COMIRB Protocol

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD
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Project Title: **Apoyo con Cariño (Support through Caring): Improving Palliative Care for Latinos with Cancer**

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Version Date: 6/15/2015

I. Hypotheses and Specific Aims

We hypothesize that this patient navigator intervention, involving patients from urban settings, will improve advance care planning, pain management, and hospice utilization for Latinos with advanced cancer.

Specific Aim 1: Implement proposed intervention of the 5 palliative care-related patient navigator visits across 3 urban and 7 rural/mountain clinical sites.
Specific Aim 2: Evaluate the effect of the intervention through a randomized controlled trial involving 240 participants with Stage III/IV cancer on *primary outcome measures*: improved palliative care overall, increased advance care planning, improved pain management, and increased hospice utilization.

II. Background and Significance

Palliative care, focusing on assistance with advance care planning, decision-making, pain and symptom management, psycho-social support, and navigation, has the potential to improve care quality and reduce medical service utilization.[1,2] Temel and colleagues[3] reported that early palliative care in patients with advanced lung cancer significantly improved quality of life, increased survival, and provided less aggressive care at the end of life. Additionally, The American Society of Clinical Oncology recently published an updated position statement supporting the need for oncologists to initiate difficult conversations with patients regarding prognosis, preferences, and palliative care options earlier in the course of illness.[4]

A. Disparities in End-of Life Care: Advance Care Planning: Advance Care planning has been characterized by significant disparities based on ethnicity. While nationwide averages of completed advance directives are low for all groups, Latinos are less likely to have a living will, durable power of attorney, or a Do Not Resuscitate (DNR) order.[5-10] Furthermore, Latinos are more likely to choose very aggressive care in the face of serious or incurable illness and less likely to acknowledge their terminally ill status.[5,6] Latinos are less likely to have knowledge of advance directives[6,11,12] and are more likely to report that they have not discussed advance care planning with their health care providers.[13] This finding is

less frequent when patients and physicians are ethnically concordant,[13] although wishes for very aggressive care persist.[11]

B. Disparities in End-of-Life Care: Pain Management: Pain occurs in approximately 25% of patients with newly diagnosed malignancies, 60% of patients undergoing treatment, and 75% of patients with advanced disease.[14,15] Expanding evidence suggests that adequate pain assessment and management is not achieved for many persons at the end of life. Kutner and colleagues report that even in the care-oriented culture of hospice, 82% of their patients listed pain as the most bothersome symptom, requiring more intensive pain management during the last weeks of life.[16]

Ethnicity is increasingly recognized as being predictive of poor pain assessment and management.[17-20] The barriers to adequate pain management have been identified at the institution level, due to physician bias, and as a result of cultural beliefs.[21-23] There is documented variation across ethnic groups in how pain symptoms are reported and how pain is managed.[17] Bernabei and colleagues reported that elderly nursing home minority (Hispanic) cancer patients were more likely than Whites not to have received any analgesia. Cleeland and colleagues[24] demonstrated that 42% of outpatient minority patients (Hispanics and Blacks) with metastatic cancer were three times more likely than patients in other settings to be inadequately medicated. In a follow-up study,[21] they found that 65% of minority patients did not receive guideline-recommended analgesic prescriptions, compared with 50% of non-minority patients. Hispanic patients in particular reported less pain relief and had less adequate analgesia. Hispanics, however, also reported more concerns about taking too much medication, were more worried about medication side effects, and felt they needed more information about pain management.

While the number of Latinos in the US continues to increase, pain treatment disparities of Latinos persist with reasons including: patients' discomfort with communicating in health care settings, patients' limited health literacy, and the lack of cultural understanding by providers.[25] Language and cultural barriers prevent many Latino cancer patients, especially those who are monolingual from obtaining proper pain management and palliative care.[20] Latino patient-level barriers include fears of addiction, language proficiency, low health literacy, prioritizing family above pain control, and a belief in the role of suffering at the end of life.[26,27]

C. Culturally Competent Care: Understanding culture or ethnicity is extremely important for gaining a deeper appreciation of how preferences for end-of-life care and pain are expressed and experienced. Cultural, spiritual, and religious values often influence how end-of-life care and pain management are perceived. Ahles and colleagues[28] suggest that a person's culture influences the pain experience. If clinicians from one culture stereotype or believe broad generalizations about patients from another culture, their beliefs or misconceptions may unintentionally affect patient care outcomes. Additionally, some languages contain many different words to describe pain whereas in other languages, a single term is the norm. If an

unpleasant sensation is not termed “pain” in a particular language, it may further complicate its detection and treatment. The linguistic screen that prevents such a sensation from being categorized as pain may also prevent the communication of the sensation to caregivers, short-cutting the option for effective treatment of the unpleasant sensation. Thus, cultural variability and differences in pain perception and response may be influenced by the language available to describe the pain experience.

D. Disparities in End-of-Life Care: Hospice and Place of Death: Hospice services are rarely accessed by non-Caucasians.[29,30] Barriers experienced by Latinos included lack of awareness of hospice, language, insensitivity of care providers, socioeconomic factors related to citizenship, prohibitive cost of care,[31] and a preference for family caregiving networks.[32] One observed outcome likely related to the low utilization of hospice services is the higher rates of death in an institutional setting rather than at home for Latinos[33] and the increased use of life-prolonging drugs and interventions[34,35] which account for substantially higher costs. Death at home is more likely to be associated with other factors commonly desired including having family present, dying with dignity,[36] not being alone, having one’s affairs in order,[33] and hospice services congruent with Latino family caregiving values. Latinos emphasize spirituality as a primary means of coping with end-of-life issues.[31]

E. Latinos of Colorado are <u>not</u> heterogeneous-Denver and Colorado Health Statistics: The ethnicity of the Denver population is as follows: Caucasian 52%, Latinos 32%, African American 11%, Asian 3%, and Native American 1%. In the state of Colorado, 20% of persons are Latino. Of the Latinos living in Colorado, 75% are of Mexican origin and 23% are of continental Central American or South American origin. Less than 2% of the Denver Latino population is of Caribbean origin: Puerto Rican 0.9%, Cuban 0.4%, and Dominican 0%.[37]

F. Navigator Interventions: Patient navigators have been involved with efforts to improve health outcomes within the Latino community for over a decade. In fact, Harlem surgeon Harold Freeman started one of the first patient navigation projects to improve screening mammography in East Harlem when he was president of the American Cancer Society (ACS).[38-41] In the decades that have followed, ACS has shown continued commitment to the patient navigator model of care and has demonstrated that navigators can help reduce health disparities in underserved and vulnerable populations by improving rates of cancer screening, follow up on abnormal diagnostic tests, and adherence to chemotherapy regimens.[42-44] Navigators have also been involved with cancer survivors to ensure emotional support and proper follow up and surveillance. While there has been interest in and acknowledgement that palliative care is an important part of the training of patient navigators, there have been no previous studies examining the effects of a patient navigation intervention to improve palliative care for cancer patients.[45] *This trial, using rigorous scientific methods and including the community from the earliest development, represents a unique opportunity to demonstrate the effectiveness of a patient navigation intervention for palliative care*. The <u>long-term</u>

vision for this intervention is to incorporate the training and intervention into ongoing patient navigator programs within the state and nationwide. When this is accomplished, the entire continuum of cancer care will benefit from patient navigators, including those in need of palliative or end of life care. Four patient-navigator projects underway in Denver, Colorado focused on cancer care will ultimately complement our proposed patient navigation intervention and provide future opportunities for collaboration: 1) La Clinica Tepayac and Promotoras, a program to increase cancer screening for underserved Latinos 2) Patient Navigation Research Program-an NCI/ACS funded multi-site project to identify underserved patients with abnormal screening tests and through patient-navigation decrease time to definitive diagnosis and cancer treatment 3) ACS navigators 4) Breast CARES Program provides psychosocial support through patient-navigation to Latinas diagnosed with breast cancer from diagnosis through treatment and into survivorship.

III. Preliminary Studies/Progress Report

A. Patient Navigator Intervention to Improve Palliative Care for Seriously Ill Latinos (5 K23 AG028957-02): A Feasibility Study (COMIRB 09-620)

Specific Aim 1: To develop and pilot-test a cultural navigator, or *guia*, intervention to improve palliative care for seriously ill older Latinos.

Specific Aim 2: To conduct a randomized controlled vanguard study of the intervention to determine refusal rates, withdrawals rates, and visit and interview completion rates to ascertain feasibility for fully powered RCT of the patient navigator intervention.

B. Intervention Development and Cultural Tailoring: To develop and inform the intervention Dr. Fischer conducted a series of focus groups addressing end-of-life care in the Latino community at a local community health clinic. The qualitative results emphasized core Latino values, *familia, confianza, espiritulismo*, and *personalismo*. This led to the development of our theoretical model (Figure 1). Key informant interviews were conducted with other community navigators, community leaders, and local community health care providers to work to operationalize values into navigator interventions. Dr. Fischer convened a bi-cultural Community Advisory Panel composed of academic experts, community leaders, and community members working in the area of patient navigation who worked together to refine the study materials and the content and structure of the home visits, transforming core values to programmatic messages.

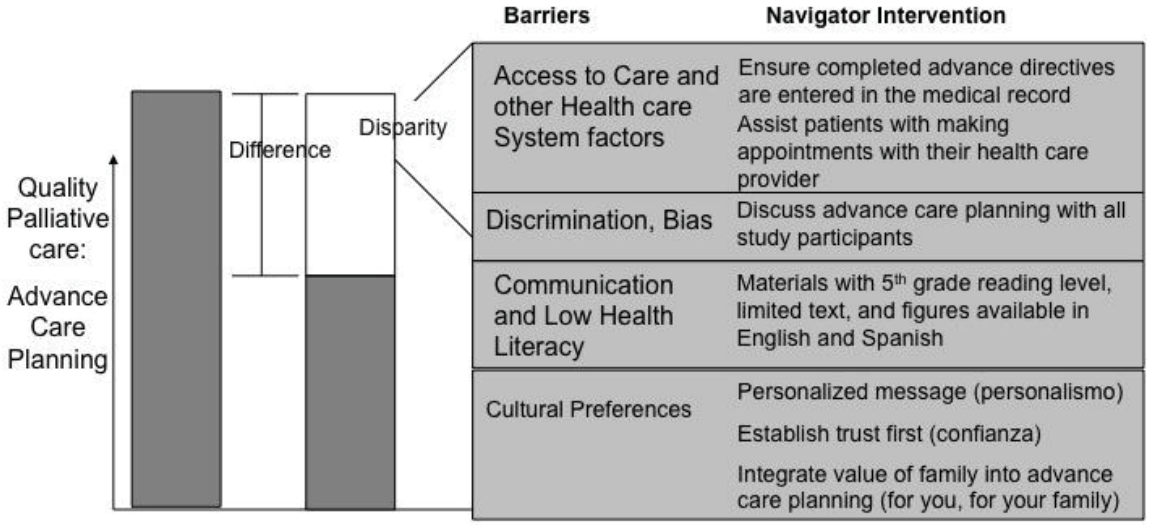
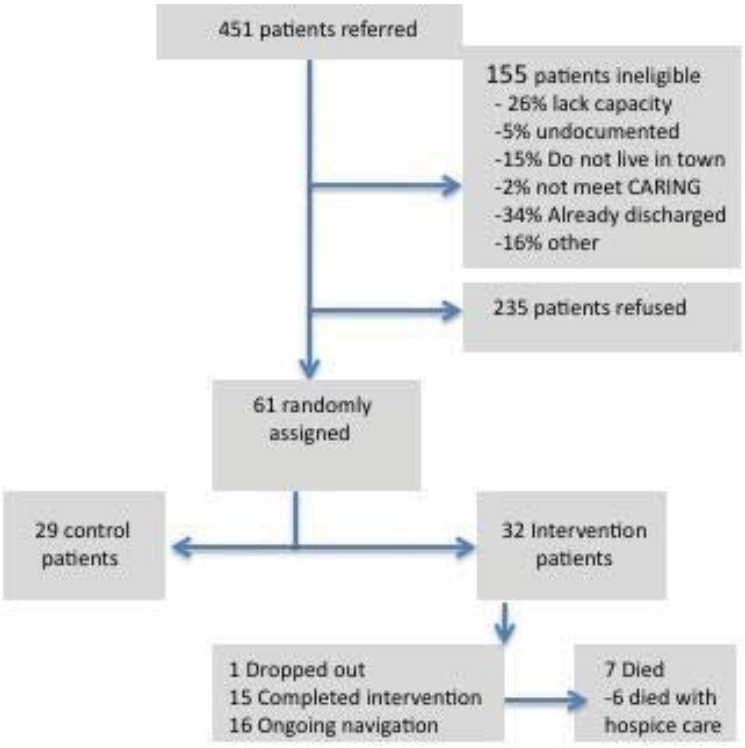


Figure 1. Theoretical Model

Pilot testing was completed in June 2010 and enrollment in the RCT of the patient navigator intervention began in July 2010. Final study materials and navigator visit structure received positive review from pilot test participants and ongoing RCT feasibility study participants.

C. Feasibility of the Patient Navigator intervention to Improve Palliative Care for Seriously Ill Latinos



The preliminary results from this feasibility study demonstrate that the patient navigator intervention is a feasible and acceptable intervention for Latinos facing serious illness. The study flow figure demonstrates that the team was able to recruit and enroll patients with a 20% enrollment rate. Of the 32 patients in the intervention arm, only 1 patient asked to withdraw from the study. Intervention participants who have completed the intervention had a mean of 5.2 $\pm$ 3.1 (SD) visits. The five navigator initiated visits took place over a mean of 5 $\pm$ 2 (SD) months. The subset of patients with cancer (n = 6) all

completed the 5 visits within 2 months. In both control and intervention groups, the rate of 3 month data collection by patient interview is 85%.

The PI has also completed qualitative analysis of the detailed field notes of the patient navigator from the preliminary studies and transcribed interviews with participants who received the navigator intervention. Themes of trust, appreciation, and gratitude demonstrated a high degree of satisfaction with the patient navigator and the intervention. The analysis also described less tangible benefits of a patient navigator many activities of the navigator beyond the scope of the prescribed intervention.

IV. Research Methods

A. Outcome Measure(s). An overview of the outcome measures and their source are listed in **Table 1** below. Primary outcome measures for the three main domains are simple objective outcomes related to end-of-life care-palliative care overall, advance care planning, pain management and hospice utilization. Secondary outcome measures include the use of aggressive care at the very end of life,[3] and quality of life.

At 3 months from study enrollment date, the PI or Co-I, who is blinded to randomization assignment, will contact participants to complete outcome measures-the Brief Pain Inventory Long Form, the McGill QOL scale, and the Patient Navigator Process and Outcomes Measure (PNPOM). Three months was chosen for the survey outcomes based on our feasibility study demonstrating that ~ 80% of patients are still alive to complete the survey. Three months is enough time to complete the intervention visits but minimize the number of patients who die before follow up data collection can occur. Upon completion of the follow up patient interview, participants in the control and intervention group will receive a $20 grocery gift card as an incentive and gesture of thanks.

At 6 months from study enrollment, the PI and Co-I (RF) will conduct a chart review to collect outcomes data. If death has occurred, the hospice will be contacted to confirm treatment history and length of stay in hospice. Six months was chosen for the chart review to ensure all participants had at least 6 months to complete an advance directive The last month for recruitment is month 41 therefore, all chart review data collection will be completed by month 47.

At month 46, the patient navigator (PRA) will call all the participants who may still be living and collect hospice utilization data. If the navigator is unable to contact the participant, then the Colorado Department of Public Health will be contacted to search for death records which will confirm date of death if the participant has died and if hospice was or was not involved. Hospices will be contacted to confirm all utilization (exact hospice enrollment date and death date). Month 46 was chosen for hospice utilization assessment to maximize the number of hospice days captured for all participants. We recognize the follow-up period will be variable for

participants (e.g. those enrolled in month 38 will have a shorter follow up time than for those enrolled in month 6) but due to the randomization scheme, it should not be biased towards intervention or control group.

At month 58 and 70 the follow up procedure for collecting hospice utilization data will be repeated. Qualitative data from our feasibility would suggest that an earlier exposure to the intervention will continue to have an impact on hospice utilization over time.

Table 1. Outcome Measures for patient navigator intervention study

Domain	Outcome measure	Source	Time of data collection		
			Baseline	3 months after enrollment	6 months after enrollment
Palliative Care Overall	Patient Navigator Process and Outcomes Measure (PNPOM)	Participant interviews		X	
	McGill Quality of Life Scale-Short form	Participant interviews	X	X	
	Aggressive care at the very end of life • Chemotherapy within 14 days of death • No hospice referral • Hospice referral within 3 days of death	Chart review of medical records	At time of participant death		
Advance Care Planning	Completed AD available in the medical record (Yes/No) (**Primary measure**) Type of AD in chart: • Living will • Durable Power of Attorney • Do Not Resuscitate Order • Five Wishes/Cinco Deseos©	Chart review of medical records	X		X
Pain management	Brief Pain Inventory-Long form (**Primary measure**)	Participant interviews	X	X	
Hospice utilization	Hospice days used (**Primary measure**)	Interview of participant, and review of hospice records	At time of participant death Record review for all participants at month 46 in the study, month 58 and month 70.		

McGill QOL: is specifically designed for a palliative care population, measuring whole-person concerns magnified by advanced life-limiting illness. It is short, reliable, repeatable, and can be used to determine changes in QOL of groups. The 18 questions are answered in reference to the prior two days.

Variables include the 0-10 global QOL assessment and the 4 individual subscales of the MQOLQ - physical symptoms, psychological, existential, and support. The psychological subscale includes two questions that assess depression (depression, sad) and two questions that assess anxiety (nervous or worried, afraid of the future).[46,47]

BPI: (BPI-LF) is a 32-item self-report instrument that assesses the severity and impact of pain in patients with chronic diseases, e.g. cancer. Available in Spanish, the validity and consistency of this instrument is based on the two-factor structure of pain severity and pain impact on function with Cronbach's alpha ranging from 0.77 to 0.91. The psychometrics of the BPI-LF have been well established with cancer patients.[48-50]

Patient Navigation Process and Outcomes Measure: (PNPOM) will capture the less tangible benefits of a patient navigator and help understand the effects of the many activities of the navigator beyond the scope of the prescribed intervention. The questions incorporate aspects of self-efficacy and patient activation (key concepts that patient navigators help improve).

Intervention Delivery Cost: We will estimate the unit cost for the *guia* visits based on the salary of the *guia*, time, resources used, and training in order to inform future dissemination. In addition, we will explore approaches to measuring cost effectiveness of the intervention in order to capture cost per successful outcome (e.g., cost per completed AD in the chart, cost per referral to hospice) in the treatment and control groups. These activities are designed to further develop a methodology that can be used in future studies. For this proposed study of comparing a patient navigator intervention to control, additional costs to be incurred by adopting the intervention should be weighed against relative benefits of the intervention. It would be difficult to convert the intervention effects (e.g. for completed AD in the chart, and referral to hospice) into corresponding cost savings in terms of dollars to calculate net gains of the intervention, whereas the intervention costs (development, including training of navigator, meetings, planning, and supervision; and implementation, including participant identification, recruitment and screening, resources used and potential replication in other locations) could be estimated.

B. Study Design and Research Methods

Description of Population to be Enrolled: Participants (n = 240) will be recruited from the following sites:

1) COMIRB: 200
2) SCL Health IRB (formerly called Exempla IRB governing Comprehensive Cancer Center at St. Joseph's Hospital): 40

Adults (≥18 years of age) who self-identify as Latino and have an advanced cancer. All types of cancer will be included. While we acknowledge that the prognosis and survival vary greatly by type of cancer, by broadly focusing on more

advanced disease, most patients will have symptom needs and all may benefit from a palliative approach.
We will preferentially enroll Stage IV cancer patients. To ensure the study population has adequate representation of more advanced disease with a poorer prognosis, patients with a Stage III cancer will comprise no more than 20% of the study population at any given period of time.

Specific inclusion Criteria:
1) Self-identify as Latino
1) Stage III/IV cancer
2) Receiving chemotherapy, biotherapy, or radiation therapy for cancer
3) Not incarcerated
4) Participants must be able to provide informed consent and speak either English or Spanish as a primary language

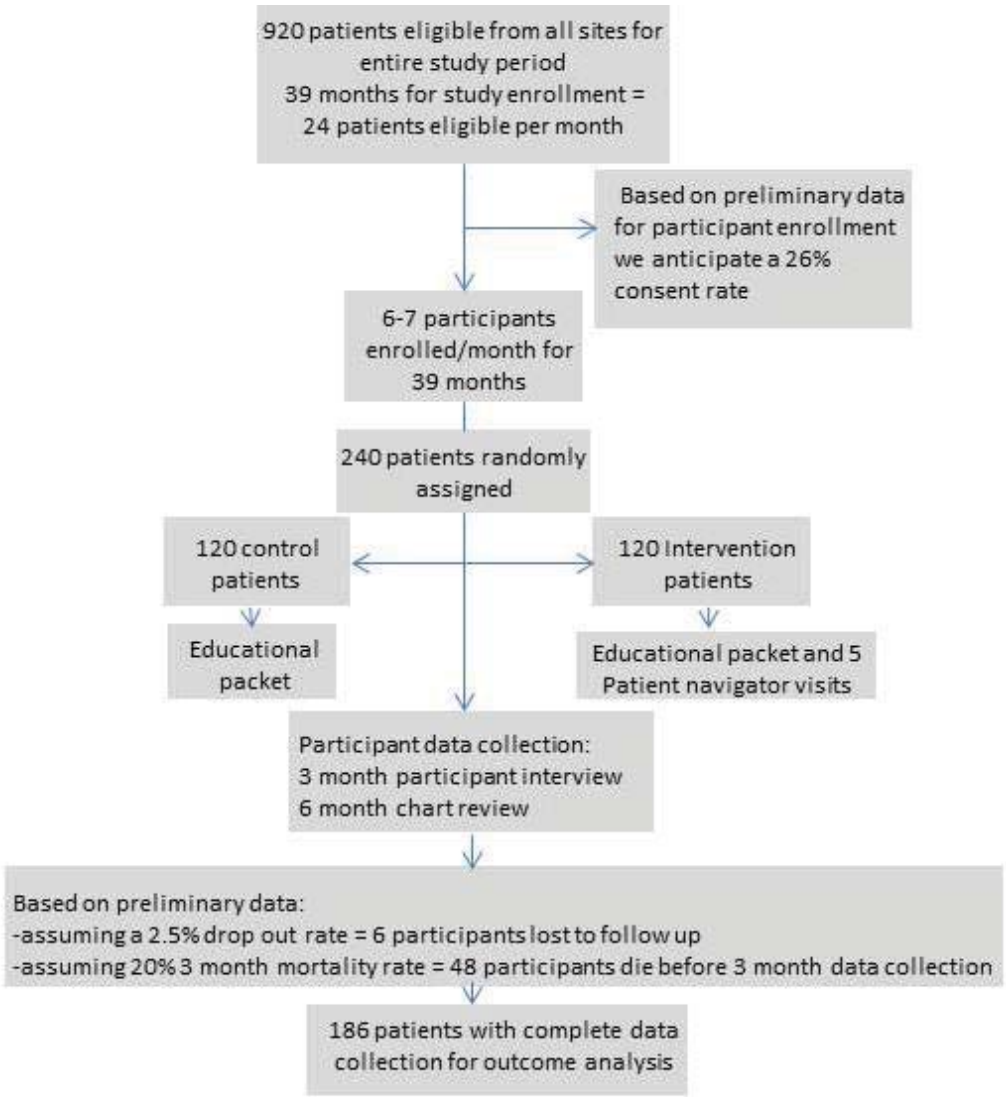


Figure 2. Study Overview and Accrual

Recruitment: At each clinic site we have identified a health care provider (e.g. nurse, clinical trials coordinator) who will be the study's onsite coordinator. If patients meet the eligibility criteria and agree to be contacted (HIPAA A) the onsite coordinator will provide patient contact information to the patient navigator (guia) who will then approach the patients for study enrollment. If patients agree to participate, they must give informed consent in writing. The patients must also agree with the HIPAA language in the consent form. These forms will be provided in English or Spanish. The *guia* will read and summarize each section of the consent form, assessing comprehension as well as willingness to consent. The consent form includes a description of the purpose of the research, risks and benefits, and contact information for the PI/Co-Is and the human participants' protection committee (IRB).

The PI (SF) and Co-I (RF) will oversee the recruitment and consent process, serve as a liaison with the oncology care teams as necessary, and problem solve barriers to palliative care if the navigators need additional assistance

Baseline Assessment: Before randomization, study participants will have an initial assessment completed by the *guia*, focusing on sociodemographic information and the Brief Pain Inventory Long Form,[48,51] the McGill Quality of Life (QOL) scale,[47] and the Patient Navigator Process and Outcomes Measure. Sociodemographic information will include contact information, date of birth, measures of ethnicity, primary language, and acculturation, and socioeconomic status (occupation-current or former, average annual income, education, and home ownership). The PI (SF) or Co-I (RF) will review medical records for detailed medical data on cancer diagnosis and treatment, for a list of current medications and dosages, and for the presence (and type, if applicable) of an advance care planning document on the chart.

Randomization: The statistician (SM) will prepare blocked randomization (random permuted blocks) for assigning participants to intervention or control group within each clinic site, stratified by Stage III or IV, to avoid serious imbalance in the number of subjects between the two groups throughout the study period. The block size also will be randomly varied between 2, 4, and 6 to preserve the randomization scheme. The PI and Co-Is will be blinded to study allocation.

Intervention: After the initial contact for the enrollment and consent process, the *guia* will schedule the first study visit. The function of the initial visit is to establish trust (*confianza*) and ensure a more personal approach (*personalismo*) with the participants. In addition, if family members are present this initial visit will provide more opportunity for the *guia* to establish a relationship with the participants' families (*familia*) as well. These core Latino values ground the intervention starting at the most preliminary stage.
Visit Content Overview: The *guia* will arrange to meet the participants at the home or another location if the participant prefers (e.g., chemotherapy infusion unit,

primary care provider's or oncologist's office). At the first visit, the *guia* will provide and review the educational materials that cover the domains (selected by the community advisory panel based on the preliminary studies qualitative work) with the participant and family. Additionally, during that visit, the *guia* will work with the participant and family to create a plan for subsequent visits based on the participants' and families' needs and acceptance of palliative care. A framework of the target domains and the planned intervention by visit is described in **Table 2**. Because participants will be at different points in their illness trajectory and participants and families will vary in their acceptance and readiness to address each of the domains, the *guia* visits will vary in both the content and activities covered during each visit as well as the number of visits. Nevertheless, all of intervention content will be covered with each participant and family during the course of their study participation. The plan will be customized to the needs of each participant. For example, a visit may include accompanying the patient to their oncology or primary care appointment. The educational materials and the visit scripts are included in attachments.

Table 2. Framework of Patient Navigator Intervention

Visit	Advance Care Planning	Pain Management	Hospice/Palliative Care
1	Review educational materials about Advance Directives; leave a blank copy of Advance Directive with participant	Review educational materials about pain assessment and management; discuss participant's current level of pain	Review educational materials about hospice care and general goals of palliative care
2	Help patient complete a goals/values history	Discuss strategy to talk about pain-related issues with primary care provider	Review hospice and palliative care key principles; discuss using goals and values history of participant as context Referral if appropriate and requested by participant

Table 2. Framework of Patient Navigator Intervention

Visit	Advance Care Planning	Pain Management	Hospice/Palliative Care
3	Help participant complete an Advance Directive	Facilitate achieving adequate pain control by empowering participant through role playing	Start working on a plan for palliative care that incorporates values and goals of participant Referral if appropriate and requested by participant
4	Reinforce benefits and limitations of Advance Care planning; ensure Advance Directive reaches medical record	Explore and help resolve barriers and problems with pain management	Review plan for palliative care; Referral if appropriate and requested by participant
5	Review Advance Directive documents	Review current pain management plan; explore and help resolve barriers	Referral if appropriate and requested by participant

Navigator Initiated Visits: Based on data from our patient navigation feasibility study, we have set a "ceiling dose" of 5 planned *guia* intervention visits. We found in our feasibility study that further time investments were unlikely to yield improved outcomes.

Patient/Family Initiated Visits: The *guia* will continue to be available to the participants on a non-urgent basis as needed throughout the time of the award. In keeping with the patient-centered approach that grounds both patient navigation and palliative care, the *guias* will always be responsive to patient or family needs. There will not be a specified limit to the number of additional patient or family initiated visits. Based on our patient navigation feasibility study to date, where 6 of the 18 patients requested 2-5 additional visits, primarily for facilitating hospice care, we expect that 30% of intervention patients may need the additional assistance of the navigator approximately 3 times. Meeting these requests will thus be feasible within the time constraints of the *guia.*

Control group: At the time of enrollment, participants in the control group will be given a packet of the same educational materials that are provided to the intervention group, covering the three domains (advance care planning, pain management, and hospice) in the appropriate language (Spanish or English).

D. Description, Risks, and Justification of Procedures and Data Collection Tools.

Fidelity to the intervention: All participants will have a study tracking chart (stored in a locked file cabinet in a locked office in a secured office suite in a secured building on campus). Using a standardized electronic form (RedCap), the patient navigator (*guia)* will record the duration of each visit and who was present

at the visit. She will also record how each domain was addressed during the visit. She will also keep detailed field notes of what occurred during the visit and how the participants responded to the discussions and activities. The *guia* will also track phone calls made to the participant. As each visit will be logged in the tracking chart, an accurate count of the total number of visits per participant will be obtained. Careful tracking of the dose of intervention each participant received will allow for a dose response analysis. If participants refuse visits, the *guia* will attempt to contact the participant or family members to understand the reason for no longer wishing to continue with the program. The reason for drop out will be recorded in the study tracking chart. The navigator will audio-record 10% of their home visits and the Co-I (RF) and PI will review the tape using a fidelity checklist to evaluate if each domain was addressed and if the core Latino values were utilized in the discussion. This detailed study tracking will allow the team to demonstrate fidelity to the intervention for each participant. This level of documentation has been identified as necessary to provide rigor and increase reproducibility.[43] Audio files will then immediately be permanently destroyed.

Data Collection: To ensure data integrity, the PI developed a data collection manual with detailed description of each measure, instructions for its accurate collection, and acceptable sources. The study will use REDCap, a secure, HIPAA compliant, web-based application for building and managing online databases and is provided free of charge by the University of Colorado CCTSI. The PI and Co-I (RF) will perform the baseline chart review to obtain data on medical diagnoses, co-morbidity measures for the Charlson Index, and current medications. Chart reviews will include 10% reliability testing by PI and Co-Is.

Source of Materials: Data gathered for this study will come from three primary sources: the research participant or family through interviews with the navigator and the participants' medical records or death records. All quantitative data will be entered into REDCap, a secure, HIPAA compliant, web-based application for building and managing online database. Participants will be assigned a unique identifier code. Field note word documents using the key identifier code (not containing protected health information) will be stored on the University of Colorado firewalled, password protected, virtual private network (VPN) on a server accessible only to study team members.

Potential Risks: There are no foreseeable physical, social, psychological, or legal risks beyond those of participating in health-related research in general.

Protection Against Risks: All efforts will be made to protect confidentiality of research participants and their families. All electronic data will be stored in a password-protected program on a password-protected computer, with encryption software, in a locked office. All written data will be stored in a locked file cabinet in a locked office in a locked office suite in a building that is secured by an electronic entry card during off business hours. It is important to note that all participants are

receiving care within an institution and the data collected will not include any information that is not readily available in a patient's chart. There will be no questions that would impose legal risk on a participant that is not also readily available in the patient's medical record. There will be no direct questions regarding a participant's immigration status (whether documented versus undocumented). Therefore, there is no significant risk to participants and the protection against risks is adequate.

Data Safety and Monitoring Plan: As this study involves providing education and facilitating selected aspects of palliative care, few adverse events are anticipated. It is possible that addressing issues related to palliative care may cause increased anxiety. As an added protection, a community advisory panel, academic and community persons involved in the development of the intervention, will continue to meet twice a year. They will review enrollment, withdrawals, and any adverse events. Any other concerns raised by the research participants or their families can be discussed in this forum with the permission of the participant or family. This panel will therefore function as a voice and advocate of the participants and the Latino community in general.

E. Potential Scientific Problems. Several important limitations must be considered. The first is the possibility that the participating sites may have a knowledge deficit regarding palliative care and a lack of actual resources to which to refer patients and families. None of the sites have an outpatient palliative care program.

Additionally, tailored interventions inherently raise concerns of reproducibility and quality control. The individualized approach to each participant/family unit is critical to address variability in acceptance of palliative care and differences along the individual's illness trajectory. Therefore, in lieu of a one size fits all approach, careful tracking and documentation of navigator interventions has been recommended to address these concerns.[24] The PI has taken significant steps to ensure the reproducibility and quality control of the intervention. These are detailed in the **Fidelity to the Intervention** section.

Another limitation is the potential to lose participants to follow up. If death is expected, immigrant patients may return home to Mexico for their final days. Loss to follow up will be minimized by building a trusting relationship with the *guias* and working with the participant and family to create a plan for the intervention that will work for them. Additionally, there are outcome measures across the three domains that rely solely on secondary data sources rather than self-report.

Finally, we have also chosen to allow a broad focus to all types of cancer. While we acknowledge that the treatments and survival will vary widely by cancer type, all may have symptom needs that are appropriate for our intervention. Our symptom management centers on pain. We felt this was absolutely key-if pain is uncontrolled it is impossible to address goals and values discussions or any other

symptoms. We understand that other symptoms may be present and while the navigator does not have written materials specific to other symptoms, by helping patients become activated and advocate for themselves, other symptoms are likely to improve as well.

F. Data Analysis Plan.

Refusal rates, withdrawals, and missing data: The PI and current patient navigator *(PRA)* have achieved good consent rates (20%) for enrollment in the feasibility RCT. We expect that refusal rates in the proposed study will be lower because the patient navigator and the study will be introduced by a provider from the clinical site and the clinical oncology providers are supportive and committed to promoting this research whereas the feasibility trial was conducted in the acute care setting. De-identified demographic data (gender, age, cancer diagnosis) will be collected on potential participants who refuse to participate to assess the extent to which study participants differ from study decliners. Participants wishing to withdraw will be asked for continued consent to review their medical records and will remain in the database for analysis as randomized (intent-to-treat analysis). If participants withdraw from the study and do not give consent to perform the medical record review, outcome variables will not be available for those subjects and it will not be possible to do a traditional intent-to-treat analysis. Therefore, the statistician (SM) will do a sensitivity analysis, assuming all possible scenarios, if the participant withdrawal rate is >5% or there is a differential withdrawal from one of the study groups. Multiple steps will be taken to minimize missing data. Appropriate imputations or likelihood inference (based on ignorable missing-data mechanism when data are missing at random) will be used to address any severe missing data problems. Due to the expected high mortality rates (~20% at three months) of the study population, sample size was calculated to ensure adequate power for outcome analysis.

Assess effectiveness of randomization: To assess the effectiveness of the randomization procedure, the two groups will be compared across a broad range of variables including but not limited to age, gender, diagnoses, degree of acculturation (e.g., language spoken in the home, immigration history versus native US citizen), baseline presence of an advance directive, and socioeconomic status. Categorical variables will be compared using chi-square tests (or Fisher's exact tests) and continuous variables will be compared using t-tests (or Wilcoxon tests). If the randomization is not effective and significant differences exist between the two groups, covariate adjustment will be used in the analysis to control for the differences.[70]

Analysis of Primary Outcome Measures: The study is designed to demonstrate the effectiveness of a patient navigator intervention compared to control using rigorous scientific methodology (randomized controlled trial). For continuous outcome measures from interview (**MQOL and Brief Pain Inventory**), improvement from

baseline to 3 months will be used as outcome variables and compared between groups using t-tests. The arithmetic mean of the four severity items in BPI can be used as a measure of pain severity. (The arithmetic mean of the seven interference items can be used as a measure of pain interference with functional status. Pearson correlations will be calculated to examine relationships between pain intensities and interference. Multiple linear regression analyses will be used to determine the extent to which the pain intensity rating contributes to pain interference once the other ratings are controlled for.) **Hospice utilization** in days for the referred to hospice will be compared using t-tests (or Wilcoxon tests if skewed). For the dichotomous outcome measure at 6 months (presence of an **Advance Directive** in the medical record), chi-square tests will be used to test the intervention effect on the outcome. If significant baseline differences exist between the control and intervention groups, then those variables will be used as covariates in linear regression (for continuous measures, potentially using log transformed hospice days as outcome variable if skewed) or logistic regression (for dichotomous measure).
In order to reduce bias from outcome variables not being available at follow-up by participant withdrawal, the variables exhibiting differential withdrawal patterns between intervention and control will be adjusted for using regression.

Secondary Analyses: Selected variables will be tested for mediator and moderator effects. Urban/rural classification of the sites will be included as a main effect and an interaction term with intervention in regression to assess the effectiveness of the intervention in the rural setting compared to the urban. Country of origin, acculturation, and belief about value of palliative care will be similarly tested for effect modification. Trust (*confianza*) and personal approach (*personalismo*) with participants, and patient satisfaction with intervention will be tested for potential mediator effects, by first fitting regression with intervention as predictor and then adding mediator as predictor.

Aggressive end of life care will be analyzed using t-tests and linear regression for continuous measures, or chi-square tests and logistic regression for dichotomous measures.

Cost-effectiveness will be assessed using incremental costs-to-effects ratio. When we examine dosage effects of the intervention (i.e. relationships between the number visits and outcomes), we will observe marginal changes in dosage and effects. We expect to see diminishing marginal returns, and we will be able to decide an upper limit of dosage beyond which gains become negligible. Nonlinear effects of number of visits will be assessed by including higher order terms for number of visits as predictors in regression. Models will be calibrated for sensitivity based on cost estimates for intervention components.

Statistical Power: Sample size calculations are based on testing the effectiveness of the intervention for primary outcome variables. A target sample size of 240 (120

patients in each group) will provide ample power to detect statistically and clinically significant differences between the two groups. For improvement from baseline to 3 months in continuous outcome measures from interview, MQOL and BPI, 186 patients after death and drop-out, will provide more than 90% power to detect a medium effect size (f=0.25) for a 2-sided test comparing two means at Type I error rate=0.05.

For the dichotomous outcome at 6 months, completed AD, chart review of 240 patients will provide more than 80% power to detect an 18 percentage point difference from the control group rate of AD in chart at 10% – 40% (w=0.18 – 0.23, small-to-medium effect sizes) for a test comparing two proportions.

For hospice utilization (days used) outcome, effect size was found to be a mean=23 (SD=36) in control and mean=48 (SD=63) in intervention. We have 88% power to detect this effect size using n=168. Dropping one extreme from each group (91 days in control and 153 days in intervention), hospice utilization mean=9 (SD=14) in control and mean=22 (SD=26) in intervention. We have 98% power to detect this effect size using n=168.
The n= 168 sample size target for total number in hospice care assumes that 210 patients will be eligible for hospice over the course of the study and that 80% of eligible patients will use hospice before death. This latter assumption is based on actual Colorado hospice utilization data that is available through Hospice Analytics.

Therefore, we will preferentially enroll persons with stage 4 cancer. We will ensure that there are no more than 20% of patient s with stage 3 disease at any given time in the sample.

The patient navigator intervention is a time and resource intensive intervention and a small effect size is not sufficient to justify the upfront costs and resources to hospitals or payer sources. Therefore, we selected a medium effect size although in fact, we will have power to detect something in between a small and medium effect size.

G. Summarize Knowledge to be Gained. Palliative care is an essential part of cancer care. Palliative Care is a medical specialty that focuses on symptom management, quality of life, and helps patients with life limiting illness match goals and preferences for care. Recent oncology literature suggests that when patients talk about end of life decisions with oncology providers, patient distress improves. Furthermore, cancer patients who die at home, as opposed to the hospital, have better symptom control and family members have less PTSD and complicated bereavement. In a recent NEJM article, Temel, et al showed in a RCT of a palliative care intervention, patients with advanced lung cancer had better quality of life, less depression, and lived longer.[(23)] The overall goal of our project is to improve palliative care for Latinos with advanced cancer by incorporating a

successful community based model-patient navigation-to deliver a culturally tailored intervention to improve palliative care outcomes. Despite the evidence-based benefits of palliative care, access remains limited. In poor urban settings, availability of palliative care is often non-existent. Cultural and linguistic barriers may also increase disparities in palliative care for Latinos. Due to a nationwide shortage of palliative care providers and the unique cultural preferences and values of patients, our innovative study has the potential to improve palliative care outcomes and reduce health disparities in both urban and rural underserved communities.

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