient reported outcome and quality of life measures and qualitative data collection also strengthens this multi-faceted study. One limitation is our lack of biological specimens to further the translational link between environment and cancer outcomes. Practically, the collection of biological specimens falls outside the scope of this trial and its funding mechanism. Our strength lies in the comprehensive collection of environmental factors extending beyond social support (Table 2 for all patient-reported outcomes measures). As part of future endeavors, we contemplate incorporating biological components through ancillary study research.

PCORI initiated the study contract on 1 April 2021, following approval for funding on 17 November 2020. The first patient was enrolled into the study on 22 September 2021 and all sites were opened by 10 August 2023. The enrollment period is expected to continue through June 2025, with primary analysis scheduled for completion in November 2025. At the time of publication of this manuscript, 114 participants had been enrolled in the trial.

Summary points

- Black women with endometrial cancer (EC) are at risk social isolation which is linked to poor prognosis; limited data exists to intervene on this disparity.
- Social isolation has been linked to decreased completion of treatment among patients with cancer.
- The Social Interventions for Support During Treatment for Endometrial Cancer and Recurrence (SISTER) study is a randomized controlled trial designed to pilot and compare two virtual-based social support interventions to enhanced usual care.
- Primary aim is to assess the effect of our intervention on completion of treatment using relative dose.
- Secondary aims are to compare the effects between two virtual social support interventions and usual care.
- Inclusion criteria include: Black patients, age >18, presenting with high-risk EC, documented provider recommendation to initiate adjuvant therapy with chemotherapy, radiation or immunotherapy.

Author contributions

A Oluloro contributed to manuscript authorship. B Comstock and S Monsell contributed to study design, data analysis and manuscript authorship and revision. E Wolff, L Sage, J Alson and D Lavallee contributed to study design and manuscript editing. B Hempstead, A Moore contributed to study conception, study design and manuscript editing. M Gross contributed to manuscript authorship, revision. K Doll contributed to study conception, design, manuscript authorship and manuscript revision.

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Competing interest disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained institutional review board approval (IRB no. STUDY00012990) from the University of Washington for the research described. The UW IRB serves as the single-site IRB with reliance agreements with other participating institutions. In addition, they have obtained verbal and written informed consent from the patients for the inclusion of their medical and treatment history within this work. IRB approval date: 27 May 2021; IRB no.: STUDY00012990; Protocol version: 1.3; Protocol date: 25 April 2023.

Data sharing statement

Data sharing is not applicable to this article as no datasets were generated or analyzed for the current publication. In accordance with the PCORI Policy for Data Management and Data Sharing, all data and metadata generated from the SISTER Study will be deposited in a PCORI-designated data repository within 1 year after completion of the study and available for third-party requests.

Open access

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