Achieving Equity through Socioculturally-informed, Digitally-Enabled Cancer Pain Management (ASCENT) - Main Trial

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IRB Minimal Risk Protocol Template

General Study Information

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Study Title: Achieving Equity through Socioculturally-informed, Digitally-Enabled Cancer Pain Management (ASCENT) - Main Trial

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Research Question and Aims

Hypothesis
This randomized controlled trial will test a pain-directed intervention whose components have been previously validated in several pragmatic clinical trials: E2C2 (#18-007779), NOHARM (#20-004839) and COPE (#11-008151), delivered remotely to rural dwelling and Hispanic cancer survivors. In a pilot among 42 participants, we refined the sociocultural, linguistic, IT, and clinical aspects of the intervention through iterative design cycles (IRB#23-004139). The ASCENT trial will use a parallel group, two-arm design at eight Mayo Clinic sites with patient-level randomization.

We hypothesize that an EHR-based modular approach that aligns intervention components with a patient's sociocultural, IT, and linguistic needs, will improve pain and physical function to a significantly greater degree than the control condition of enhanced usual care among our target population of Hispanic, rural dwelling, and rural dwelling Hispanic cancer survivors experiencing pain.

Aims, purpose, or objectives
To test a validated collaborative care model-based intervention aimed at improving pain control among rural dwelling and Hispanic cancer survivors by promoting multimodal pain care (MMPC) to reduce inappropriate opioid use and by addressing social determinants of health (SDOH) that impede a patient's access to appropriate care.

Background
Cancer pain is a key case study in health disparities in the US. Cancer pain is prevalent, undertreated, and remains a major cause of suffering, impairment, and disability for millions of Americans. Individual pain interventions and care models show promise for cancer pain in controlled settings. Unfortunately, typical approaches too often target limited aspects of the whole, fail to consider health disparities populations (HDPs), and are unable to serve broad and diverse populations. This situation will only worsen with time. For example, by 2030, the number of already underserved Hispanic cancer survivors in the U.S. will increase to 4 million.

Hispanic and rural-dwelling cancer survivors stand to benefit the most from EHR innovations, as each of these HDPs experience profound disparities in pain outcomes, including marked under- and over-prescribing of opioids. Additionally, Hispanics not only comprise a steadily growing proportion of cancer survivors, but are also increasingly immigrating to rural communities, potentially placing them at "double risk" for poor clinical outcomes. Digitally facilitated solutions are especially well matched for these disparities, and can be customized to address the overlapping, yet distinct, needs of these HDPs. Doing so would provide a vital proof of concept and may illustrate the promise of digitally based patient-centered approaches to mitigating other disparities.

This study will allow testing of intervention components and will optimize patient-facing cancer pain support components of an EHR-facilitated, evidence-based bundle in a manner that meets the diverse needs of the target sample.

Study Design and Methods

Overview

In this trial, we will test the ASCENT intervention compared to a usual care control arm at the following Mayo Clinic Enterprise locations: Rochester, Arizona, Florida, Mankato, Eau Claire, La Crosse, Austin, and Albert Lea. For this minimal risk study without in-person patient contact, patients will be recruited from the forementioned locations. Research activities will only be conducted at Mayo Clinic Rochester and Mayo Clinic Arizona. We will purposively recruit equal numbers of rural and hispanic participants. Participants who report at least moderate cancer-related pain (defined as $\geq$ 5/10 on an 11-points numerical rating scale) and who meet inclusion criteria will be invited to participate. Consented patients who are randomly assigned to the intervention group will have the opportunity to receive education material, navigational and coaching services, as well as support from Pain Care Managers (PCMs) and Community Health Workers (CHWs) to manage their pain. The study team will provide materials in Spanish for participants who speak only Spanish or prefer to read in Spanish. The study team includes multiple members who speak Spanish fluently. These members may include, but are not limited to study coordinators, PCMs, CHWs, and other support staff. If a patient speaks only Spanish and a Spanish-speaking member of the research team is unavailable, a telephone interpreter will be utilized. PCMs and CHWs will follow a validated pain management algorithm for MMPC, the current international standard. The ASCENT intervention algorithms are based on the NCCN guideline for the management of cancer-related pain. The ASCENT intervention additionally incorporates guideline-endorsed best practices for addressing Social Determinants of Health (SDOH)-related barriers to receipt of recommended care.

Patient Identification, Recruitment and Consent

Patient Identification

Potentially eligible participants will be identified using data found in the Epic EHR Chronicles database, including qualifying appointments, ethnicity, zip code, and cancer diagnoses (Approved in IRB# 22-008103). Patients who meet the electronic criteria listed in this protocol will receive a pain Numeric Rating Scale (NRS) questionnaire and, if they report a qualifying pain score, information about the ASCENT trial via the patient portal, Welcome tablet or printed mailer for portal non-users,. Potentially eligible patients may also be identified through Patient Navigators. Patients with a qualifying pain score will be able to note their interest in speaking with a research coordinator for more details about the study and to potentially enroll. Patients will be

able to opt out of hearing more information or being contacted by a study coordinator at multiple points in the trial recruitment and enrollment procedures. Patients will have access to an informational video (in English and Spanish) that explains key points of the study, which will be available via their portal, study website or other appropriate modes. The oral consent document will also be made available via their portal, study website and mail, which will allow them to review information prior to a study coordinator reaching out to them about participating.

We are seeking a waiver of consent for the initial pain questionnaire due to the lack of feasibility of contacting and assessing pain for the large volume of patients who would need to be screened.

Recruitment

Potential participants may be recruited in person or via telephone, Electronic Health Record (EHR) message and mail/printed materials. Using existing Patient Reported Outcome Measure (PROM) tools, potentially eligible participants with a scheduled encounter in Medical Oncology, Hematology, or Community Medicine at the ASCENT trial sites will be identified via an EHR report, which the study coordinator(s) will pull regularly. Those with a patient portal will be sent a study invitation via portal message prior to their encounter. Nonresponders will receive the invitation during registration for their clinical encounter on an Epic Welcome tablet. Patients who do not interact with the invitation via their portal or Welcome tablet will be sent the invitation by mail. Any follow-up recruitment attempts will be conducted via portal message, telephone, or mailed print materials. Patients who do not have a portal set up will be initially invited to participate via Epic Welcome tablet and nonresponders will be approached via mail or telephone, with follow-up recruitment attempts being done via telephone. Patients who are sent a paper mailing will have a copy of the video pictorial document included in their mailing, in case the patient is uncomfortable with (or unable to) accessing the video via the web. Potential participants will not be contacted more than 3 times total.

Consenting

During the recruitment telephone call, interested individuals will be asked questions to confirm eligibility, to determine their access to and facility with technological devices, and the extent to which they can access broadband internet. Should the participant need a device to participate in the visits described in this protocol, the study team will send a device with Wi-Fi and cellular data capabilities for participants' temporary use. Eligible participants will be consented orally, assigned Outcome Measure surveys, and then assigned to a study arm (*see randomization section below*). Participants assigned to the Intervention arm will be scheduled additional visits with a Pain Care Manager (PCM) and Community Health Worker (CHW). Interested individuals will not be assigned to an arm until their Outcome Measure surveys are completed. This same Outcome Measure survey bundle will be assigned to enrolled participants either on paper or electronically at 3 months and 6 months post enrollment. Enrolled participants will be mailed a copy of the oral consent so the discussed details and team contact information is readily available to them.

We are seeking a waiver of signed informed consent as well as a waiver of signed HIPAA for this protocol. Due to the minimal risk posed by this study, as well as the complexities of recruiting rural and Hispanic populations and the likelihood of including undocumented Hispanic participants, we believe that a waiver is justified and consistent with the intent of existing regulations.

Randomization

This will be a two-arm, parallel group randomized clinical trial. Research coordinators will register participants

on a password protected MC Cancer Center remote registration/randomization application. Randomization will use a dynamic allocation procedure that balances the marginal distributions of the stratification factors per Pocock-Simon randomization method.[1] Stratification factors will include cancer stage, rural residence, MC HCS site, and Hispanic ethnicity.

The participants randomized into the control group will receive enhanced usual care which will include access to the educational and pain self-management materials developed for the ASCENT trial. Those randomized into the intervention will follow the process outlined in the "Intervention" section of this protocol.

Remuneration
Participants will be reimbursed for their participation in this study. They will receive $50 for the completion of the 3-month Outcome Measure questionnaire bundle and an additional $50 for the completion of the 6-month Outcome Measure questionnaire bundle. All questionnaires in the bundle need to be completed in order to receive compensation. In total, participants can earn up to $100 for their complete participation in the study, whether they are on the control or intervention arm. Payment will be submitted within 2 weeks of study completion after which Mayo Accounting will process a check or direct deposit via payroll for Mayo Employees. If a participant specifically requests payment after the 3-month questionnaire bundle completion, the study team will do their best to accommodate this request by paying the participant at each collection point.

Study Newsletters
All participants (control and intervention) will receive newsletters at three timepoints during their study involvement. The newsletters will be sent at the following timepoints: 2 months, 3.5 months, and 5 months. Topics of the newsletters include general reminders to complete their questionnaires, information on non-pharmacological pain management options, puzzles to increase engagement, study contact information, and other information appropriate for both study arms.

Intervention
Recruitment Call
The research coordinator will formally recruit interested and eligible participants. Patients who consent to participate will be asked questions to determine their access to and facility with technological devices and determine the extent to which they can access broadband internet. Should the participant need a device to participate in the visits described in this protocol, the study team will send one to them for temporary use.

Welcome Call
The CHW will meet with the participant via video visit or telephone to discuss the ASCENT study, gain an initial understanding of the patient's pain, and introduce the practice of keeping a pain journal. The CHW will also obtain patients' SDOH background to identify barriers that may impact their ability to access pain treatment. The CHW will review primary and additional pain management options so that the patient is aware of the treatment options available to them. This conversation will be enhanced by The ASCENT Guide which will be provided to the patient. Participants' preferred mode of digital interface will be confirmed.

Discovery Call
The PCM will meet with the participant via video visit or telephone to discuss the cancer-related pain they are experiencing. They will work to develop an action plan to help address their pain by utilizing The ASCENT Guide developed for the study. This guide will share approved patient education materials for self-guided pain

management, provide information on online tools (such as the study website), and structure interaction between the participant and study team. Participants will be able to receive The ASCENT Guide in a variety of formats per their preference (portal, paper mailing, web, email, etc). Use of the Guide creates a standardized framework for the PCM to take a comprehensive pain history and share self-management recommendations during the Discovery Call.

All participants will be encouraged to actively participate in developing MMPC programs that include analgesic, movement approaches, and cognitive behavioral elements (ASCENT Primary approaches); a pain management best practice. Initially, the PCM will encourage participants to *focus on a simple activity from one of these therapeutic domains* to increase autonomy and self-efficacy. Patients who are new to MMPC may begin by simply tracking their analgesic use or pain levels. PCMs will guide participants to select pain management approaches from the Primary treatments, see below. Primary treatments are more robustly evidence-based per a systematic reviews and guideline generated by the Agency for Healthcare Research and Quality (AHRQ). Additional treatments are included for patients with chronic pain who may have exhausted the Primary approaches or have advanced cancer and require a more palliative and/or interventional approach.

Primary	Additional
Movement approaches	Integrative Medicine
Cognitive Behavior Therapy (CBT)	Acupuncture, acupressure
Pain medicine	Progressive muscle relaxation
	Music therapy, music listening
	Spiritual Support
	Pain Clinic Referrals
	Palliative and Spiritual Care Referrals

Care Management Conference

Within approximately 2-3 business days of the Discovery call, depending on availability, the PCM will present a participant's case to specialists in pain care at the case management conference (CMC). The participant will not attend the CMC. The ASCENT study team will work collaboratively with Medical Oncology, Social Work, Physical Therapy, Palliative Care, and other applicable areas to address patient needs. Care Manager Conferences will take place weekly during this pilot to ensure that participant situations requiring a collaborative approach can be addressed in a timely manner. During the conferences, the PCM will present the patient's pain and related clinical issues to an interdisciplinary group of pain specialists potentially including Rehabilitation Medicine, Hospice and Palliative Medicine, Pain Medicine, and Pain Psychology. This is a best practice approach that is integral to clinical practices across the Mayo Clinic Enterprise. Participants and their caregivers will not be involved in these conferences. Pain specialists' recommendations at the CMC will direct the PCM and CHW to individualize a participants' multimodal pain care plan. During the CMC, contingent on contextual and clinical factors, additional recommendations for diagnostic testing, and frequency and type of pain monitoring may be provided. Any changes to a participant's management plan will be communicated to the participant by the PCM and CHW during a post-CMC call.

Personalize Call

A post-CMC call, referred to as the "Personalize Call," will be scheduled with the patient, CHW, and PCM approximately 1 week after the Care Management Conference depending on availability. In this visit, the

participant will be presented with specialist recommendations for their MMPC plan and encouraged to ask questions. Remote monitoring will be described. Additionally, an update on their pain and additional resources may be suggested by the PCM and/or CHW, as required.

Follow Up touchpoints & numerical rating scale pain surveys
Participants will have weekly contact with the ASCENT intervention following the Welcome, Discovery, and Personalize calls. Touchpoints with the PCM or CHW will occur approximately every other week. Pain PROM measures, which are collected every other week, will not be included as trial outcome measures. PCM and CHW touchpoints may be confined to brief check-in messages and information exchange to confirm that a participant is doing well or may include a discussion via telephone or videoconference. On alternate weeks, participants' pain will be monitored by automatically assigning a pain PROM for completion via portal or interactive voice response (IVR). PROM scores will automatically upload into Epic allowing PCMs to monitor participants for increases in pain intensity and will be used solely to tailor participants pain management programs.

The CHW or PCM may initiate touchpoints between their scheduled visits. As pain intensity, related symptoms, SDOH-related barriers, and level of needed assistance will fluctuate over time, these "as needed" touchpoints will be scheduled as needed on a participant-by-participant basis at the discretion of the PCM/CHW and participant. Additionally, the participant will receive regular surveys via EHR portal, text, and/or IVR to assess pain levels.

Aim 3

Aim 3 of the ASCENT study will involve interviewing a sub-set of enrolled participants after their involvement in the intervention is complete. Up to 40 participants will be interviewed about their experience in the ASCENT study. Interviews will be one-time only, will take approximately 30-45 minutes and can be done via telephone or zoom. In the ASCENT Feedback Questionnaire participants will indicate whether they're not interested, not interested or would like more information about being contacted regarding taking place in an interview. Research coordinators will contact participants by phone, portal message or mail who are interested, want more interested or don't respond. No remuneration will be offered for this interview. Interviews will be recorded and transcribed (names and identifying information removed).

Also included in this aim are interviews or focus groups with the study interventionalists (PCMs & CHWs). We provided extensive training to the ASCENT CHWs and PCMs, discussed role delineation between the PCM and CHW roles, provided role playing opportunities, and held weekly touchpoints with the PCM and CHW interventionalists. However, opportunities remain to further refine the CHW role in the context of the ASCENT intervention and identify additional training needs. To study this, we will hold quarterly-biannual focus group/debriefings with interventionalists (e.g., CHWs, PCMs) to understand their needs for additional role clarification, training, and ongoing challenges. There will be no compensation for participating in these focus groups/interviews, interested team members will be given a consent document and the option to decline. The debriefings will be recorded for transcription and data analysis purposes.

Control Condition

Patients randomized to usual care group will be administered trial PROM outcomes. Their scores will be viewable

in the EHR by their care teams. Patients will be encouraged to discuss moderate or severe pain with their care teams and to track their pain via print log or portal. In addition, control group participants will be provided access to the ASCENT multi-modal pain management materials and self-management instruction. A few materials (pain log, general pain education material and wifi guide, etc) will be included in their study post randomization/welcome mailing. Other than this, there will be no attempt by study personnel to influence pain management. While randomization by patient means oncologists will have both intervention and control patients in their practices, numerous effectiveness trials of collaborative care for symptom management by us as well as others have shown there is little spillover of the intervention to usual care patients in the absence of the care management, symptom monitoring and treatment adjustment that occurs with enhanced care of varying types.[2-6] Any minor spillover that does occur results in a conservative estimate of the intervention's effectiveness.

Intervention Fidelity

Measures of actual adoption, fidelity, and penetration will be abstracted from administrative data and utilization tracking data mined within the Epic EHR. In addition, CHW/PCM initial and follow up calls will be recorded, with patient permission, and reviewed using a key element check list, that incorporates sociocultural elements. Strategies to improve intervention fidelity will be based on conventional methods but expanded to include awareness and sensitivity to sociocultural issues. We will assess fidelity by reviewing recordings from intervention touchpoints using check lists of essential elements. Two individuals will separately review transcripts of the touchpoints and document whether $\geq$95% of essential elements are present. If an encounter includes fewer that 95% of the elements, the interventionalists will review training materials and role play the touchpoint with ASCENT team members.

Data Collection

Data to estimate the effectiveness of the ASCENT intervention and characterize the trial cohort will include clinical and demographic information, pain specifics, and PROM assessments. Data collection approaches will include abstraction from the Epic EHR, collection from participants by Research Coordinators, clinical documentation by PCMs, and PROMs administered by patient portal, IVR, and mailed questionnaires depending on patient preference. Included in questionnaires will be a final ASCENT Feedback survey at the 6 month timepoint as participants finish their study completion, which may be disbursed by patient portal or mail.

IVR will be utilized to supplement the collection of PROMs. These PROMs will include the pain assessments used to tailor and individualize the ASCENT intervention, as well as the ASCENT trial outcomes. Trial primary and secondary outcomes will be collected at 3- and 6-months from the patients who do not complete them via Epic Welcome tablet or patient portal. The RevSpring platform will be used to collect IVR data. The IVR data will be maintained on password-protected secure Mayo Clinic servers within the firewall. No PHI data will be released to RevSpring. RevSpring has been used by the Mayo Clinic Spine Center to securely administer follow-up PROMs to over two thousand patients. Data going to the RevSpring platform is transient in nature and is purged once the results are uploaded into Epic. TAP approval has been granted to RevSpring's IVR system and there are Business Associate Agreements (BAA) and Information Security Agreements (ISA) in place, which covers how PHI can be used and stored. The ASCENT pain NRS questionnaire responses will reside on our server and will not go outside of the firewall. Additionally, RevSpring is providing the platform for the texting

capabilities, mentioned in the "follow up touchpoints" section. Study team members will only text study participants and participants will be asked to "opt in" to start receiving the messages.

ASCENT Trial Outcomes

Trial outcomes will include PROMs, healthcare utilization, and employment status. NIH Helping to End Addiction Long-term (HEAL) Initiative Clinical Pain Common Data Elements will be used if validated Spanish translations are available excepting QoL, for which no HEAL measure has been specified. PROMs, **Table 2**, will be administered at baseline by a study coordinator and at 3 and 6 months by a blinded, bilingual, assessor. Valid Spanish translations are available for all PROMs.

Primary outcome The Brief Pain Inventory SF (BPI SF), has been used among diverse populations.[7-9] Its psychometric performance characteristics have proven excellent and robust in diverse types and stages of cancer.[10,11] The BPI SF has been used in disparity-focused trials among Hispanic persons.[12] A Spanish version has been widely used for almost two decades.[13]

Secondary outcomes Will include physical function (PROMIS Physical Functioning SF 6b), quality of life (EQ5D-3L),[14] depression (PHQ-2), anxiety (GAD-2), sleep (PROMIS Sleep Disturbance 6a), and self-reported employment status.

Mediators Will include self-efficacy for managing symptoms (PROMIS SF 4a), adherence to behavioral MMPC plan components (logged count data), use of ASCENT e-tools (minutes/week), social isolation (PROMIS SF 4a), informational support (PROMIS SF 4a), and opioid consumption in oral morphine equivalents (OMEs) collected via EHR prescriptions.

Measure	Domain	Items	Time min.	HEAL data	Collected 0,3,6 mo.
Primary					
BPI SF	Pain	7	3	✓	✓
Secondary					
PROMIS SF	Physical Function	4	2	✓	✓
EQ-5D-3L	QoL	5	2.5		✓
PHQ-2	Depression	2	2	✓	✓
GAD-2	Anxiety	2	1	✓	✓
PROMIS SF	Sleep	6	3	✓	✓
Mediators					
PROMIS SF	Self-efficacy	4	2		✓
PROMIS SF	Social isolation	4	2		✓
PROMIS SF	Informational support	4	2		✓

Health care utilization Healthcare utilization for ASCENT will consider hospitalizations and ED visits which will be ascertained using EHR entries and administrative billing data. Data collected for hospitalizations will include admission and discharge diagnoses, length of stay, whether an admission was planned for anti-cancer treatment or unplanned. The majority, but not all, of patients' health care utilization will occur at MC facilities. Established patterns suggest that 80% of patients care will occur at an MC facility. However, we will use imputation methods and sensitivity analyses to assess the impact of mis-ascertainment of utilization data.

Risks and Benefits

The risks of the ASCENT trial study are minimal as participants are being potentially offered additional support and expertise to manage pain. Nothing in this trial will impede patients them from receiving whatever pain

treatment they and their team agree are appropriate and evidence-based. The benefits to patients include the potential for safer and more guideline-concordant pain management and lower risk of opioid exposure and dependency.

Protection of Human Subjects

Care will be taken to ensure that patients' data are protected. Data from chart review, patient-reported preferences, and patient-reported outcomes will be stored securely on password protected Mayo Clinic research servers within the firewall. Clinicians will still be able to make professional judgments about the appropriateness of engaging patients in specific conversations about pain management throughout their post-surgical recovery and may disregard EHR-prompts as appropriate.

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: Up to 660

Subject population (children, adults, groups): Adults

Inclusion Criteria:

- A qualifying liquid or solid cancer diagnosis with visits at a participating Mayo site in the past 15 years
    - Including malignant hematology
        - Lymphoma
        - Myeloma
        - Chronic Leukemias
- Age ≥18
- NRS pain score of ≥ 5/10
- Pain that developed or worsened following cancer diagnosis.
- Fit the description of either rural or Hispanic or both.

Exclusion Criteria:

- PHQ8 score of ≥13.
- Hospice enrollment
- Skilled nursing facility, inpatient rehabilitation facility, or long-term care placement
- Encounters with Palliative Care or the Pain Clinic in the past two months or upcoming two months
- Any mention of hospice referral in medical oncology encounter notes (assess through textual search of the Mayo Data Explorer)
- Affirmative response to, "Are you usually confined to a bed or chair more than a third of your waking hours because of your health?"
- Currently homeless.
- Do not feel safe in their home.

- New or worsening chest pain, chest tightness, or chest pressure.
- Back pain that is associated with a new or worsening weakness, control of bowels/bladder, or difficulty walking.
- Lightheadedness, inability to keep down food or fluids, or vomiting blood or dark coffee-grounds-like material.
- New or worsening headaches that are associated with vision changes, nausea, balance issues, or problems with speech.
- Screens positive for use of non-cannabis drug use at a frequency of monthly or greater
- Inability to engage with the intervention due to medical or psychological reasons

Review of medical records, images, specimens

Check all that apply (data includes medical records, images, specimens).

☐ Only data that exists before the IRB submission date will be collected.

Date Range for Specimens and/or Review of Medical Records:
Examples: *01/01/1999 through 12/31/2015*, or all records through *mm/dd/yyyy*.

Note: The Date Range must include the period for collection of baseline data, as well as follow-up data, if applicable.

☒ The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

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Data Analysis

All methods will be appropriate for a patient-randomized, multi-site study. In addition, because our primary aim is to assess effectiveness in two potentially overlapping subgroups, we will use a Sidak corrected alpha of a = 0.0253[15] to assess significance. We will summarize patient characteristics by study arm, and report standardized mean differences (SMDs) to assess balance; we will do this for the entire cohort as well as separately for Hispanic and rural patients. Then, to assess the effectiveness of the intervention on the primary and secondary outcomes we will estimate a series of generalized linear models, each estimated separately for Hispanic and rural patients, respectively, with outcome as dependent variable and intervention status indicator. Each model will be specified with a link and distribution appropriate for the outcome, e.g., logit or linear, and include indicators for randomization factors and any characteristics that have SMD > 0.1 across groups. By testing whether the coefficient of the intervention status differs from zero we can assess whether the intervention has an impact on the outcome.

All variables will be assessed to ensure that distributional assumptions are met and, if not, different strategies considered, including transformations, categorization, and revised model specifications. For outcomes which are collected multiple times we will include random latent effects (mixed effects models) for each patient. All models will be assessed for goodness of fit using methods appropriate for the specification, including C-statistics, R^2 values, and residual plots. All variables will be assessed for missingness; patterns of missingness will be examined and if appropriate multiple imputation used to account for missing values in model estimation.

Exploratory Subaims: We will undertake several exploratory analyses. First, to gain insights into the intervention pathways we will undertake a mediation analysis including only patients randomized to the intervention group. This will employ structural equation models, which will allow us to partition the overall effect of the intervention into direct and indirect effects and compare their magnitude.[16,17] The results of these analyses will provide information about the relative importance of the mediators on the intervention effect. A second exploratory aim will assess whether there are particular subgroups of patients in which the overall intervention is more effective. Rather than prospectively identify subgroups as in a conventional heterogeneity of treatment effect analysis, we propose to use machine learning tools to cluster intervention patients that respond well or poorly to the intervention. Specifically, we will use a 2/3 random sample of intervention patients to train an unsupervised hierarchical clustering algorithm to identify clusters of patients based on all baseline factors; hierarchical clustering is a machine learning approach that requires no assumptions about numbers of clusters or the relationships between factors, and has been used previously to cluster patients into similar groups.[18,19] Clusters will then be assessed for relative treatment effectiveness by including cluster indicators in the main models, along with interactions with the intervention indicator. This will allow us to identify clusters which have higher or lower response to the intervention. Finally, we will validate these results using the 1/3 remaining (validation) sample. The results of this aim will provide insights into the types of patients for which the intervention is likely to be most or least effective.

C.9.viii. Sample size. Our sample size is determined by the number of patients needed to detect a standardized effect of 0.40 between intervention groups, within either the Hispanic or rural subgroup of patients. The choice of 0.40 SD was informed by the 11-point NRS pain score, which we expect to closely align with the BPI. In preliminary analyses using data from the ongoing E2C2 study,[20-22] we found the standard deviation for the NRS pain score to be 2.7 for Hispanic cancer patients and 2.5 for rural dwelling cancer patients. Thus 0.40 SD corresponds to approximately a 1 point difference in the NRS pain score; 0.40 also conventionally corresponds to a 'medium' effect size.[23] Notably, a 1-point difference on the BPI as well as other 0 to 11 pain NRS has been shown to be a clinically important difference.[24,25] The sample size needed to detect a standardized effect of 0.40

with a power of 1-b = 90% and an a = 0.0253 (Sidak adjusted for 2 comparisons) is 156 per arm or 312 per group. We anticipate that approximately 10% participants will be rural dwelling Hispanics, based on the fact that ~90% of Hispanic cancer survivors treated at the Mayo Clinic Comprehensive Cancer Center are urban dwelling, RUCA 1 and 2, so assume approximately 10% overlap between the two groups. Allowing for a 10% loss to followup, we therefore plan to enroll 312 x 1.9/(90% followup) = **659** patients, of whom at least 50% are Hispanic and 50% rural dwelling.. For other outcomes, we assume followup on 593 patients and will have 90% power to detect a smaller standardized effect of 0.3 with an uncorrected a = 0.05. The exploratory subaim will be used to generate hypotheses for further work; results will be descriptive, with confidence intervals reported as appropriate.

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