NIH
HEAL
INITIATIVE

HEAL: Use of Spanish CRFs in clinical pain studies

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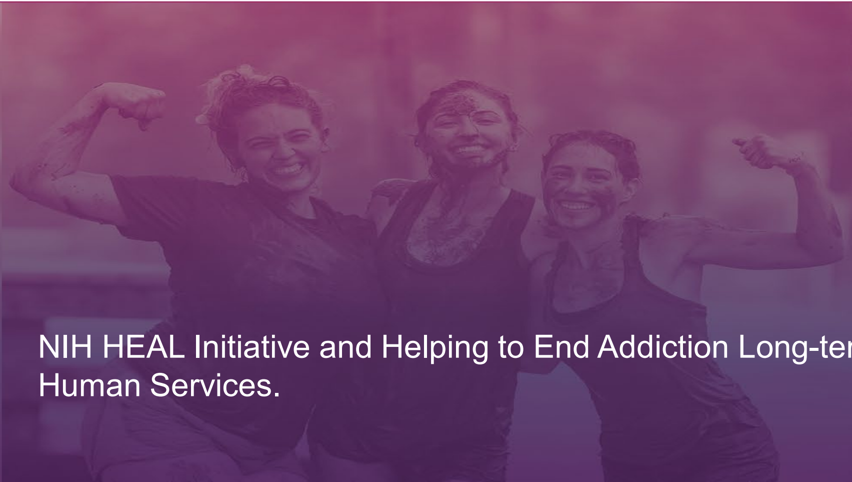
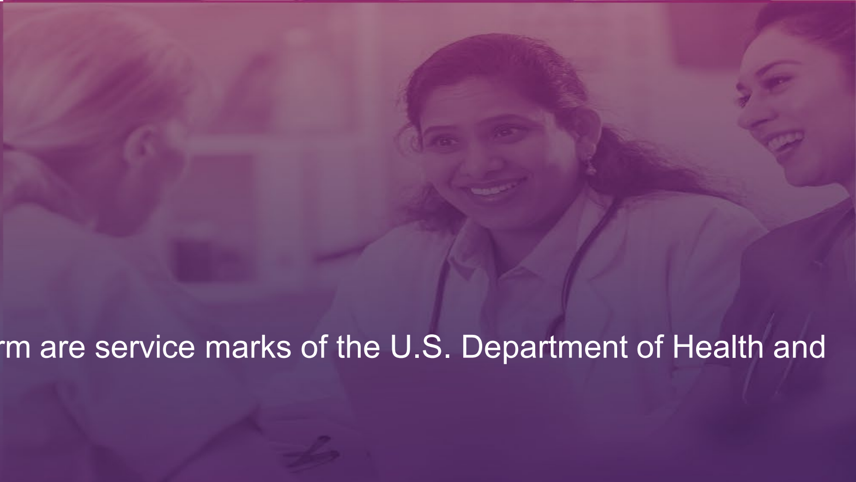
Program Director
OPPP, NINDS

5/23/23

NIH National Institutes of Health
HEAL Initiative

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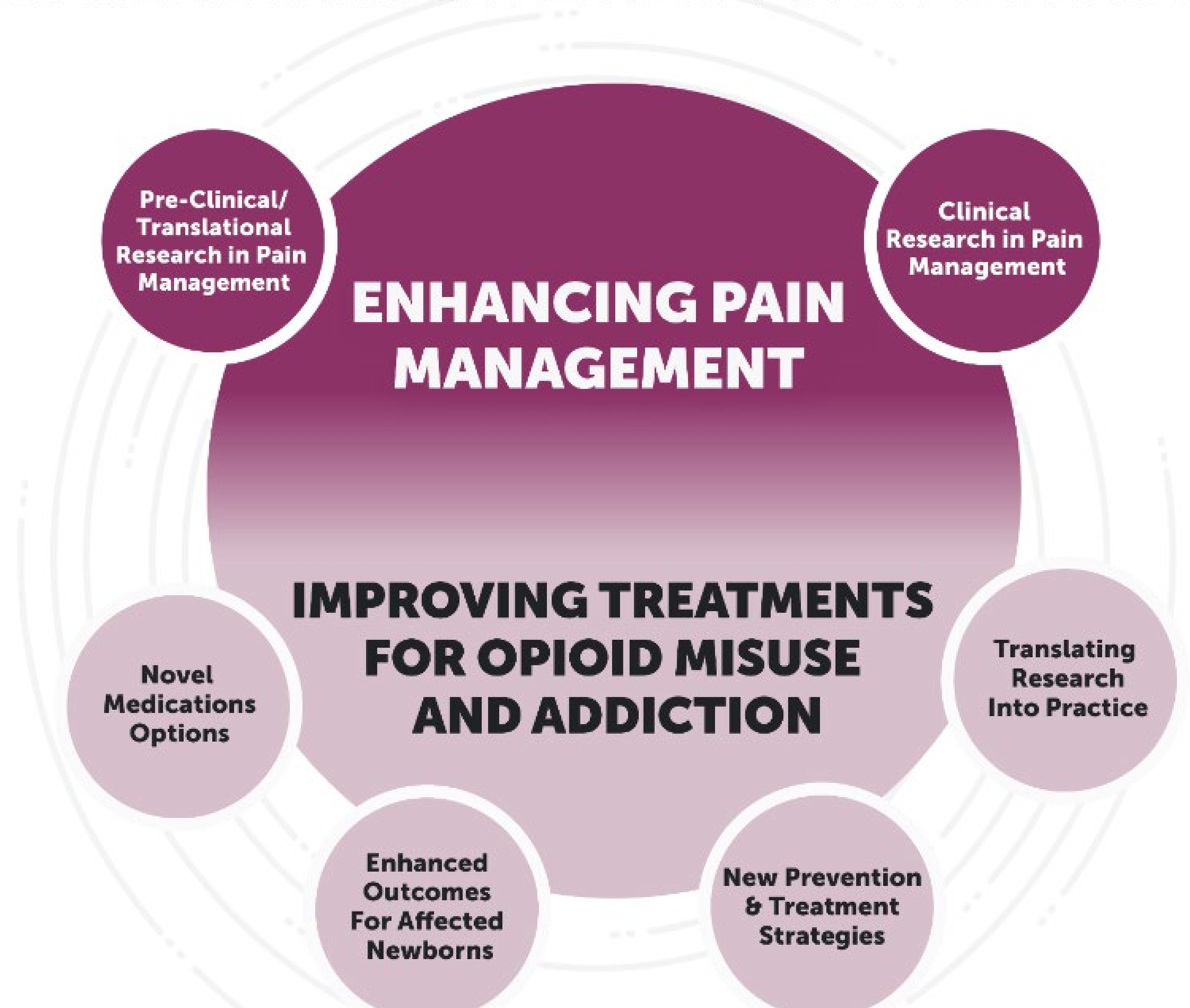

NIH HEAL INITIATIVE RESEARCH OVERVIEW
Pre-Clinical/ Translational Research in Pain Management
Clinical Research in Pain Management
ENHANCING PAIN MANAGEMENT
IMPROVING TREATMENTS FOR OPIOID MISUSE AND ADDICTION
Novel Medications Options
Translating Research Into Practice
Enhanced Outcomes For Affected Newborns
New Prevention & Treatment Strategies

Reaching People in Multiple Languages

- 1 in 5 people in the U.S. speaks a language other than English at home.
- Approximately 60 percent speak English very well, and about 40 percent have limited English proficiency.[1]
- Language can be a barrier to health literacy and participation in research.
- People with limited English proficiency may be unable to read, understand health information, or to have a conversation with healthcare professionals/RAs in English.
- Providing information in ways that people can understand is an important part of reducing health disparities and increasing access to care.

NIH HEAL Initiative

- HEAL is encouraging PIs/studies to:
  - Enroll participants at percentages that represent the US population
  - Recruit participants in the language(s) in which they are most comfortable engaging
- If a study includes a second or third language, then PIs are encouraged to use the same protocols

HEALs efforts in this space

- HEAL OD has implemented an enrollment system where POs assess and track enrollment numbers
- HEAL has translated the core common data elements into Spanish and are encouraging PIs to share other languages with HEAL
- HEAL has funded multiple diversity grants that, for example:
  - Translated apps and protocols into Spanish
  - Hire translators or RAs who can facilitate engagement of participants where English is not their primary language
  - Hire coordinators to help increase recruitment and retention of underrepresented participants

CORE CDEs

- **Core Common Data Elements (CDE)s**: a minimal and defined set of patient report outcome screening tools for each pain domain that all HEAL pain clinical trials are required to collect.

- Core CDEs were released on 1/14/20

- Core Demographics were re-released and made CDISC compliant on 3/16/20

- **Core Spanish case report forms (CRFs) were released on 9/10/21**

Core – Adult CDEs

Adult Acute Pain*

Pain Intensity	Pain Interference	Physical Functioning/ QOL	Sleep	Pain Catastrophizing	Depression	Anxiety	Global Satisfaction with Treatment	Substance Use Screener
BPI Pain Severity	BPI Pain Interference	PROMIS Physical Functioning Short Form 6b	PROMIS Sleep Disturbance 6a + Sleep Duration Question	Pain Catastrophizing Scale – Short Form 6	PHQ-2	GAD-2	PGIC	TAPS 1

Adult Chronic Pain*

Pain Intensity	Pain Interference	Physical Functioning/ QOL	Sleep	Pain Catastrophizing	Depression	Anxiety	Global Satisfaction with Treatment	Substance Use Screener
PEG		PROMIS Physical Functioning Short Form 6b	PROMIS Sleep Disturbance 6a + Sleep Duration Question	Pain Catastrophizing Scale – Short Form 6	PHQ-2	GAD-2	PGIC	TAPS 1

*Questions are required to be asked at two time points
*Monitoring opioid use will be required by HEAL, however, the method by which it will be assessed is still pending. PIs will be asked to monitor opioid use (including dosage) by appropriate PRO, EHR, or other measures.

Core – Pediatric CDEs

Pediatric Acute and Chronic Pain*

	Pain Intensity	Pain Interference	Physical Functioning / QOL	Sleep	Pain Catastrophizing	Depression	Anxiety	Global Satisfaction with Treatment	Substance Use Screener
Child	BPI Pain Severity	BPI Pain Interference	PedsQL Inventory	AWS + Sleep Duration Items	Pain Catastrophizing Scale for Children	PHQ-2	GAD-2	PGIC	NIDA Modified Assist Tool - 2
Parent					Pain Catastrophizing	PHQ-2	GAD-2		

*Questions are required to be asked at two time points
*Monitoring opioid use will be required by HEAL, however, the method by which it will be assessed is still pending. PIs will be asked to monitor opioid use (including dosage) by appropriate PRO, EHR, or other measures.

Core Demographics (Adult and Pediatric)

- Date of Birth
- Age
- Sex at Birth
- Gender Identity
- Ethnicity, Race
- Zip Code
- Highest Level of Education
- Employment Status
- Relationship Status
- Annual Household Income
- Application for Disability Insurance
- Pain Duration
- RUCA Code (based on Zip code)

*Demographics are, for the most part, CDISC compliant

Languages being used within the clinical pain portion of HEAL

Language	Number of Studies
Japanese	1
Korean	1
Simplified Chinese	22
Spanish	22
Swedish	1
Traditional Chinese	1

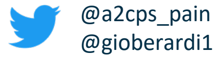
21% of the supplemental CRFs have been translated into Spanish

Questions?

Please feel free to contact me: Laura.Wandner@nih.gov

Reference

1. Ryan, C. (2013, August). *Language use in the United States: 2011.* American Community Survey Reports. Washington, DC: U.S. Census Bureau. Retrieved from https://www.census.gov/prod/2013pubs/acs-22.pdf



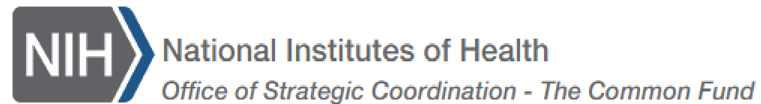
A2CPS

Acute to Chronic Pain Signatures

Acute to Chronic Pain Signatures Consortium: Implementation of Spanish Speaking Materials in a Multicenter Study

Berardi, Giovanni; Sluka, Kathleen A.; Frey-Law, Laura; Coffey, Christopher; Bayman, Emine; Ecklund, Dixie; Vance, Carol GT; Dailey Dana, Wager, Tor; Lindquist, Martin; Kahn, Ari; Ford, James; Jung, Heejung; Burns, John; McCarthy, Robert; Jacobs, Joshua; Buvanendran, Asokumar; Brummett, Chad; Clauw, Dan; Chang, Andrew; Waljee, Jennifer; Harris, Richard; Williams, David; Harte, Steven; Olivier, Michael; Langefeld, Carl D.; Howard, Timothy D.; Jepsen, Kristen; Laurent, Louise; Fisch, Kathleen; Jacobs, Jon; Qian, Weiji; Lokshin Anna; Saterlee, John; Labosky, Patricia; Sankar, Cheryse; Porter, Linda; Wandner, Laura; **A2CPS Consortium**

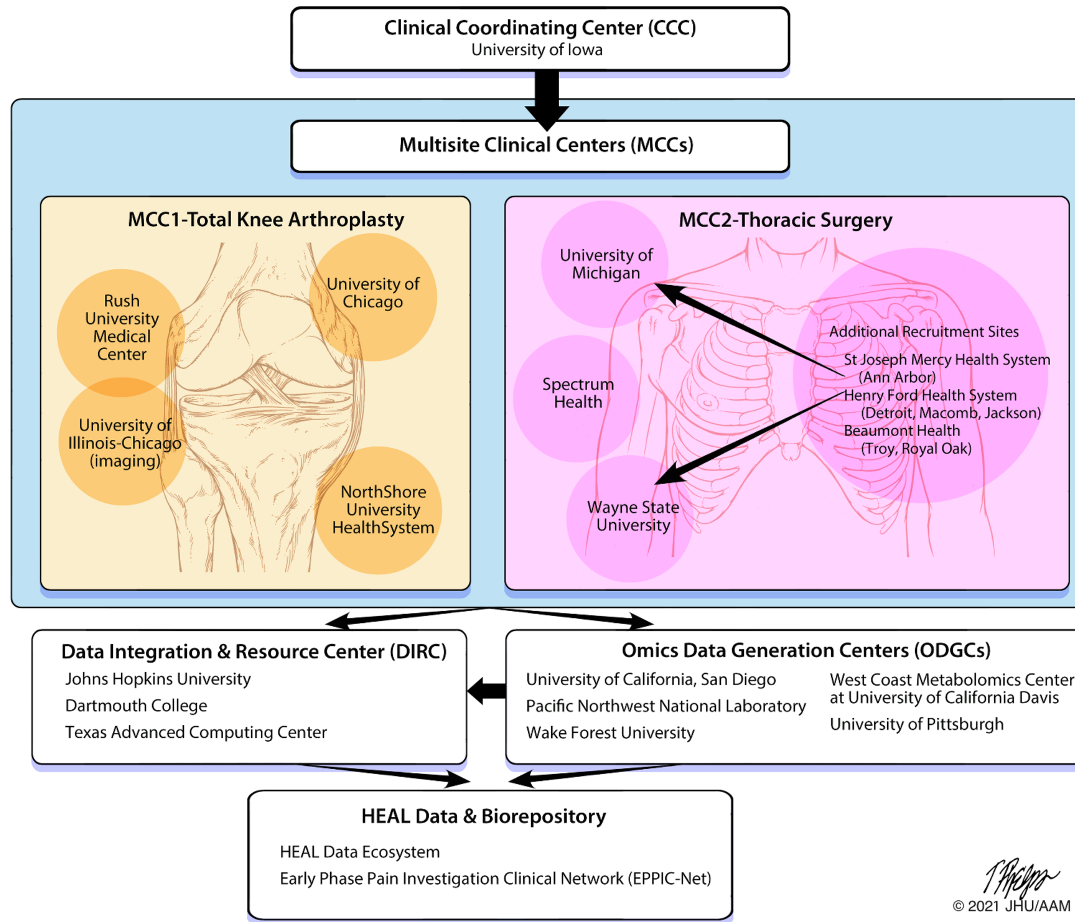
Giovanni Berardi, PT, DPT, PhD, OCS
Postdoctoral Research Scholar
Neurobiology of Pain Laboratory
Department of Physical Therapy & Rehabilitation Science

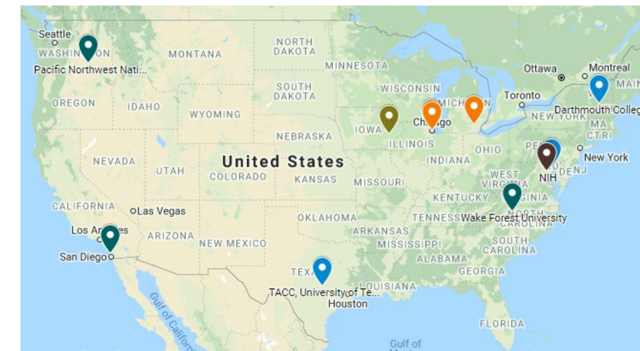


Goal

- Identify biomarkers and their collective biosignatures (a combination of several individual biomarkers) that predict susceptibility or resilience to the development of chronic pain after an acute pain event.
- Cohorts Selected
  - Knee replacement & thoracotomy

A2CPS





Objectives

- Considerations prior to initiating multilingual research
- A2CPS approach

Identifying the correct language for your audience

Aim to make your message sound natural to people living in your target locale.

- When you must reach a wide audience of speakers originating in different locales, a non-localized, neutral variant is the most practical.
- When targeting a highly specific audience, consider a localized message that includes regional nuance.

A good translation agency will help you pinpoint the right form of _____ for your audience.

Spanish

- Spoken by over a half-billion people
- Official language of 20 countries
- U.S. has the 2nd to 4th largest Spanish-speaking population in the world
- Different written and spoken variants, and it may be difficult to determine which form is best for your audience.
- Which form of Spanish is best?

Considerations for multilingual studies

- Regulatory
  - What are your institutional requirements
  - Institutional vs Central IRB requirements
    - Some CIRBs may require input of the local institution
- Same vs Different Protocols

Site Manual of Procedures

Acute to Chronic Pain Signatures Program (A2CPS)

MOP Version: 3.0

July 2022

This MOP coincides with Protocol Number: 7.0 (May 2022)

Which language services do you need?

Translation Services

- Cost & Time determined by word count
- A2CPS Initial Costs: $7,000
  - 41 separate items (recruitment materials, ICFs, surveys, emails, instructions)
- Additional translations: $1,610
  - ICFs revised three times
- Forward translation vs forward and backward translation
- Notarized Certification to IRB

Translation Services

- Which materials to translate?
  - Informed Consent Document
    - Each site
    - Recurrent cost
  - Recruitment Documents
  - All participant facing materials (Pain NRS)
  - Any standardized instructions
  - Surveys / PROs
    - NIH HEAL Common Data Elements
  - Digital interface (REDCap, MyDataHelps)

A2CPS

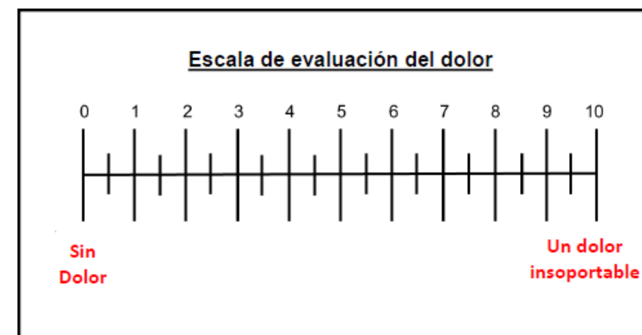
Verbal Pain Rating Scale Instruction

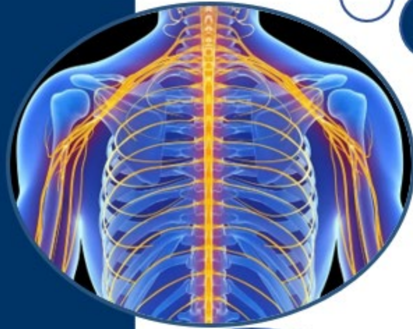
This pain rating scale will be used with each QST assessment. Describe use of the scale with each participant with the following script prior to starting QST assessments.

[Show the participant the large-scale format of the pain rating scale when providing instruction.]

Script (show the scale to the participant as you read the script)

- *Esta es la escala de 0 a 10 que usamos para evaluar el nivel de dolor que siente en diferentes momentos durante la prueba de hoy.*
- *Cero (0) en el extremo izquierdo significa que no tiene dolor y 10, en el extremo derecho, significa que tiene dolor insoportable.*
- *Quiero que use esta escala para decirme cuánto dolor siente. Cuando le pregunte, dígame el número que mejor corresponda a su nivel de dolor, usando números medios o enteros.*





Lo invitamos a participar en un estudio para personas que tienen programada una cirugía de tórax.

DOCUMENTO DE CONSENTIMIENTO INFORMADO

Título del Proyecto: Programa de firmas de dolor agudo a crónico (A2CPS)

Este formulario de consentimiento describe el estudio de investigación para ayudarlo a decidir si quiere participar. Este formulario da información importante sobre lo que se le pedirá que haga durante el estudio, sobre los riesgos y beneficios del estudio, y sobre sus derechos como sujeto de investigación.

- Si tiene alguna pregunta sobre el formulario o no entiende algo del mismo, pida más información al equipo de investigación.
- Debe hablar de su participación con cualquier persona que elija, como familiares o amigos.
- No acepte participar en este estudio, a menos que el equipo de investigación haya respondido sus preguntas, y usted decida que quiere ser parte del mismo.

¿CUÁL ES EL PROPÓSITO DE ESTE ESTUDIO?

Este es un estudio de investigación. Lo estamos invitando a participar en este estudio de investigación porque tiene una cirugía de tórax programada.

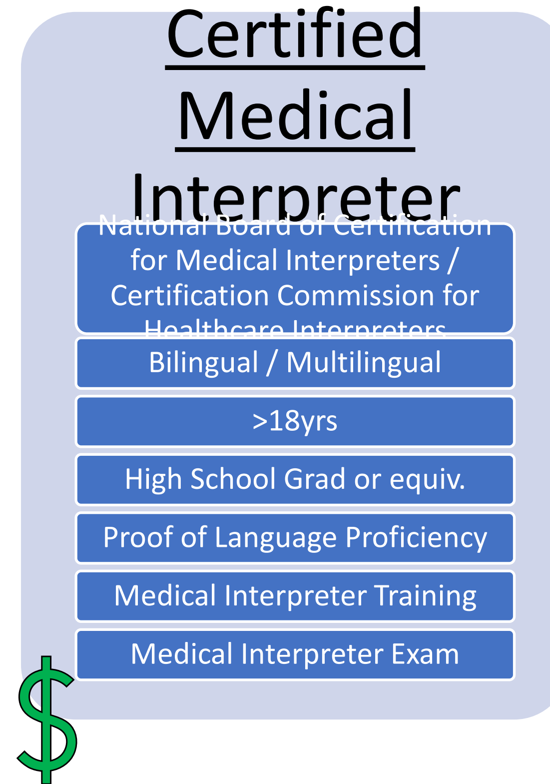
El propósito de este estudio de investigación es identificar los factores asociados con la recuperación del dolor en comparación con el dolor persistente después de una cirugía de tórax.

Time & effort for integration in your data collection system

- REDCap & MyDataHelps introduced a Multi-Language Management module
  - A framework to create and display multiple languages for surveys, forms, and communications with participants
  - Streamline research conducted in multiple languages
  - **Does Not** translate content or check for accuracy
  - Language Preference Survey
  - Upload each CRF, survey, automated communications, etc.

A2CPS

Interpreter Services



Medical Translator

- Institutional requirements
- Bilingual / Multilingual
- Language Proficiency Test and/or Medical Translator Certification
- **Spanish speaking only may not be appropriate or sufficient**

Interpreter Services – Costs & Training

Certified Medical Interpreter

$

On-Demand services

- Phone
- Live video

$1.50/min
$1.75/min
$2.00/min

$

Scheduled Services

- Phone
- Live video

$1.75/min
$1.75/min
$90-120/hr

Partnering With and Accessing An Interpreter

LanguageLine Solutions®

Partnering with Your LanguageLine Solutions® Interpreter to Ensure Effective Communication

TO ACCESS A PHONE INTERPRETER:	
Client Name:	UIowa Dept. of Physical Therapy & Rehab Science
Dial:	(866) 874-3972
Provide:	Client ID number, which is
Indicate:	Language Needed
Provide:	Access Code, which is

1 **STARTING THE SESSION**

- Allow the interpreter to start the session by giving you their name and Interpreter ID. Document this information for reference.
- Introduce yourself to the interpreter.
- Brief the interpreter and state the goal of the session and provide any specific instructions.
- Introduce yourself and the interpreter to the limited English proficient, Deaf, or Hard-of-Hearing individual.

2 **DURING THE SESSION**

- Address the limited English proficient, Deaf, or Hard-of-Hearing individual, not the interpreter. The interpreter will be your voice. Keep in mind that everything stated will be interpreted.
- State information in short, concise sentences. When stating complicated or detailed information, speak at a slow pace and pause often. This allows the interpreter to note, retain, and relay the information. The interpreter may sometimes ask for repetitions or clarification.
- Avoid technical jargon and try to explain specialized terms or concepts.
- Avoid interrupting the interpreter or talking at the same time.
- Do not ask interpreters for their opinion.

3 **ENDING THE SESSION**

- Ask the limited English proficient, Deaf or Hard-of-Hearing individual if they understood, or if they have any questions or concerns.
- Allow the interpreter to interpret everything before ending the session.

FOR MORE INFORMATION

A2CPS Implementation Strategy & Challenges

- Initiated with few sites with greatest demographic representation
  - Option to expand
- Implemented translated documents & interpreter services
  - First 6mo → services used for 3 participants
  - Additional Spanish speaking participants with Language Preference Survey = English
    - Relying on family members
    - Need to consider computer/tech proficiency and availability

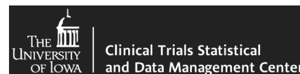
Lessons Learned

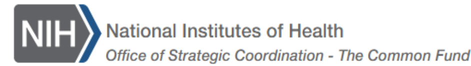
- Implement Spanish enrollment with a clinic or community champion of similar ethnicity and/or race
  - NIH Supplement – focus on increasing recruitment from diverse populations
    - Phase 1
      - focus groups (patients & caregivers) of diverse individuals to seek their feedback and suggestions
      - open ended interviews identify barriers and facilitators to recruitment into the A2CPS protocol
    - Phase 2
      - Place navigators in clinical settings to enhance information provided to Spanish speakers and other diverse populations

Acknowledgments

A2CPS Consortium

- CCC collaborators
  - Kathleen Sluka, PT, PhD, FAPTA
  - Laura Frey-Law, PT, PhD
  - Christopher Coffey, PhD
  - Emine Bayman, PhD
  - Carol GT Vance, PT, PhD
  - Dana Dailey, PT, PhD
  - Vince Magnotta, PhD
  - Dixie Ecklund, RN, MSN, MBA
  - Tina Neill-Hudson, BBA
  - Maggie Spencer, MA
  - Candy Wilson, BS
  - Zackary Lemka, MA





- Clinical Coordinating Center (UO1NS077179)
- Data Integration and Resource Center (UO1NS077352)
- Omics Data Generation Centers (U54DA049116, U54DA049115, U54DA09113)
- MCC 1 (UM1NS112874)
- MCC 2 (UM1NS118922)
- Postdoctoral training [GB] (U24NS112873-03S2)

Diversity in an Acupuncture Trial

Raymond Teets, MD
Institute for Family Health and Icahn School of Medicine at Mount Sinai
rteets@institute.org

Embedding research in an FQHC

Acknowledgements

- IFH Team
  - Matt Beyrouty MPA; Project Manager
  - Donna Mah DACM, MSW; Intervention Clinics Director
  - Arya Nielsen PhD; Design Consultant
  - Phoebe Rosenheim MPH; Lead CRC
  - Estefhany Soto Cossio MD; CRC
  - Research Acupuncturist Team
  - IFH Clinical Colleagues
  - HEAL Study Collaborators

Back in Action (BIA) Trial

- HEAL* funded BIA Trial
  - Multicenter: Institute for Family Health (IFH), Kaiser Permanente (WA, No. CA) and Sutter Pragmatic trial, re: acupuncture effectiveness and safety in adults ≥ 65 years old
  - Chronic lower back pain (cLBP) diagnosis
    - *HEAL = Helping Ease Addiction Long-Term, NIH funded initiative
- 3-arm trial
  - Standard acupuncture (SA) up to 15 sessions over 90-day period
  - Enhanced acupuncture (EA) adds 6 more sessions in second 90-day period
  - Control group of Usual Care (UC)
  - IFH *n* = *123*

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Back In Action at IFH

- IFH is a Federally Qualified Health Center (FQHC)
  - Serving under-represented community, including Spanish-speaking patients
  - Recruitment & Intervention through urban clinical sites in Brooklyn, Manhattan & Bronx
    - 2 family medicine residencies
    - 8 Recruitment sites
    - 3 intervention sites by area of NYC
  - Use of EPICCare® EMR
  - IFH NYC Spanish-speaking patients 15.6%
- Need to include Spanish-speaking participants
- ‘Lean’ Research Administration at IFH

Spanish-speaking participants

- Access issue of Spanish language
  - Cultural issues specific to ethnicity
  - Technical aspects of translation
- Issues germane to IFH Spanish-speaking patients as under-represented groups
  - Historical marginalization
  - Access issues around socioeconomic status
  - Outreach difficulties
    - NYC inconsistencies of mail delivery
    - Less frequent email use
  - Incentive specific issues – Clincards® used
  - Less formal education

Punchline: We were successful ☺

Primary language (*n* = 124*)		
English	87	70%
Spanish	36	29%
*One person withdrew and asked personal info not be included		
Ethnicity		
Hispanic or Latino	46	37%
Not Hispanic or Latino	51	41%

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IFH Participant demographics

Sex (assigned at birth)		
Female	89	72%
Male	34	28%
Race (can choose multiple)		
Black or African American	49	38%
White	30	23%
Other	41	32%

Socioeconomic measures

Income		
Less than $10,000	28	23%
$10,000--- $24,999	29	24%
$25,000--- $34,999	12	10%
$35,000--- $49,999	10	8%
$50,000--- $74,999	8	7%
Don’t know	28	23%
Insurance		
Medicaid	63	52%
Medicare	23	19%
Private	31	25%

How to Research Underrepresented Populations at IFH

- Short answer: leverage clinical operations resources
  - Use trust (mindfully) of clinical milieu
  - Normalize the research intervention
  - Communications with clinical ops colleagues
- Impact on recruitment and intervention
- Labor intensive Issues of administrative / design and post intervention assessment
- Close collaboration with Diversity Supplement Team

Administration & Design

- IRB
  - Central IRB (Kaiser Northern California)
    - Significant number of documents to handle with 4 sites and some necessary local divergences
    - Delays where Spanish language docs couldn't be submitted til English docs approved, this was done sequentially
- Database builds – have to account for Spanish speaking
- Assessments need to be in Spanish
- Personnel
  - IFH CRCs speak Spanish
  - Spanish/English bi-lingual staff not present at all participant-facing domains in study so special workflows created to manage post-enrollment study interaction
- Cost of labor highest at this phase

Recruitment: leverage clinical ops

- Recruitment
  - Begin recruitment out of clinical setting with referral from participant's (often Spanish-speaking) provider
  - IT built report to identify all eligible patients per day throughout institution → roughly 10-20 per day
  - In "real time" with research prompts concurrent to patient appointment, via email and EMR
    - EPIC inbasket: same-day reminders to clinicians
      - Research parameters & patient eligibility
    - Best Practice Alerts (BPA) set up as second reminder
    - One click = referral to Clinical Research Coordinator (CRC)
      - CRC has EPIC access and makes outreach call
  - CRC can circle back to clinician to let them know if not eligible or other issues via EPIC
  - CRCs who speak Spanish ideally needed for recruitment (especially given all phone activity)

Intervention

Acupuncture appointments scheduled in EPIC

- Separate department to avoid scheduling and billing issues
- Arrivals through normal clinical operations
- Very important in managing separate intervention arms

Acupuncture offered at or in proximity to Patient Participant's Home Medical Clinic

- "Pop up" clinic set up in conference rooms with massage tables for affordability
- Translation services available during intervention if acu doesn't speak Spanish

Acupuncture intervention documented in EMR

- Specific template built by IT, within research guidelines
- Data capture seamlessly exported for collection with Research Coordinating Center
- Intervention transparency: notes viewable in patient's chart

Follow Up & Assessments

- Coordinating Center does assessments
  - Spanish-speakers needed
  - Management of different area code and call centers
  - Reminder calls important
- Follow-up / troubleshooting
  - Collaboration needed between CC and IFH for Spanish-speakers
    - Incentive management with Clincards®
    - Any other troubleshooting
    - Mindful around handoffs between teams

Successes!

Research embedded in Electronic Medical Record

BPA's and reminders for recruitment accepted by colleagues

Rate of recruitment of eligible participants variable but roughly 17-20%

Met recruitment goal of 123 by projected date

Good diversity

Spanish speaking participants 30%

Low no show rate for intervention (10%)

Appointments and Attendance within standard clinical flow

Good relationship around physical plant

Low impact on clinical operations

Data sharing with CC fine

The end

And to our colleagues…

Diversidad en la Investigación de Ensayos Clínicos (DCTR)

SUPLEMENTO NIH HEAL para el ensayo Back in Action

Eve Walter, PhD, El Instituto para la Salud de la Familia, Escuela de Medicina Icahn en Mount Sinai, AllianceChicago

Mirta Milanés, MPH, El Instituto para la Salud de la Familia, Escuela de Medicina Icahn en Mount Sinai

SCT
SOCIETY FOR CLINICAL TRIALS

Diversity in Clinical Trials Research (DCTR)

NIH HEAL SUPPLEMENT for Back in Action trial

Eve Walter, PhD, Institute for Family Health, Mount Sinai School of Medicine, AllianceChicago

Mirta Milanes, MPH, Institute for Family Health, Mount Sinai School of Medicine

Divulgaciones

- No Divulgaciones Relevantes

Disclosures

- No Relevant Disclosures

Diversidad en la investigación de ensayos clínicos (DCTR)
SUPLEMENTO DE NIH a BIA HEAL TRIAL

Las minorías étnicas tienen menos probabilidades de participar y, por lo tanto, están subrepresentadas en una gran proporción de la investigación de ensayos clínicos.

Los participantes de color corren un mayor riesgo de perder el seguimiento debido a problemas con el transporte, las finanzas, las responsabilidades de trabajo/cuidado infantil, la falta de confianza o satisfacción con el estudio, y la incomprensión del compromiso involucrado.

Los pacientes que se identifican como hispanos/latinos experimentan más barreras, incluido el conocimiento de los ensayos clínicos, las barreras del idioma, y las creencias culturales.

Diversity in clinical trial research (DCTR) NIH SUPPLEMENT to BIA HEAL TRIAL

Ethnic minorities are less likely to participate and are therefore underrepresented in a large proportion of clinical trial research.

Participants of color are at greater risk for lost to follow-up due to issues with transportation, finances, work/child care responsibilities, lack of trust or satisfaction with the study, and misunderstanding of the commitment involved.

Patients identifying as Hispanic/Latino experience further barriers, including awareness of clinical trials, language barriers, and cultural beliefs.

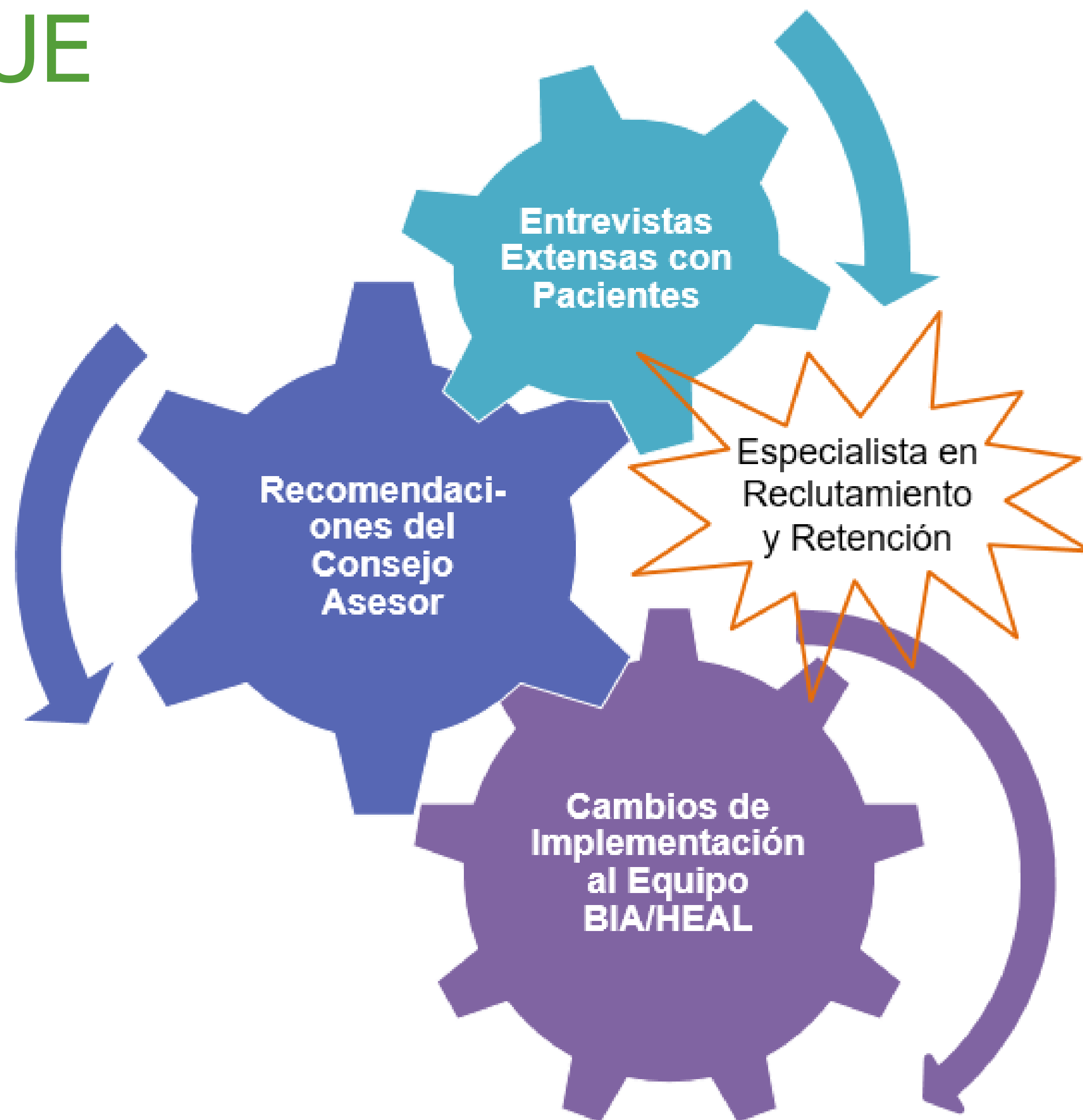
La inclusión del Instituto para la Salud de la Familia fue intencional para aumentar la diversidad en el ensayo clínico multicéntrico.

- Varios meses de retraso en el reclutamiento de pacientes hispanos/latinos debido a la falta de un guión de reclutamiento en español pre-aprobado.
- Las encuestas de seguimiento en español no fueron aprobadas a tiempo.

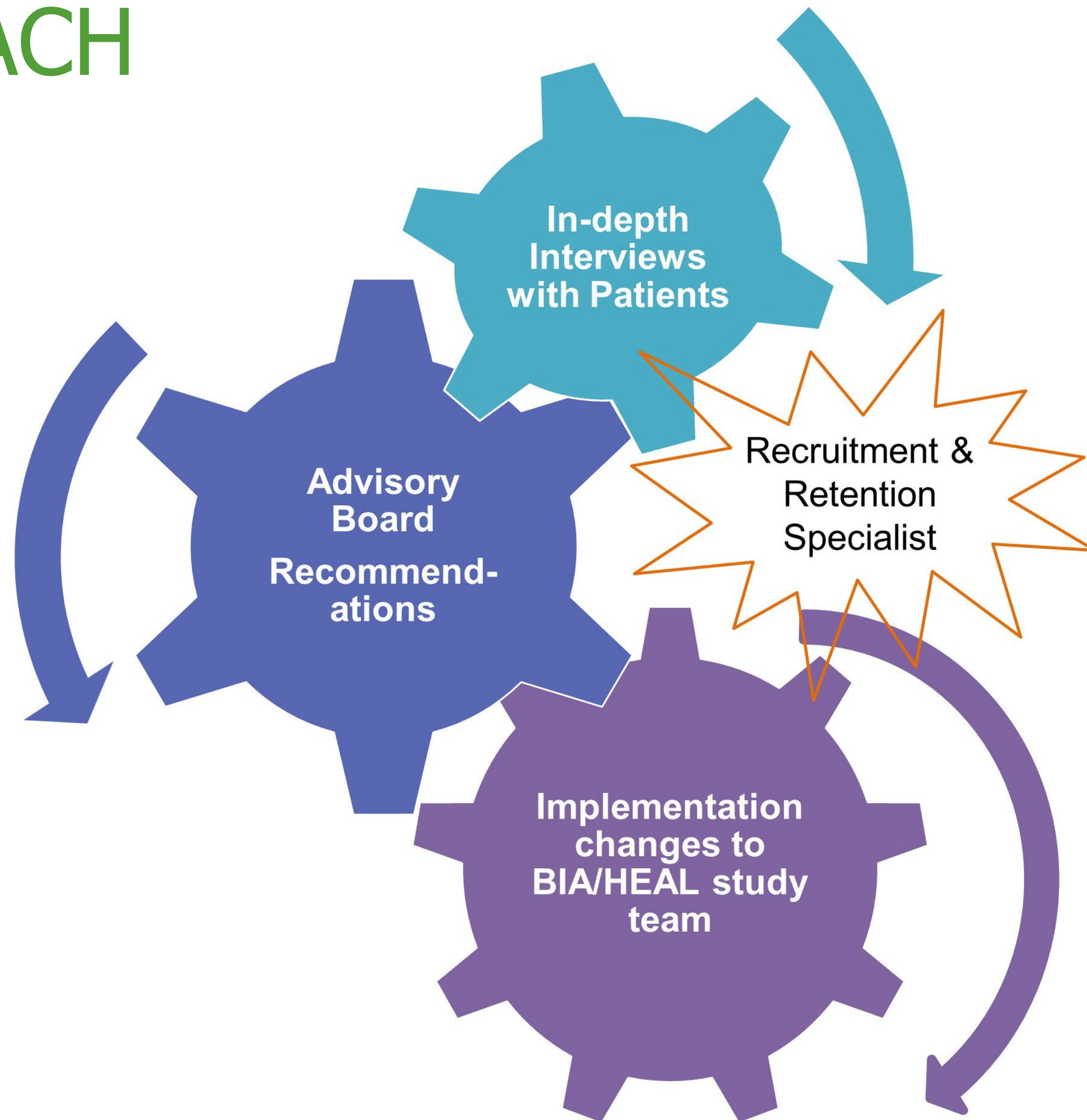
Inclusion of the Institute for Family Health was intentional to increase diversity in the multi-site clinical trial.

- Several month delay in recruiting Hispanic/Latino patients due to no pre-approved Spanish recruitment script.
- Spanish follow-up surveys were not approved on time.

ENFOQUE



APPROACH



Algunas Lecciones Aprendidas

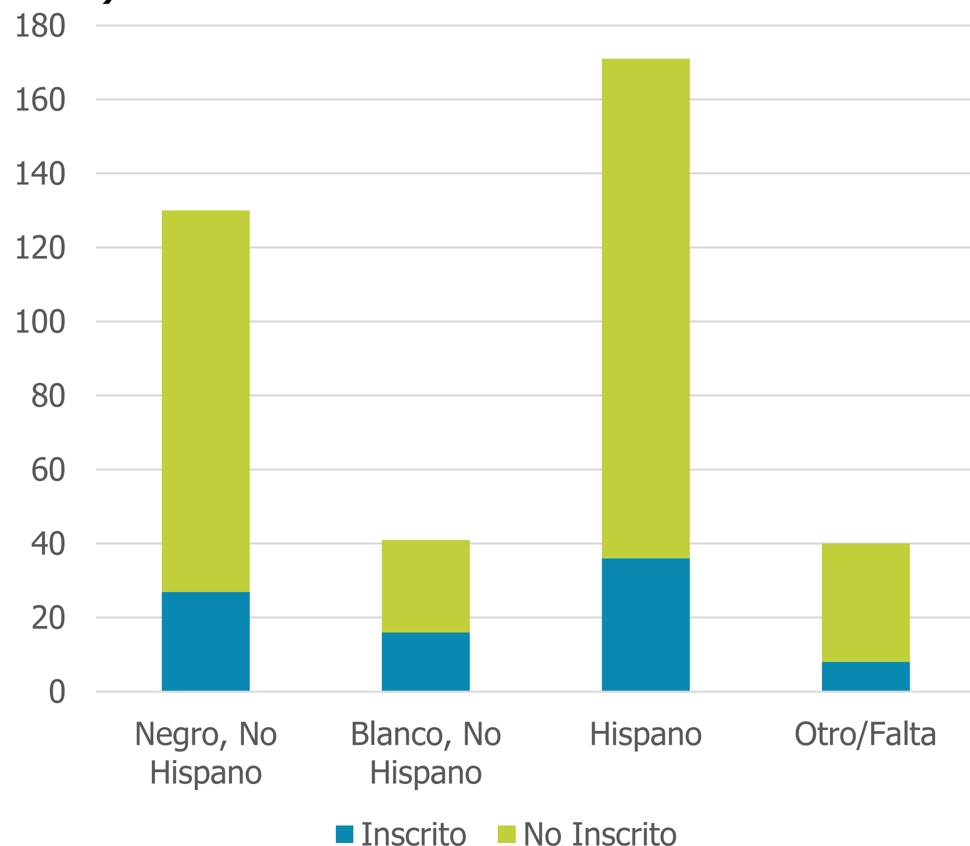
Problemas Identificados	Soluciones
• Los guiones para clínicos solo estaban en inglés. • La mayoría de los pacientes no entienden que decir que están "interesados" a su médicos no significaba que lo estábamos inscribiendo.	• Proveer un guión en español para los médicos que están introduciendo el estudio a los pacientes hispanohablantes. • Cambiar el lenguaje sobre el reclutamiento clínico de RME de "interesado" (sugiriendo interés en estar en el estudio) a "interesado en aprender más"
• Pacientes sintiendo molestias o no experimentan beneficios del tratamiento, pero no los discuten con los investigadores/médicos • Las demandas familiares de los pacientes tienen prioridad	• Aumentar entrenamiento para aquellos que brindan la intervención clínica para iniciar discusiones sobre molestias y la respuesta. • Aumentar entrenamiento para el alcance para incluir un lenguaje culturalmente apropiado y centrado en el paciente, para empatizar y apoyar al paciente a través de estas demandas.

Some Lessons Learned

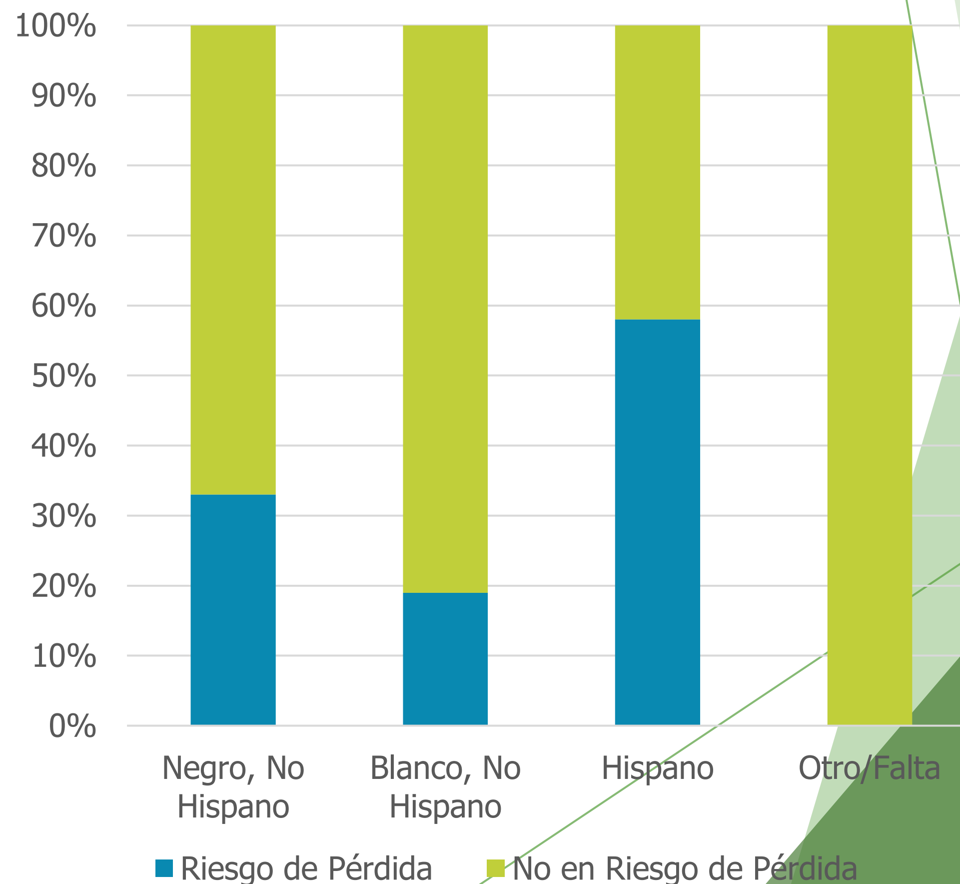
Issues Identified	Solutions
• Clinician scripts were only in English. • Most patients do not understand that saying they are "interested" to their clinician did not mean enrolling them.	• Provide a Spanish script for clinicians who are introducing the study to Spanish-speaking patients. • Change the language on the clinical EHR recruitment from "interested" (suggesting interested in being in the study) to "interested in learning more"
• Patients feeling discomfort or experiencing no benefits from the treatment but are not discussing these with researchers/clinicians • Patients' family demands take precedence	• Enhanced training to those providing the clinical intervention to initiate discussions about discomfort and response. • Enhanced training for outreach to include culturally appropriate, patient-centered language to empathize and support patient through these demands.

Barreras Continuas

Mientras más hispanos/latinos fueron identificados como elegibles, tuvieron la tasa más baja (21%) de inscripción (p = 0.05)

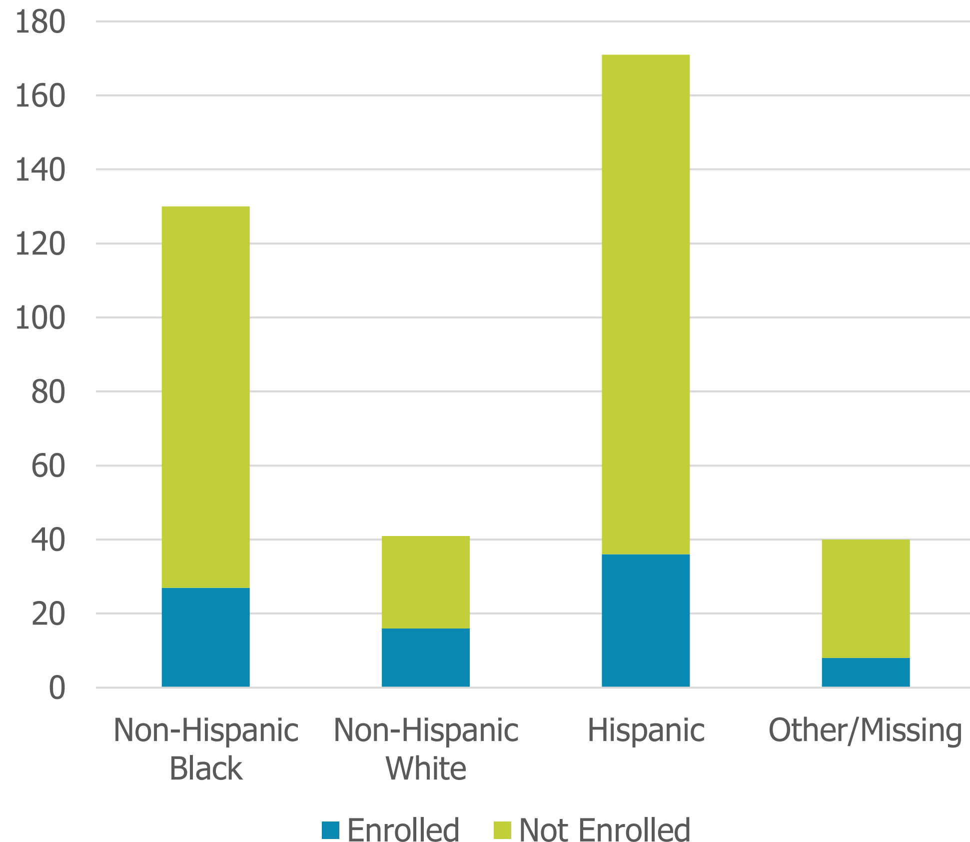


Los hispanos/latinos también tuvieron el mayor riesgo de pérdida de seguimiento (p = 0.01)

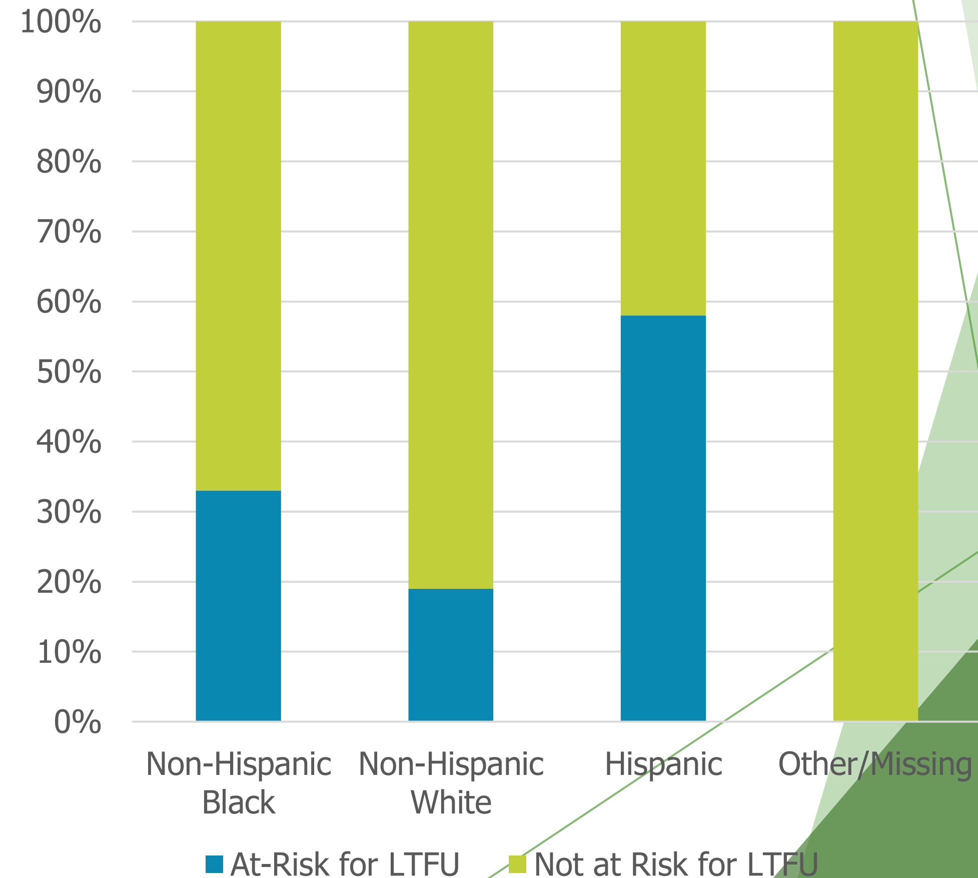


Continued Barriers

While more Hispanic/Latinos were identified as eligible they had the lowest rate (21%) of enrollment (p=0.05)



Hispanic/Latinos also had the greatest risk for loss-to follow up (p=0.01)



Pasos Futuros

- Asegurar la participación de los hispanos/latinos en el equipo del estudio al inicio
  - Abordar las barreras culturales y educativas
  - Asegurar invitaciones, reclutamiento, guiones, encuestas, etc. en español antes de la implementación
  - Asegurar que un hispanohablante los implemente a los pacientes que identifican el español como su primer idioma
- Utilizar el respeto por los médicos por parte de las poblaciones hispanas/latinas para mejorar el reclutamiento y la retención
- Identificar las barreras y brindar apoyo centrado en el paciente durante todo el estudio.

Future Steps

- Assure Hispanic/Latino engagement in study team at initiation
  - Address cultural and educational barriers
  - Assure Spanish invitations, recruitment, scripts, surveys etc. prior to implementation
  - Assure a Spanish-speaker implements these to patient who identify Spanish as their first language
- Utilize the respect for clinicians by Hispanic/Latino populations to improve recruitment and retention
- Identify barriers and provide patient-centered support throughout the study.

Lessons Learned on Increasing Diversity and Inclusion in Clinical Trials: a KALPAS Case Study

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Disclosures

- No Relevant Disclosures

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Study Background

20%

Postoperative patients develop chronic postsurgical pain

high → **association**

Chronic Opioid Use & Dependence

Multimodal Analgesia

Acetaminophen, NSAIDs, and anti-neuropathic agents

mild-moderate → **efficacy**

Preventing CPSP

KALPAS

Ketamine Analgesia for Long-lasting Pain relief After Surgery (KALPAS)

Post-mastectomy Pain Syndrome (PMPS)

Incidence	3 mos, any pain	3 mos, pain >=4	6 mos, any pain	6 mos, pain>=4
% (95% CI)	68% (65, 71)	25% (21, 29)	63% (60, 66)	19% (17, 21)

Women are:

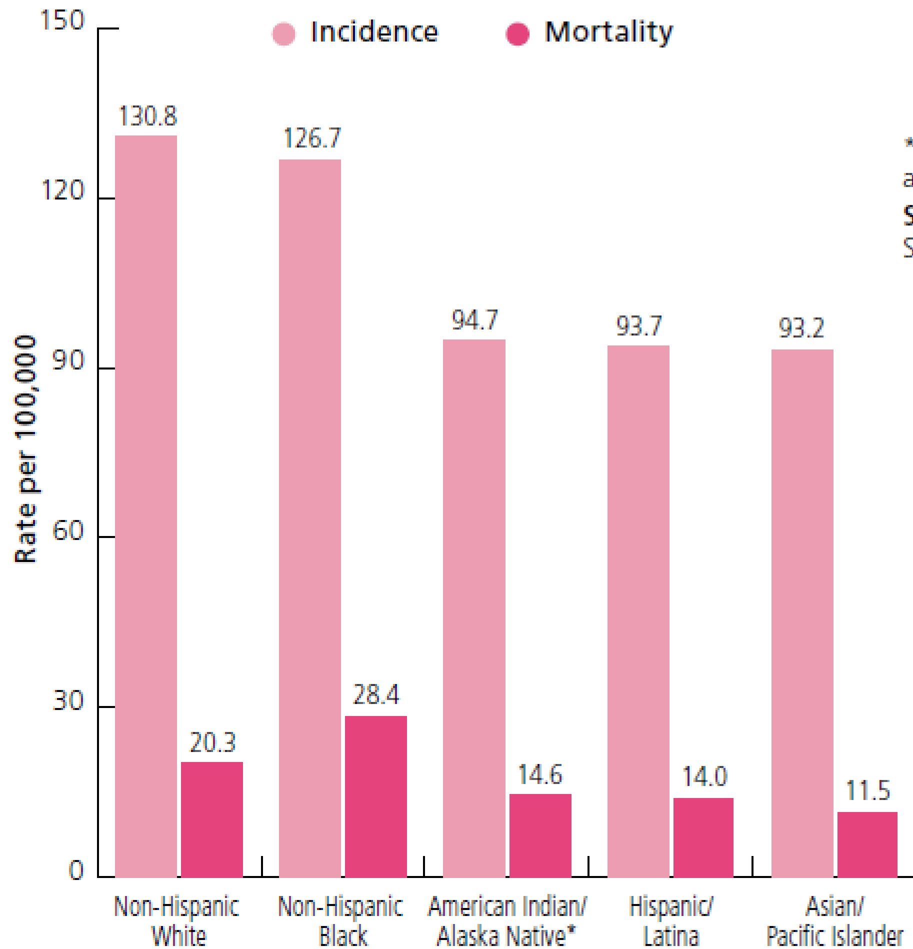
- More likely to experience chronic pain
- Under-represented in pain studies

Women of color are:

- Disproportionally affected by PMPS
- Traditionally under-enrolled and under-represented in pain studies

Miaskowski et al, 2012; Karmakar et al, 2014; Andersen et al, 2015; Spivey et la, 2018; Kang et al, 2020

Epidemiology



*Statistics based on data from PRCDA counties. Note: Rates are per 100,000 and age adjusted to the 2000 US standard population.

Sources: Incidence – NAACCR, 2019. Mortality – National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, 2019.

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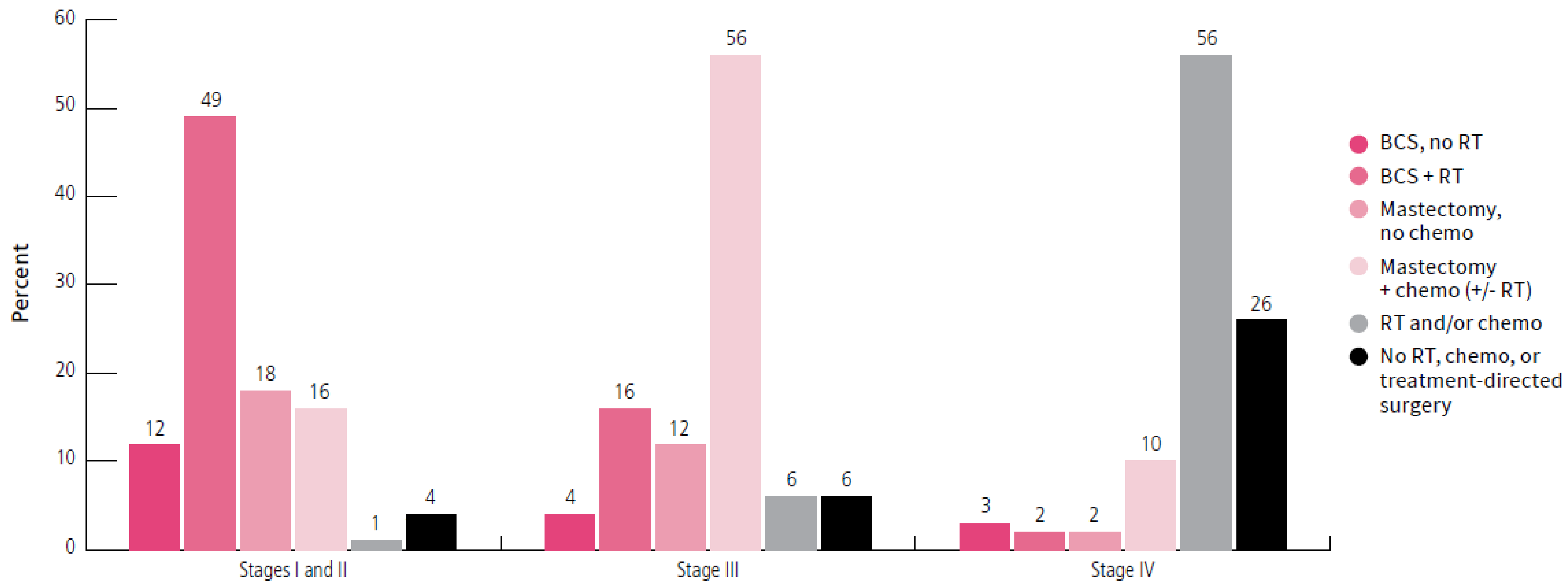
https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf

Treatment Options by Stage

Figure 12. Female Breast Cancer Treatment Patterns (%), by Stage, US, 2016



BCS = breast-conserving surgery; RT = radiation therapy; Chemo = chemotherapy and includes targeted therapy and immunotherapy.

Source: National Cancer Data Base, 2016 as provided in *Cancer Treatment & Survivorship Facts & Figures 2019-2021*.

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https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf

Study Rationale: Risk Factors

Known risk factors for acute → chronic pain transition

Acute Pain

Anxiety

Depressed Mood

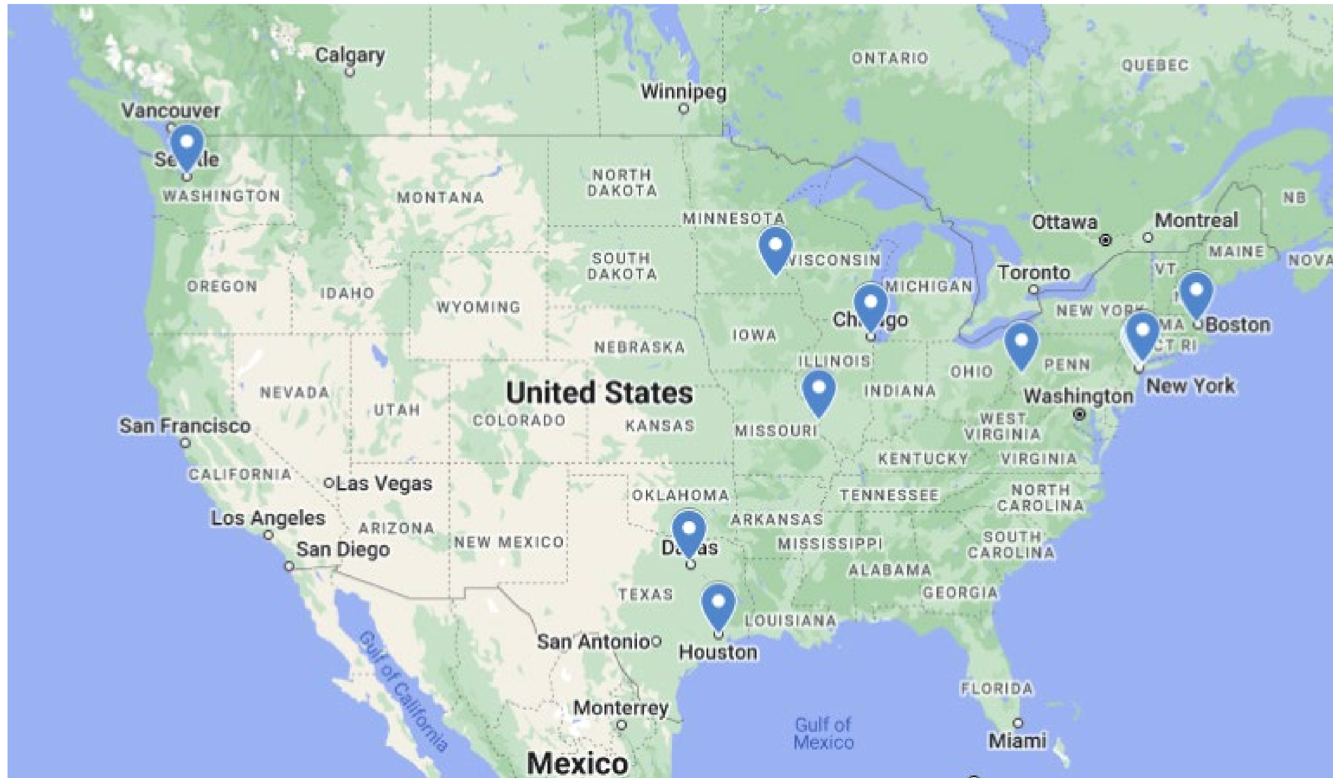
Ketamine: a non-opioid analgesic and antidepressant

KALPAS

Ketamine Analgesia for Long-lasting Pain relief After Surgery (KALPAS)

Protocol Synopsis

- Multi-site, double blind, 3-arm randomized control trial (RCT)
- Target Enrollment: 750 Patients *(n=250 subjects per arm)*



KALPAS

Ketamine Analgesia for Long-lasting Pain relief After Surgery (KALPAS)

Outcomes

Primary Outcomes
Brief Pain Inventory (BPI) Severity ***(3 Months)***

Secondary Outcomes
(1) Brief Pain Inventory (BPI) *(pain severity and interference scores)*
(2) Breast Cancer Pain Questionnaire (BCPQ)
(3) PROMIS anxiety and depression

Tertiary Outcomes		
Pain	***Function***	***Mood***
PROMIS neuropathic scale	PROMIS physical function	Pain Catastrophizing Scale
	PROMIS fatigue	TAPS
	PROMIS sleep disturbance	

KALPAS
Ketamine Analgesia for Long-lasting Pain relief After Surgery (KALPAS)

Race/Ethnicity in KALPAS

Race	Met Inclusion Criteria (n=1116)	Actual Enrollment (n=195)
American Indian/Alaskan Native	4 (0.4%)	0 (0%)
Asian	78 (7%)	15 (7.7%)
Hawaiian/Pacific Islander	2 (0.2%)	1 (0.5%)
Black	131 (11.7%)	13 (6.7%)
White	770 (69%)	152 (77.9%)
Other/unknown	131 (11.7%)	14 (7.2%)

Ethnicity	Met Inclusion Criteria (n=1116)	Actual Enrollment (n=195)
Non-Hispanic	1013 (90.8%)	171 (87.7%)
Hispanic	95 (8.5%)	18 (9.2%)
Other/not reported	8 (0.7%)	6 (3.1%)

Language in KALPAS

Primary Language	Met Inclusion Criteria (n=1116)	Actual Enrollment (n=195)
English	1043 (93.5%)	192 (98.4%)
Spanish	26 (2.3%)	3 (1.5%)
Other	47 (4.2%)	N/A

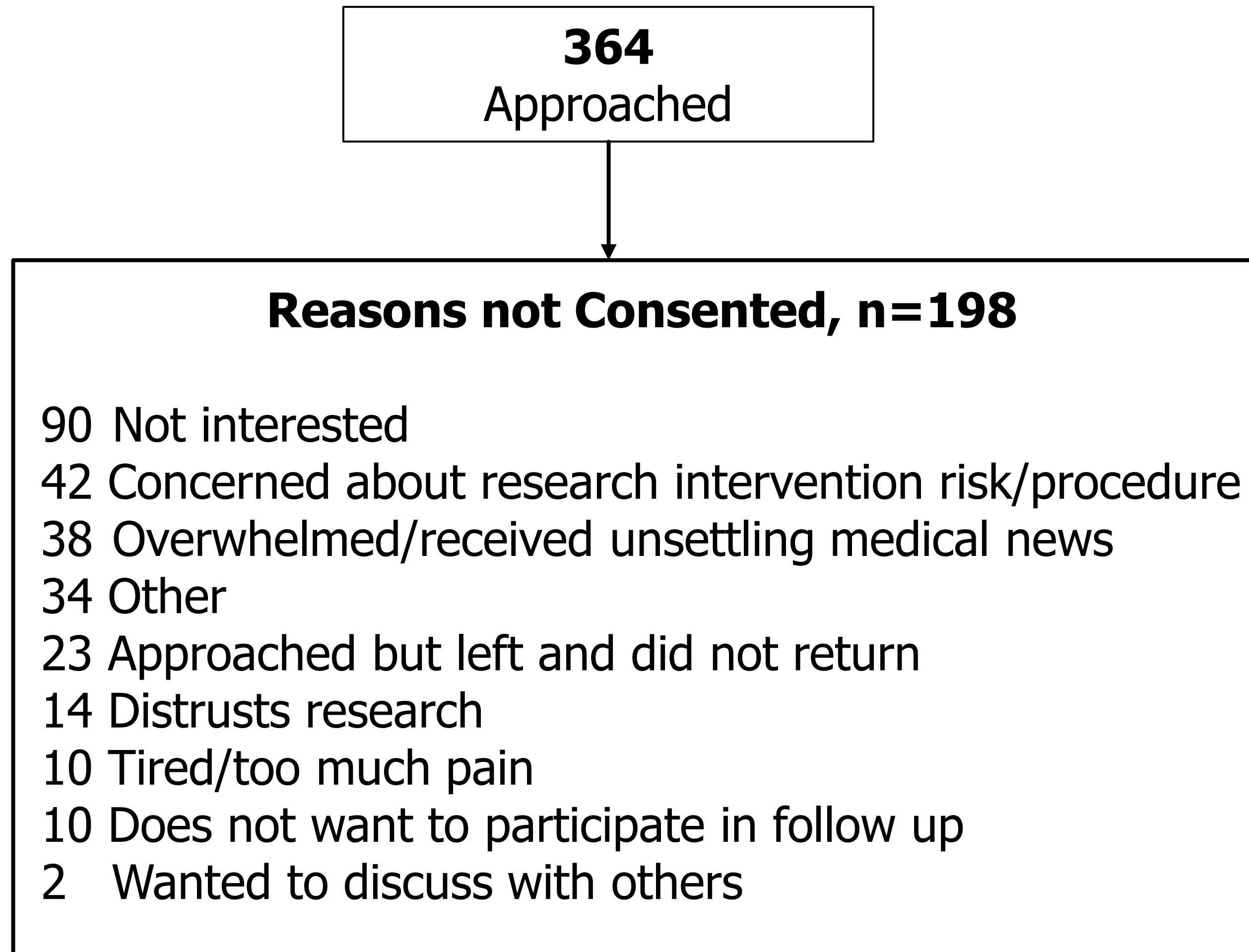
Barriers at the Study Level

- Recruitment of Spanish-speaking participants and the cost of translation and interpreter services were not originally included in our proposal, budget, or recruitment strategy
- Not all English version questionnaires are available in other languages
- Spanish database did not go live until a later date than the English database

Barriers at the Site Level

- 6/16 sites opted not to recruit Spanish speaking participants
  - Low Spanish speaking population
  - Lack of funds for interpreter services

Other Barriers



Note: some may have more than one reason for not consenting

Strategies to Bolster Enrollment Among Minority or Historically Underrepresented Populations

- Supplemental funding for Spanish interpreter services and increased site payments (did not receive)
- Perform site evaluation assessments, including demographics of patient population, when selecting sites for a multicenter study
- Ensure that screening process includes collection of pertinent demographic information, reasons for declining participation, and exclusions met

Strategies

- Adjust eligibility criteria
  - Currently, BMI > 35 kg/m^2 is excluded
  - Of 417 ineligible patients, 139 (33%) were excluded due to BMI > 35.
    - Of these, 22% Black and 19% Hispanic
- Will modify protocol to increase threshold to BMI > 40 kg/m^2
  - Will track whether this change is associated with more diverse accrual

Recommendations for Future Studies

- Budget
  - Licensing fees
  - Translation of questionnaires
  - Funds for interpreter services
- Site selection
- Cultivate study team members who may be representative of and/or speak language of target population

Bibliography

- Andersen KG, et al. Predictive factors for the development of persistent pain after breast cancer surgery. Pain 2015;156:2413-2422.
- Kang C, et al. Effects of intraoperative low-dose ketamine on persistent postsurgical pain after breast cancer surgery: a prospective randomized, controlled, double-blind study. Pain Physician 2020;23:37-47.
- Karmakar MK et al. Thoracic paravertebral block and its effects on chronic pain and health-related quality of life after modified radical mastectomy. Reg Anesth Pain Med 2014;39:289-98.
- Kummerow KL, et al. Nationwide trends in mastectomy for early-stage breast cancer. JAMA Surg 2015;150:9-16.
- Miaskowski C, et al. Identification of patient subgroups and risk factors for persistent breast pain following breast cancer surgery. J Pain 2012;13:1172-87.
- Spivey TL, et al. Chronic pain after breast surgery: a prospective, observational study. Ann Surg Oncol 2018;25:2917-2924.
- https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf

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  - Brigham and Women's
  - Columbia
  - UPMC Magee-Women's Hospital
  - Mayo Clinic
  - MD Anderson
  - MetroHealth
  - Memorial Sloan Kettering Cancer Center
  - Rush
  - Washington University
  - University of Arkansas
  - University of Alabama
  - University of Texas Southwestern
  - University of Washington