

# **SEQUENTIAL AND COMPARATIVE EVALUATION OF PAIN TREATMENT EFFECTIVENESS RESPONSE (THE SCEPTER TRIAL)**

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# **VA COOPERATIVE STUDIES** **PROGRAM PRIMER**



**VETERANS HEALTH ADMIN**  
**Office of Research &  
Development**

**Biomedical  
Laboratory  
R&D**

**Clinical  
Science  
R&D**

**Health  
Services  
R&D**

**Rehabilitation  
R&D**

**Cooperative Studies  
Program**

# COOPERATIVE STUDY

- **Facilitates recruitment of patients sufficiently large to provide definitive answer to a research question**
- **Characteristics include:**
  - **investigators from 2 or more sites (e.g., VAMCs)**
  - **agreement to study a research question in a uniform manner**
  - **use a common protocol and central coordination**

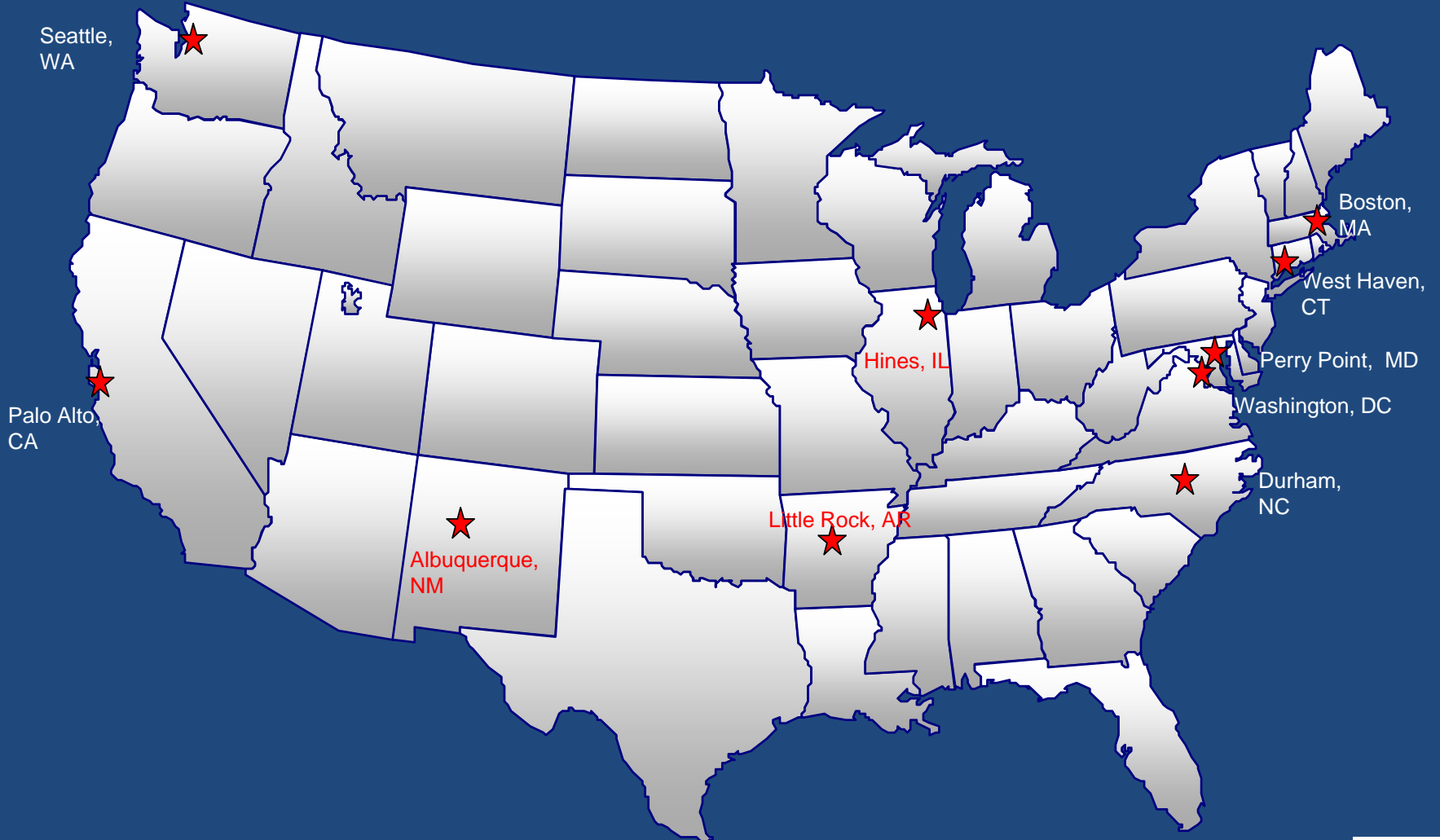
# **VA COOPERATIVE STUDIES PROGRAM**

- **National infrastructure for sponsoring, developing & executing:**
  - **Multi-site clinical trials**
  - **Epidemiological & population research**
  - **Genomic medicine research**

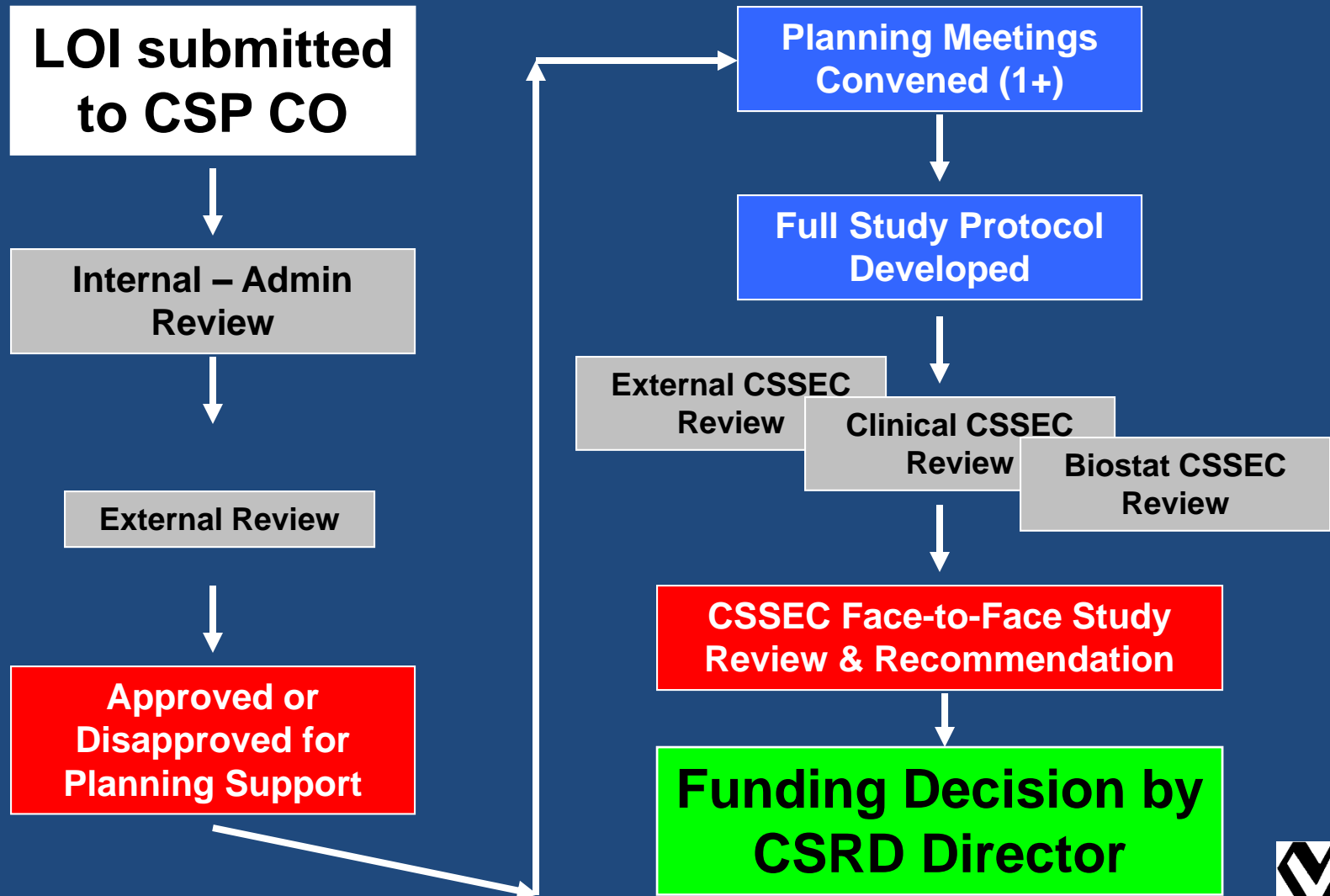
# CSP ROLES

- **CSP provides central coordination & policies for conducting multi-site clinical research studies**
- **Biostatistical / epidemiological expertise**
- **Clinical expertise**
- **Safety and regulatory oversight**
- **Health economics expertise**
- **Pharmaceutical management**
- **Clinical research project & fiscal management**

# CSP CENTER LOCATIONS



# CSP SCIENTIFIC REVIEW PROCESS





# **CSP STUDY PLANNING TEAM**

- **Principal Proponents**
- **Study Biostatistician**
- **Clinical Research Pharmacist**
- **Health Economist**
- **Subject matter experts**
- **Project managers**
- **Data managers**
- **CSP Coordinating Center Director**

# **SCEPTER (Sequential and Comparative Evaluation of Pain Treatment Effectiveness Response)**

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CSP #2009

# Why study chronic low back pain?

- **Chronic low back pain is common**
- **Enormous economic burden**
- **Most common cause of disability**

# Low back pain is common

- ~ 20% of US population develops yearly
- 2nd most common symptom leading to MD visits
- ~ 80% of population will have LBP at some time in their lives; recurrence is common
- The prevalence of chronic low back pain is increasing:
  - 10.2% (Increased from 3.9% in 1992) Freburger et al., JAMA Int. Med., 2009

# Low back pain is common in Veterans

- **CLBP in ~ 50% of veterans with chronic pain**
- **# of Veterans w/ CLBP is growing**  
(Sinnott & Wagner, 2009)

# Chronic low back pain is costly

- **Costs > \$100 billion per year in the US**
  - Evaluations and treatments
  - Compensation payments
  - Lost productivity
  
- **Costs for spine pain treatment increasing more rapidly than overall healthcare costs** (Martin et al. JAMA, 2008)
  
- **One of most costly conditions in the VA** (Yu et al., Med. Care Res. Rev., 2003)

# Chronic low back pain is disabling

- **2010 Global Burden of Disease Study: CLBP is most common cause of disability in world**
- **In the US**
  - **Disability rates related to spine pain are increasing**

# Optimal Approach for Treating Chronic Low Back Pain?

- **Options – Many!**
  - Medications
  - Injections
  - Physical
  - Psychological
  - Surgery
  - Complementary
- **Evidence for individual approaches**
  - Many publications, but often of limited quality
  - Limited time frames
  - “Efficacy” rather than “Effectiveness”
- **Optimal treatment sequence is undefined**



# Chronic Low Back Pain Treatment Guideline

- Chou et al. Ann Intern Med. 2007;147(7):478-491
- Authors suggest self-care, NSAIDs, acetaminophen first
- No order for other therapies suggested

	Low Back Pain Duration	Acute < 4 Weeks	Subacute or Chronic > 4 Weeks
Self-care	Advice to remain active	•	•
	Books, handout	•	•
	Application of superficial heat	•	
Pharmacologic therapy	Acetaminophen	•	•
	NSAIDs	•	•
	Skeletal muscle relaxants	•	
	Antidepressants (TCA)		•
	Benzodiazepines	•	•
	Tramadol, opioids	•	•
Nonpharmacologic therapy	Spinal manipulation	•	•
	Exercise therapy		•
	Massage		•
	Acupuncture		•
	Yoga		•
	Cognitive-behavioral therapy		•
	Progressive relaxation		•
	Intensive interdisciplinary rehabilitation		•

# Recent guideline and recommended treatments

	Acute low back pain (<6 weeks)	Persistent low back pain (>12 weeks)
<b>Education and self-care</b>		
Advice to remain active	First-line treatment, consider for routine use	First-line treatment, consider for routine use
Education	First-line treatment, consider for routine use	First-line treatment, consider for routine use
Superficial heat	Second-line or adjunctive treatment option	Insufficient evidence
<b>Non-pharmacological therapy</b>		
Exercise therapy	Limited use in selected patients	First-line treatment, consider for routine use
Cognitive behavioural therapy	Limited use in selected patients	First-line treatment, consider for routine use
Spinal manipulation	Second-line or adjunctive treatment option	Second-line or adjunctive treatment option
Massage	Second-line or adjunctive treatment option	Second-line or adjunctive treatment option
Acupuncture	Second-line or adjunctive treatment option	Second-line or adjunctive treatment option
Yoga	Insufficient evidence	Second-line or adjunctive treatment option
Mindfulness-based stress reduction	Insufficient evidence	Second-line or adjunctive treatment option
Interdisciplinary rehabilitation	Insufficient evidence	Second-line or adjunctive treatment option

# Pharmacological therapy

Pharmacological therapy		
Paracetamol	Not recommended	Not recommended
Non-steroidal anti-inflammatory drugs	Second-line or adjunctive treatment option	Second-line or adjunctive treatment option
Skeletal muscle relaxants	Limited use in selected patients	Insufficient evidence
Selective norepinephrine reuptake inhibitors	Insufficient evidence	Second-line or adjunctive treatment option
Antiseizure medications	Insufficient evidence	Role uncertain
Opioids	Limited use in selected patients, use with caution	Limited use in selected patients, use with caution
Systemic glucocorticoids	Not recommended	Not recommended

# Interventional therapies & surgery

## Interventional therapies

Epidural glucocorticoid injection (for herniated disc with radiculopathy)	Not recommended	Limited use in selected patients
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## Surgery

Discectomy (for herniated disc with radiculopathy)	Insufficient evidence	Second-line or adjunctive treatment option
Laminectomy (for symptomatic spinal stenosis)	Insufficient evidence	Second-line or adjunctive treatment option
Spinal fusion (for non-radicular low back pain with degenerative disc findings)	Insufficient evidence	Role uncertain

# Chronic Low Back Pain Treatment Guidelines

- **Lancet (Foster et al., 2018)**
  - **Combined ACP (2017), Danish (2018), UK (2016) guidelines**

	<u>First Line</u>	<u>Second line</u>
<b>Ed/Self-Care</b>	Advice, Education	
<b>Non-Pharm</b>	Exercise, CBT	Spinal Man., Massage, Acupuncture, Yoga, Mindfulness
<b>Pharmacological</b>		NSAIDs, SNRIs
<b>Interventional</b>		Epidural (Limited)
<b>Surgery</b>		Disc/Lami (Limited)

# VA/DoD Guidelines (2017)

## “Recommend”

## “Suggest”

Self-Care

Education/Activity

Multi-component self-mgt.

Non-Pharm

CBT

Exercise, Spinal Manip, Yoga,  
Acup., Mindfulness

Pharm

NSAIDS

SNRIs

Other

“Team Approach”  
Physical Component +  
Psych/Occ/Social

# Pilot Survey

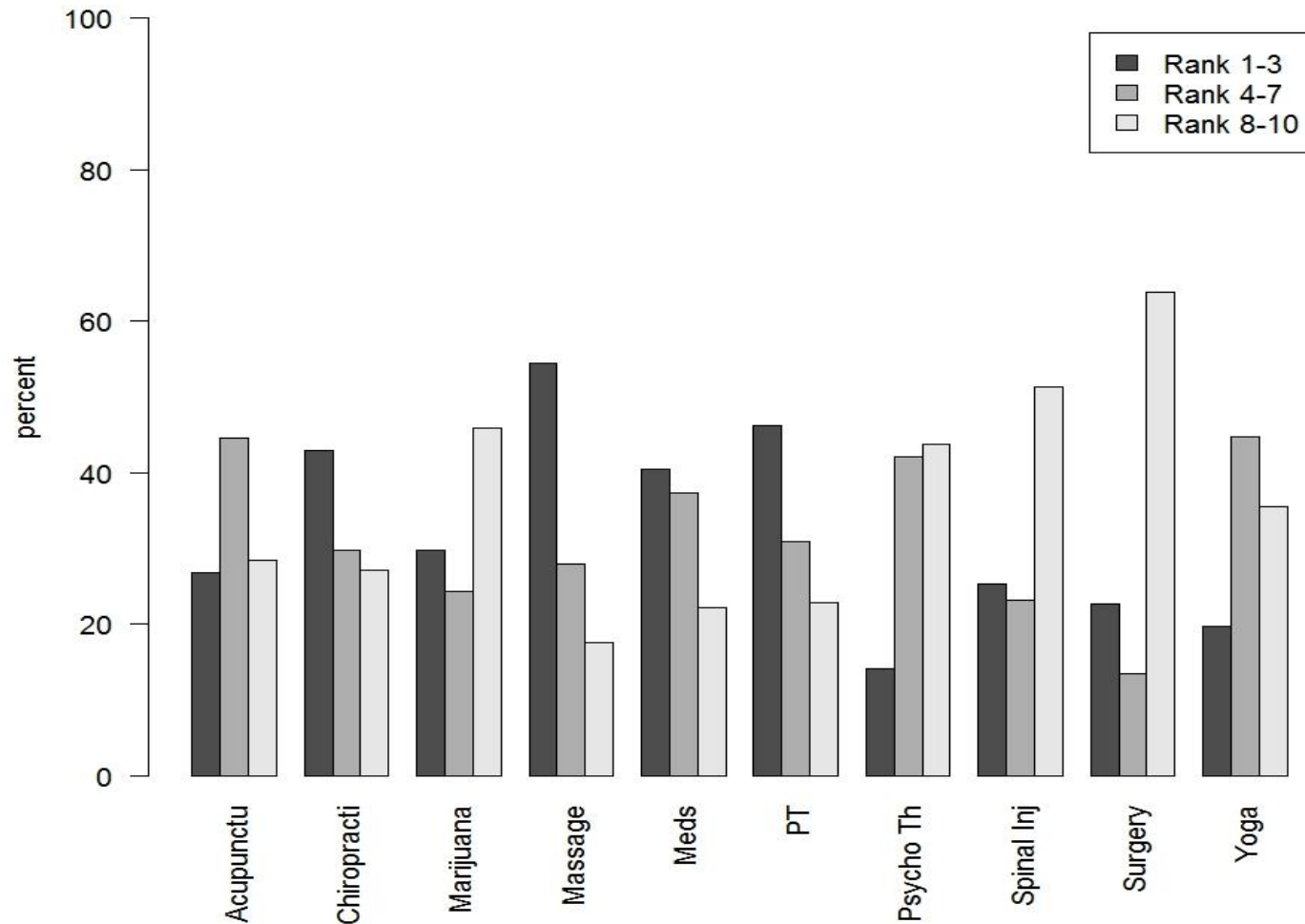
- **5 sites (Indy, Ann Arbor, Palo Alto, San Diego, and West Haven)**
- **1000 surveys sent to Veterans with ICD10 code for chronic low back pain**
- **Received 228 surveys back (22.8% response rate)**

# Key findings

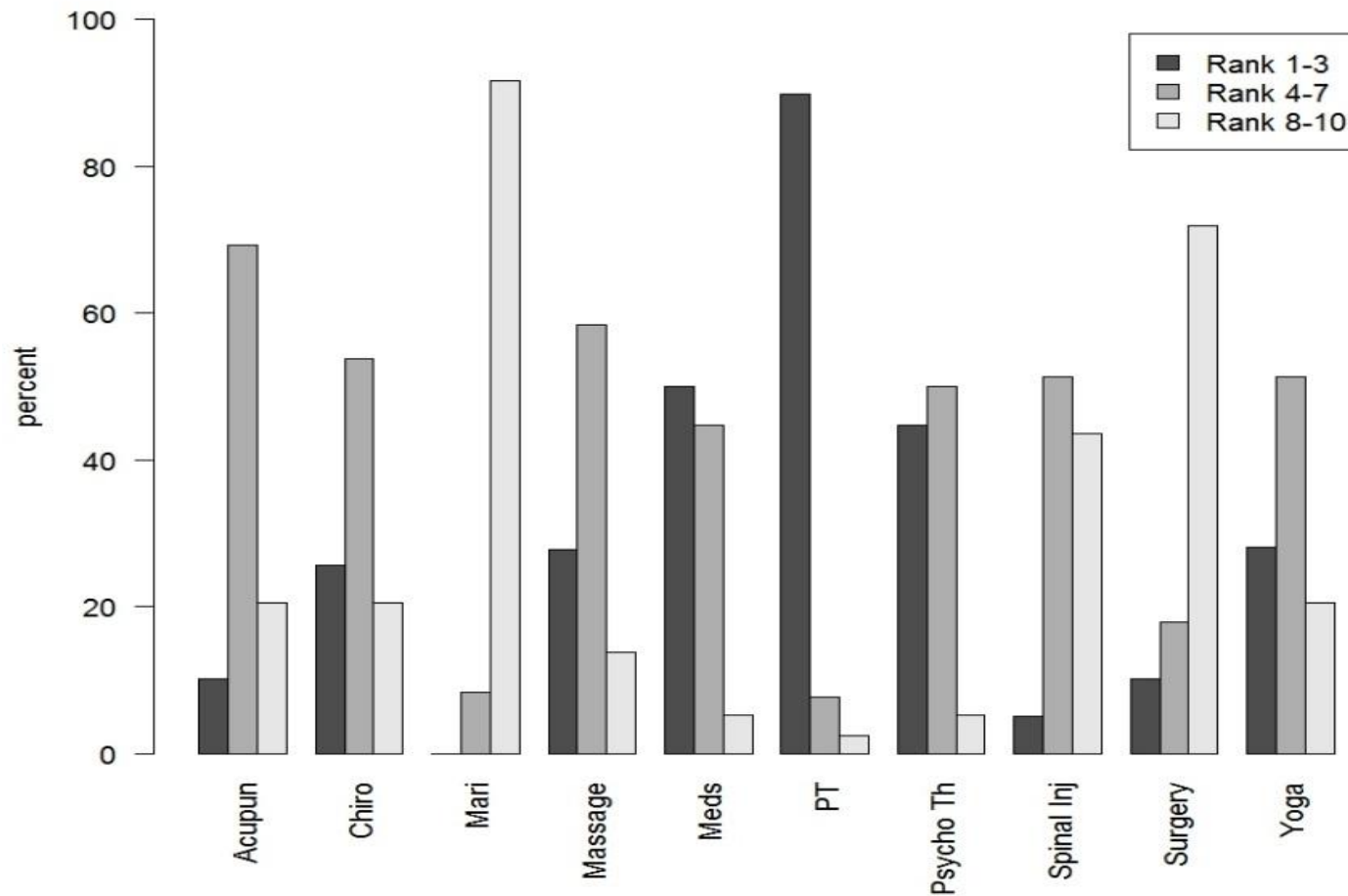
- **Age = 63 years (SD = 14)**
- **“Pain every day”—59%**
- **“Pain > 4 years”—78%**
- **“Very Interested” in participating—59%-72%**
- **Moderate to severe pain—82%-93%**



# Patient treatment preferences



# Provider treatment preferences (n=44)



# VA DoD Stepped Pain Care

RISK

Comorbidities

Treatment  
Refractory

Complexity

## Tertiary, Interdisciplinary Pain Centers

Advanced pain medicine  
diagnostics & interventions;  
CARF accredited pain  
rehabilitation

STEP  
3

## Secondary Consultation

Multidisciplinary Pain Medicine Specialty  
Teams; Rehabilitation Medicine;  
Behavioral Pain Management; Mental  
Health/SUD Programs

STEP  
2

## Patient Aligned Care Team (PACT) in Primary Care

Routine screening for presence & severity of pain;  
Assessment and management of common pain conditions;  
Support from MH-PC Integration; OEF/OIF Post- Deployment  
Teams; Expanded care management; Pharmacy Pain Care  
Clinics; Pain Schools; Integrative Medicine; Signature  
Consent for COT

STEP  
1

## Patient/Family/Caregiver Learning and Self Care

Nutrition/weight management, exercise/conditioning, ice &  
stretch; sufficient sleep; mindfulness meditation/relaxation  
techniques; engagement in meaningful activities; family &  
social support; safe environment/surroundings

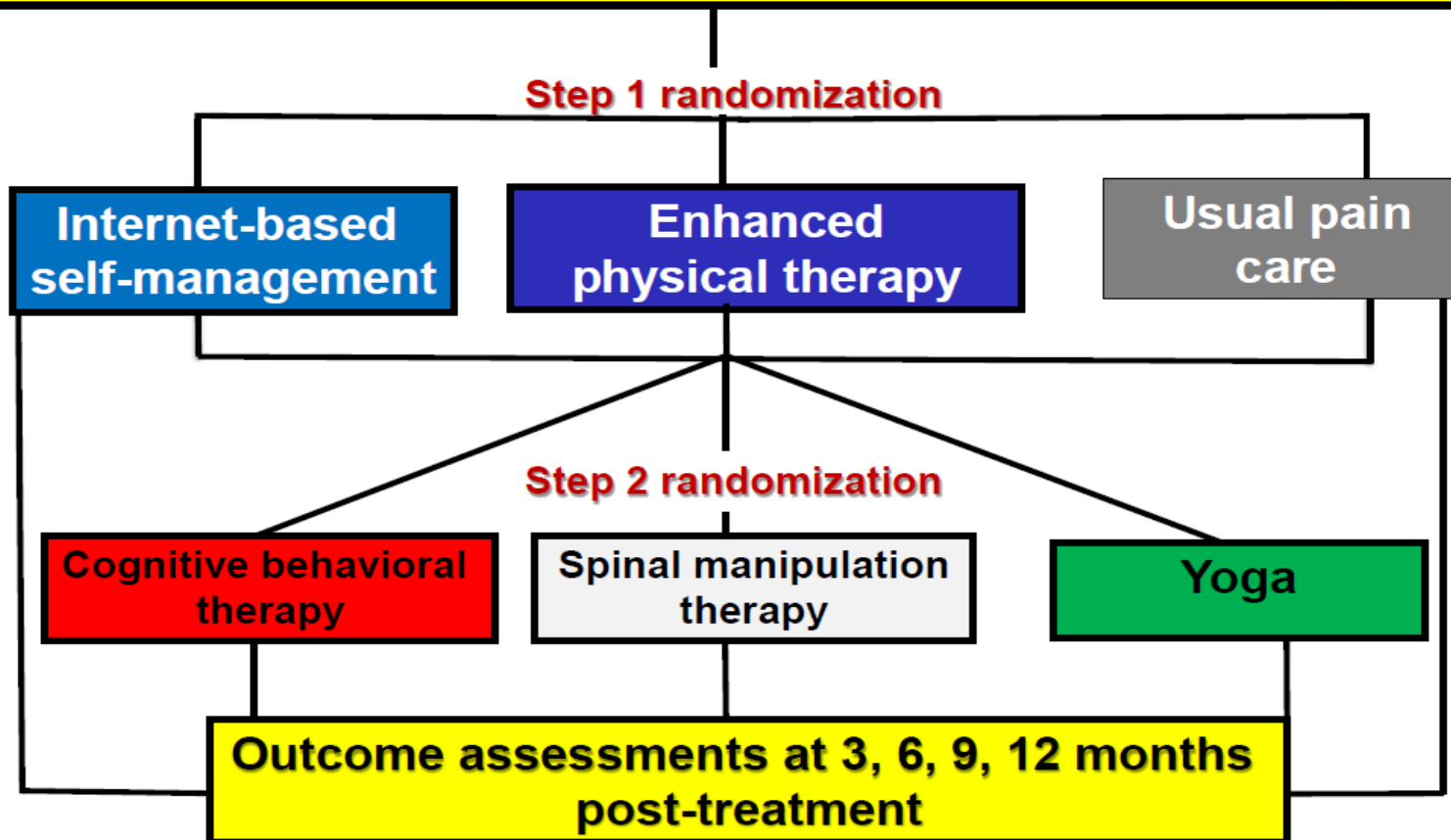
# Overall Study Description

**SCEPTER is a:**

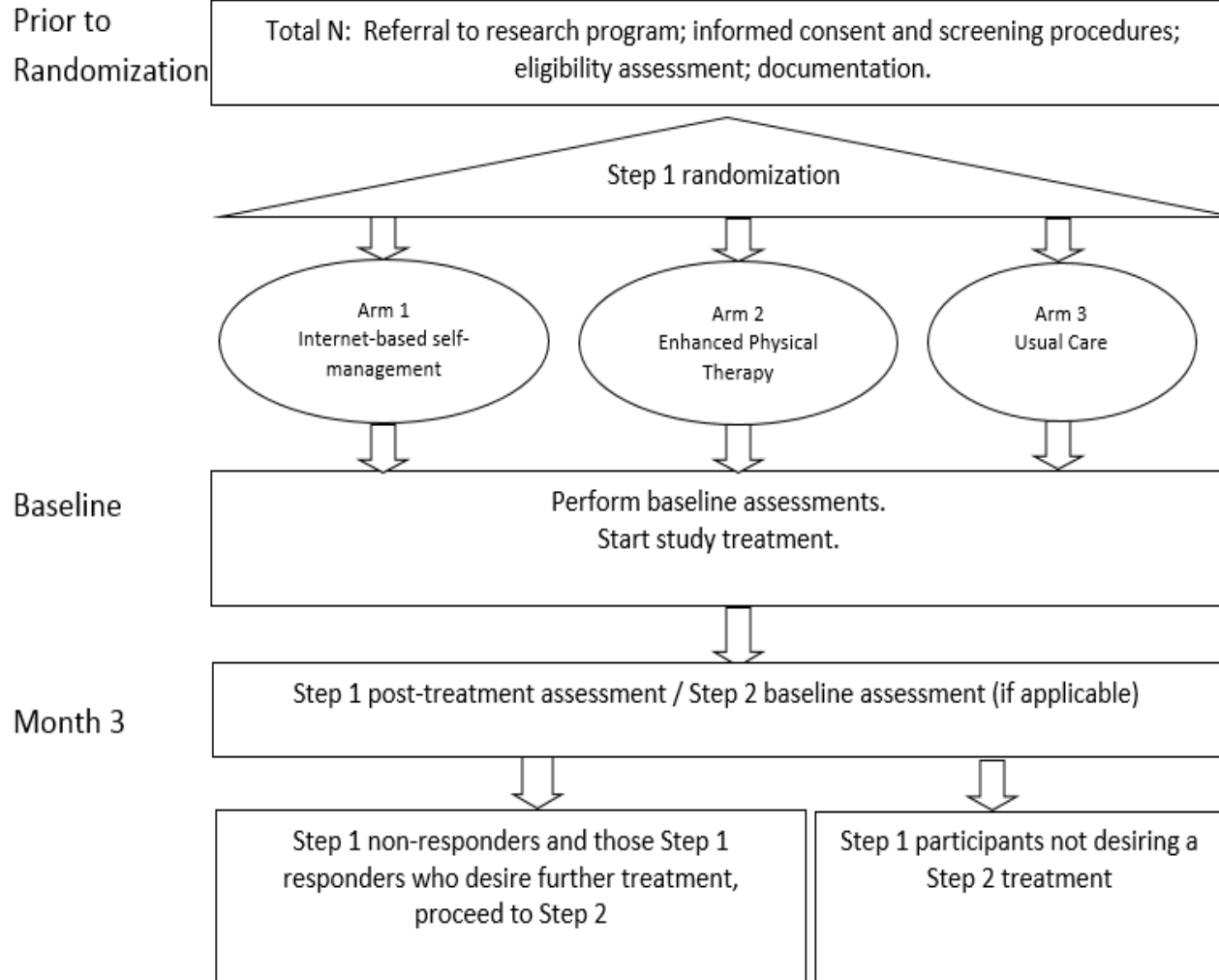
- **Sequential randomized**
- **Pragmatic**
- **2-step comparative effectiveness trial**
- **To identify the optimal approach to chronic low back pain treatment**
- **Uses commonly recommended non-surgical, non-pharmacological options**
- **Single-blinded (outcome assessors)**

# SCEPTER Study Design

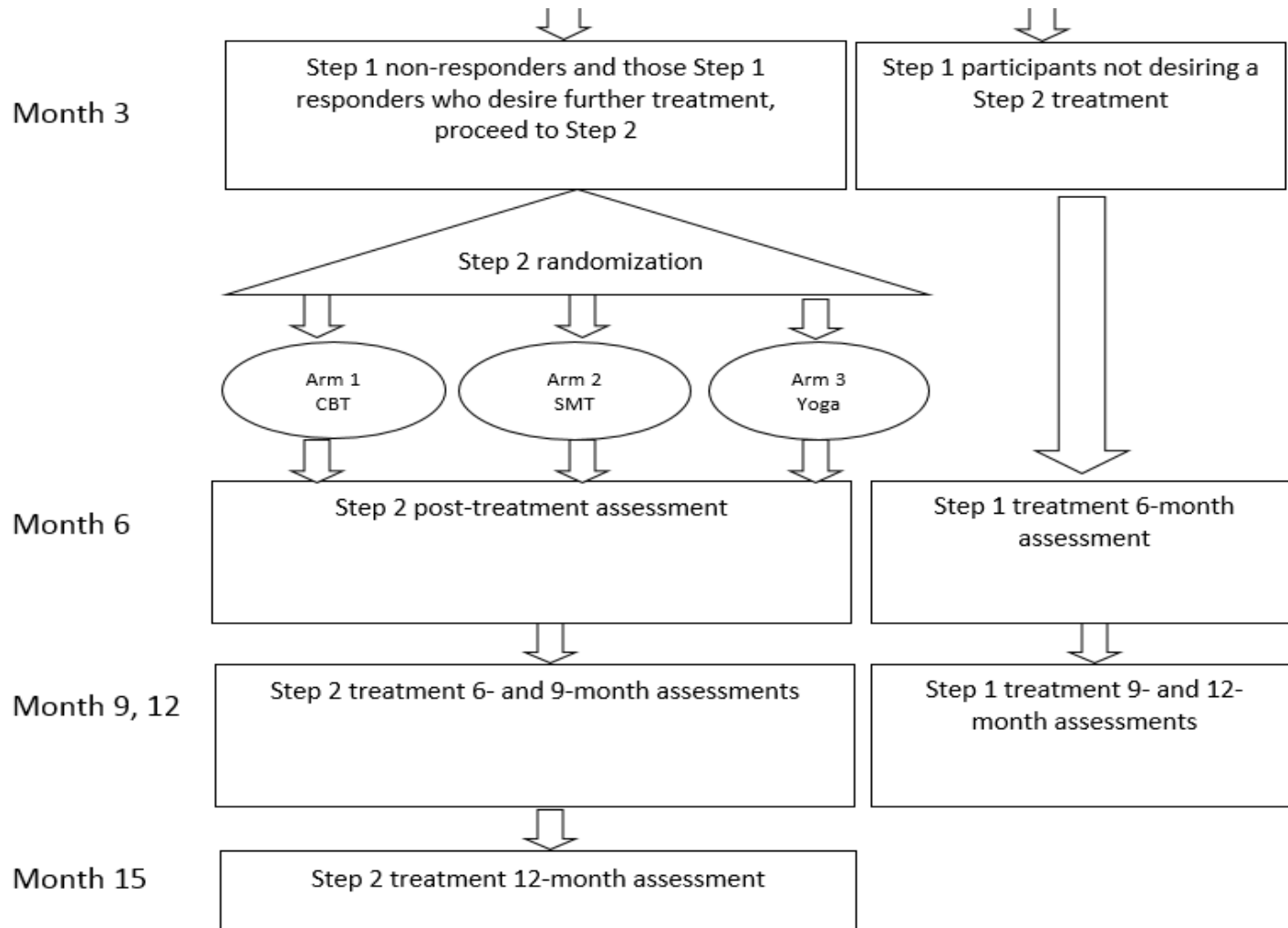
**Veterans with chronic low back pain**



# SCEPTER – Step 1



# SCEPTER – Step 2



# Study Objective #1

- **To compare the effectiveness of:**
  - **Internet-based pain self-management program**
  - **“Enhanced physical therapy”**
  - **Usual care**



# Hypothesis #1

- **The internet-based self-management program will significantly reduce pain interference and pain severity**
- **The enhanced physical therapy intervention will be more effective than the internet-based self-program program alone and usual care**

# Study Objective #2

- **To compare the effectiveness of:**
  - **Cognitive behavioral therapy (CBT)**
  - **Spinal manipulation therapy (SMT)**
  - **Yoga**
- **In veterans w/o a clinically meaningful response (Step 1 non-responders)**

# Step 1 Non-responders

- **Participants who do not have:**
  - **30% or 2-point reduction in Brief Pain Inventory (BPI) pain interference score after 3 months of Step 1 treatments**

# Hypothesis #2

- **The proportion of treatment responders will significantly differ across the 3 step 2 treatments**

# Secondary Objectives

- **To compare secondary outcomes and durability**
- **To evaluate safety, treatment adherence, and satisfaction**
- **To identify predictors of treatment response**

# Secondary Objectives

- **To evaluate the feasibility, barriers and facilitators to implementation of treatments**
- **To perform a cost and budget impact analysis of treatments**

# Additional hypotheses

- **Patient preferences, opioid use, emotional status, sleep and fatigue will predict treatment response**
- **Treatments will have different effects on opioid use, emotional status, sleep and fatigue**
- **Significant differences in cost effectiveness will be found between the treatment options**
- **The durability of treatment effects will differ**

# **Internet-based pain self-management program**

- **Developed by Diana Higgins, PhD and Alicia Heapy, PhD**
  - **Pain EASE and COPES programs**
- **10 pain coping skill modules:**
  - **pain education, setting goals, planning meaningful activities**
  - **physical activity, relaxation, healthy thinking patterns**
  - **pacing and problem-solving, improving sleep, effective communication, and planning for the future**
- **Pedometer-tracked step counts, sleep tracking, relaxation practice**



# Enhanced physical therapy

- **Combination of:**
  - Internet-based pain self-management program
  - Tailored exercise and physical activity
  - Guided by a physical therapist
  - Up to 8 sessions
- **Initial visit guided by Keele STarT Back Screening Tool**
- **Focus on walking in addition to motor control and stabilization exercises**
- **Flexibility exercises if stiffness present**

Treatment program being developed and led by Dan Riddle, PT, PhD

# Usual care

- **Non-standardized**
- **May involve pharmacological and non-pharmacological treatments for CLBP**
- **Current analgesics and non-pharmacological treatments may be continued by participants**
- **Will be discouraged from starting CBT, chiropractic (SMT), or yoga**

# Cognitive Behavioral Therapy

- **Face-to-face individual (or group) treatment**
- **10 treatment sessions (45 minutes in length)**

Table 6.1. VA CBT Chronic Pain

Session	Content
1	Interview and Assessment: Clinical pain evaluation and baseline assessment measures
2	CBT-CP Orientation: Pain education and familiarization with the CBT-CP approach to treatment
3	Assessment Feedback and Goal Planning: Clinical implications of assessment and development of treatment goals
4	Exercise and Pacing: Importance of movement and thoughtful approach to physical activities
5	Relaxation Training: Relaxation benefits and techniques
6	Pleasant Activities 1 and 2: Identification of meaningful and pleasurable activities/ Implementation of selected valued activities
7	Cognitive Coping 1: Understand automatic negative thoughts and how they impact pain experience
8	Cognitive Coping 2: Monitor and challenge automatic thoughts
9	Sleep: Strategies for improving sleep despite pain
10	Discharge Planning: Plan for flare-ups and review CBT-CP skills

**Based on CBT-CP treatment manual developed by Jennifer Murphy, PhD**

# Spinal manipulation therapy (SMT)

- Up to 10 treatment sessions in 3 month treatment period
- Delivered by DCs

Therapy	Target	Indication
Spinal manipulation and/or mobilization	Lower thoracic, lumbar and/or sacroiliac joints	Findings of excessive stiffness, tenderness and/or pain provoked on clinical examination
Myofascial (massage) and/or stretching techniques	Lower thoracic, lumbar, gluteal and/or lower extremity muscles	Findings of excessive tightness, tenderness and/or pain provoked on clinical examination

Treatment program being developed and led by Paul Dougherty, DC

# Yoga

- **Yoga for Veterans with CLBP program developed by Eric Groessl, PhD**
- **10 weekly, 60-minute instructor-led sessions**
- **Emphasis on home practice**
- **Classical hatha yoga with influences from Iyengar and Viniyoga yoga**
- **Series of 23 yoga poses (32 total variations) at a slow-moderate pace**

# Study Participants and Sites

- **N = 2529 Veterans**
  - **Moderate to severe CLBP**
- **20 VA Medical Centers**
- **Study duration = 6 years**

# Site Selection

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- **Identified sites most likely to meet enrollment goals**
- **Targeted larger VA's with high numbers of veterans with chronic low back pain**
- **Targeted NODES sites and sites interested in participating based on site survey**

# Nominated sites

- Asheville, NC
- Atlanta, GA
- Baltimore, MD
- Bay Pines, FL
- Boston, MA
- Hampton, VA
- Indianapolis, IN
- Las Vegas, NV
- Loma Linda, CA
- Long Beach, CA
- Nashville, TN
- Orlando, FL
- Palo Alto, CA
- Phoenix, AZ
- Portland, OR
- Richmond, VA
- Salisbury, NC
- Salt Lake City, UT
- San Antonio, TX
- St. Louis, MO



# Eligibility Criteria

- **Major inclusion criteria**

- Chronic low back pain (cLBP) present for at least 6 months
- Numeric Pain Rating Scale  $\geq 4/10$
- Roland Morris Disability Questionnaire  $\geq 7$
- Internet access

- **Major exclusion criteria**

- Concomitant interventional study enrollment
- Use within past 3 months Step 2 treatments (CBT, SMT, Yoga)
- Severe psychiatric or medical illness preventing participation and/or follow-up
- Undergoing evaluation for back surgery

# Primary Outcome: Brief Pain Inventory- Interference

How has pain interfered with your...

- **General activity**
- **Mood**
- **Walking ability**
- **Work**
- **Relationships**
- **Sleep**
- **Enjoyment of life**

# Additional Study Outcomes

## **Domain**

## **Measure**

**Physical function**

Roland-Morris Disability Questionnaire

**Pain severity**

Numeric rating scale

**Psychological**

PHQ-9 Depression, GAD-7 Anxiety, PTSD, catastrophizing

**Pain**

**Sleep**

PROMIS-Sleep

**Fatigue**

PROMIS-Fatigue

**Treatment response**

Global Impression of Change

General Physical Health-2, GMH-2 Outcomes

**Generic HRQL**

EuroQuol Quality of Life/5

**Concomitant meds/Treat**

Opioids, Other medications

Non-pharmacological cLBP treatments

**Satisfaction**

Pain treatment satisfaction

**Safety**

AE/SAE

**Health economics**

Employment/Productivity, Caregiving

Non-VA healthcare utilization

# Implementation

- **Monitor implementation fidelity and minimize variation**
  - **Assessment of how treatments are being provided, dose and fidelity**
- **Understand key challenges to implementation of study treatments to facilitate translation of findings into practice**
  - **Patient and treatment provider surveys of experiences, difficulties, etc.**
- **Identify possible provider level mediators or moderators of primary trial outcomes**
  - **Assessment of provider and organizational readiness for change**

Led by Karleen Giannitrapani, PhD

# Economic Analyses

- **Costs of the stepped treatments have not been carefully defined**
  - **Intervention costs:**
    - **Self-mgt. (web-based), exercise therapy (individual), CBT (individual), SMT (individual), yoga (group)**
  - **Consequence costs:**
    - **Measures overall healthcare costs in the year following cLBP interventions**
  - **Integrated analysis:**
    - **A comparison of the costs of intervention relative to the costs of overall healthcare on a month-by-month basis**
- **Broader Economic Analyses**
  - **To be completed if particular treatments appear more effective**
  - **Formal cost-effectiveness analyses, budget impact analyses**

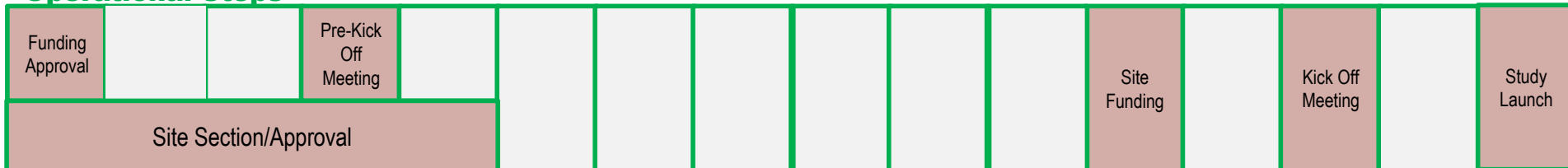
# Key Needs and Impacts

- **Trials of guideline-concordant therapy (especially for stepped-care options)**
- **Comparative effectiveness data**
- **Outcomes beyond pain and function**
  - **Anxiety/Mood, Sleep, QOL**
- **Predictors of responsiveness**
- **Incorporates treatment preferences into design**
- **Implementation and cost-effectiveness data**

# TENTATIVE TIMELINE

Mar 2019   Apr 2019   May 2019   Jun 2019   Jul 2019   Nov 2019   Dec 2019   Jan 2020   Mar 2020   Apr 2020   May 2020   Jun 2020   Jul 2020   Aug 2020   Sep 2020   Oct 2020

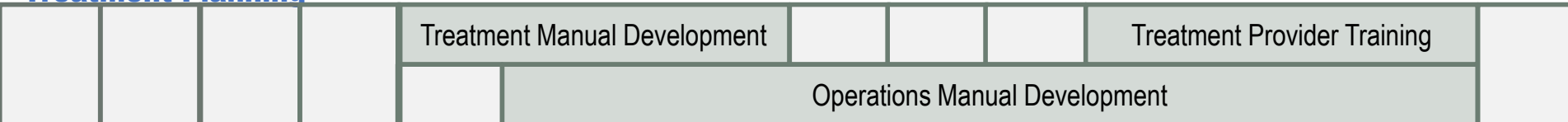
## Operational Steps



## Data Management



## Treatment Planning



## Regulatory



Mar 2019   Apr 2019   May 2019   Jun 2019   Jul 2019   Nov 2019   Dec 2019   Jan 2020   Mar 2020   Apr 2020   May 2020   Jun 2020   Jul 2020   Aug 2020   Sep 2020   Oct 2020

# Challenges

- **Interventions need to “absorbed” by clinical programs– not funded by research**
- **Competing trials/studies**
- **Standardizing interventions across sites**



# Study Chairs Office

- **David J. Clark, MD, PhD, Study Co-Chair, Palo Alto VA Medical Center**
- **Matthew J. Bair, MD, MS, Study Co-Chair, Indianapolis VA Medical Center**
- **Colleen Fitzsimmons, BS, National Study Coordinator, Palo Alto VA Medical Center**

# **Cooperative Studies Program Coordinating Center, Palo Alto VA:**

- **Ilana Belitskaya-Lévy, PhD,  
Biostatistician**
- **Mei-Chiung Shih, PhD, Senior  
Biostatistician, CSP Director**
- **Lisa Zehm, MS, Study Project Manager**

# **Cooperative Studies Program**

## **Coordinating Center, Palo Alto VA:**

- **Lauren Uyeda, MS, Data Manager**
- **Ania Ray, Research specialist**
- **Amy Morrow, Data manager**
- **Alison Quien, Data manager**
- **Lori Nielsen, Budget manager**

# Treatment Champions

Champion	Treatment
<b>Diana Higgins, PhD</b>	<b>Internet-based pain self-management</b>
<b>Dan Riddle, PT, PhD</b>	<b>Enhanced Physical Therapy</b>
<b>Jennifer Murphy, PhD</b>	<b>Cognitive Behavioral Therapy</b>
<b>Paul Dougherty, DC</b>	<b>Spinal Manipulation Therapy</b>

# Safety Monitors

- **Christina Clise, PharmD**
- **Alexandra Scrymgeour, PharmD**
- **Lawrence Calais, RN**

# Funding

- **Grant Huang, MPH, PhD, Director for the Cooperative Studies Program (CSP)**
- **Rachel Ramoni, DMD, ScD, Chief Research and Development Officer**
  - **Office of Research & Development**

# Thank you



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