Cost-effectiveness of spinal manipulation therapy for neck or back pain

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Abstract

Chronic pain is a major public health problem, affecting more adults in the United States than heart disease, diabetes, and cancer combined. Low back and neck pain are the most common chronic pain conditions and are two of the most disabling and costly conditions in the U.S. Approximately 4% of all healthcare spending in the U.S. is directed towards the management of back and neck pain, more than any other condition. Spine pain management has gathered increased scrutiny amidst concerns about overutilization of costly and potentially harmful interventions such as opioids, injections, and surgeries. Complementary and integrative interventions may reduce the clinical and cost burden of spine pain and are now recommended by clinical guidelines, but their use remains limited.

This dissertation addresses the cost-effectiveness of spinal manipulation therapy and other complementary and integrative therapies for neck or back pain. First, we used individual patient data from eight randomized trials to conduct standardized cost-effectiveness analyses of spinal manipulation therapy (SMT), one of the most common complementary and integrative interventions, compared to home exercise or supervised exercise approaches. We found the cost-effectiveness of SMT varied by population and comparison. When compared to or added to home exercise, cost-effectiveness findings were favorable for acute neck pain, chronic neck pain in older adults, and chronic back-related leg pain; however, SMT was not likely cost-effective for chronic back pain. When compared to or added to supervised exercise, cost-effectiveness findings were favorable for chronic back pain in multiple age groups (adolescents, adults, older adults) and older adults with chronic neck pain. For adults with chronic neck pain, findings were mixed where SMT was not likely cost-effective relative to supervised exercise, but maybe cost-effective when added to supervised exercise.

Next, we assessed the generalizability of the randomized clinical trial populations by comparing socio-demographic characteristics and clinical features to representative samples of US adults with chronic spine pain using data from the National Health Interview and Medical Expenditure Panel Surveys. We found the clinical trials had an under-representation of individuals from underserved communities with lower percentages of racial and ethnic minorities, less educated, and unemployed adults relative to the U.S. population with spine pain. While the odds of chiropractic use in the U.S. were lower for individuals from underserved communities, the trial

populations also under-represented these populations relative to U.S. adults with chronic spine pain who visit a chiropractor.

Finally, we estimated the cost-effectiveness of spinal manipulation and other complementary and integrative approaches for spine pain using a decision analysis model incorporating multiple sources of evidence. We found that yoga resulted in the lowest costs and largest health benefits relative to all other treatments across multiple populations. Other complementary and integrative approaches such as massage, mindfulness-based stress reduction, cognitive behavioral therapy, and SMT were also shown to be cost-effective options relative to home exercise and advice for chronic spine pain across different populations. Findings for these treatments were not sensitive to changes in key model parameters impacting costs or effectiveness.

In summary, our work contributes to the understanding of the cost-effectiveness of complementary and integrative approaches including spinal manipulation in U.S. healthcare settings. We used both clinical trial-based and decision model analyses to assess cost-effectiveness and found general consistency of findings across the two approaches. There is a need to better understand the impact of these approaches in populations most severely impacted who are often under-represented in clinical trials.

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Introduction to Dissertation

Chronic pain is a major public health problem, affecting more adults in the United States than heart disease, diabetes, and cancer combined.[1] Low back and neck pain are the first and third most common chronic pain conditions in U.S. adults with nearly one of three Americans experiencing chronic neck or low back pain (LBP) in their lifetime.[2,3] While the prevalence of spinal pain has been stable over the past two decades, the global burden (measured by disability adjusted life years) has increased 42% due to aging and population growth.[4,5] Roughly 25% of U.S. adults with spine pain report limitations with physical function, 11% report limitations with social function, and 19% report limitations with work, school or household activities.[6] With low back pain and neck pain both considered among the most disabling conditions worldwide, spine pain has become a burdensome health condition with considerable public health consequences.[7]

The economic impact of spinal pain and associated comorbidities is also substantial. An estimated $134.5 billion in healthcare expenditures (over 4% of total healthcare spending) was directed towards low back and neck pain within the U.S. in 2016, more than any other condition including diabetes, heart disease, or cancer.[8] While direct expenditures for spinal pain are large, total healthcare expenditures are even greater due to comorbidities (such as depression).[3] When total healthcare costs are considered, for example care of spinal pain plus associated comorbid conditions, expenditures increase to 9% of total U.S. healthcare costs (2005 data).[6] In addition, reduced work productivity accounts for a large proportion of the financial burden in individuals with back or neck pain. Lost productivity costs for back pain were estimated at $19.8 billion per year in 2002, with reduced productivity while still at work (i.e. presenteeism) accounting for nearly 70% of total lost productivity costs.[9]

Spine pain management has gathered increased scrutiny amidst concerns about overutilization of costly and potentially harmful interventions and diagnostic tests. Over the past decade the number of epidural injections, opioid prescriptions, and spinal surgeries for back pain has more than doubled with little positive impact on patient outcomes. [10] Annual healthcare expenditures for individuals with spinal pain increased by 95% from 1999 to 2008 largely due to increases in medical specialist expenditures.[11] From 1996 to 2013, the U.S. spent an additional $57.2 billion dollars per year on the management of spinal pain, which represents one of the larger increases in healthcare spending for any condition.[12] While more conservative and potentially less costly alternatives are available to treat spinal pain, including spinal manipulation therapy (SMT), exercise therapy, and self-management, they are often underutilized. An analysis of administrative data from across the U.S. found low back pain patients are more likely to receive opioids (41%) than visit a chiropractor (39%) or physical therapist (34%).[13] Spine pain is the most common non-cancer reason for opioid prescriptions.[14] Importantly, the American College of Physicians has recognized this issue and currently advocates the use of several complementary modalities (including SMT) as alternatives to drugs and other invasive treatments in their guidelines for the management of LBP.[15]

Complementary and integrative interventions may reduce the clinical and cost burden of spine pain. Analyses using data from the U.S. Medical Expenditures Panel Survey and Medicare (one of which I co-authored) suggest complementary and integrative therapies, including SMT, reduce healthcare expenditures for spinal pain conditions; however, the cost-effectiveness of SMT within U.S. healthcare settings has not received much attention.[16-19] Given the increasing financial and societal burden of spinal pain, and concerns surrounding current management strategies, robust cost-effectiveness analyses (CEAs) of SMT and other complementary and integrative treatments for spine pain are much needed. Accordingly, there has been a call for robust CEAs of SMT and other complementary and integrative health (CIH) treatments for spine pain.[19-21]

While there is preliminary evidence suggesting SMT is cost-effective, existing CEAs are marred by several limitations. First, few existing CEAs have incorporated data from pragmatic randomized clinical trials (RCTs) performed in the United States. Findings from other countries are not readily transferable due to major differences in healthcare costs. Further, existing CEAs conducted alongside RCTs have experienced difficulty collecting cost and quality of life outcomes. In addition, while RCTs are recognized as the gold standard for determining clinical effectiveness, there are concerns regarding generalizability, especially when used for CEAs. Important limitations inherent to RCT-based CEAs include the small number of available treatments assessed (typically two or three strategies), the limited time horizon (often one year or less), and the narrow patient populations included in RCTs (less inclusive population relative to how intervention is applied in general practice). Incorporating RCT-based analyses into decision analytic models that include other evidence is a recommended framework for overcoming the inherent limitations in trial-based CEAs. The number of decision models assessing the cost-effectiveness of SMT for neck or back pain are limited and none have incorporated benefits, harms, and costs into a single analysis. Consequently, there is a need to address the prevailing limitations related to the cost-effectiveness of SMT for spinal pain, using rigorous and state-of-the-art methods.

My long-term objective is to identify cost-effective complementary and integrative health interventions for spinal pain. My dissertation projects addressed existing knowledge gaps regarding the cost-effectiveness of spinal manipulation for neck or back pain in the U.S.

My dissertation had the following specific aims:

Aim 1: To estimate the cost-effectiveness of spinal manipulation relative to exercise therapy and self-management for spinal pain using an individual participant data meta-analytic approach.

We conducted cost-effectiveness analyses incorporating both societal and healthcare perspectives using an individual patient data meta-analytic approach that combines previously un-analyzed cost data from eight U.S. RCTs with comparable clinical and cost outcomes.

Aim 2: To evaluate the generalizability of randomized clinical trial populations from Aim 1.

We compared trial participants' socio-demographic characteristics and clinical features to a representative sample of 1) US adults with chronic spine pain and 2) US adults with chronic spine pain receiving chiropractic care using secondary data from the National Health Interview and Medical Expenditure Panel Surveys.

Aim 3: To estimate the cost-effectiveness of spinal manipulation relative to other commonly used conservative interventions for spine pain using a decision analysis model incorporating the latest evidence to inform model parameters.

We developed a decision model which includes studies from Aim 1 and other relevant literature to estimate the cost-effectiveness of commonly used treatments for spine pain in the U.S.

This work substantially increases the number of RCT based CEAs available for SMT relevant to the U.S. population and improves the quality of CEA estimates of SMT for spine pain worldwide. Further, the findings will enhance our ability to design future cost-effectiveness studies that best represent the U.S. spine pain population, facilitating the translation of results to practice.

Aim 1 Paper: Cost-effectiveness of spinal manipulation therapy for neck or back pain using an individual participant data meta-analysis approach

Background

Chronic pain is a major public health problem, affecting more adults in the United States than heart disease, diabetes and cancer combined.[22] Spine pain (back and/or neck pain) is the most common chronic pain condition in the U.S. and the most expensive health problem.[2,3,8] There is a growing recognition that many of the current spine pain management strategies are costly, potentially harmful, and largely ineffective, and the use of safe and cost-effective treatment options has become a national imperative.[10,11,13,23] Spinal manipulative therapy (SMT) is a conservative, manual treatment commonly employed by chiropractors and other provider types including osteopaths and physical therapists. While there is evidence supporting the clinical effectiveness of SMT for treating spine pain,[15,20,24,25] the cost-effectiveness of the approach in the U.S. has been inadequately addressed. While systematic reviews have noted promising evidence that SMT may be cost-effective for spinal pain, particularly when productivity costs are considered, there are limitations of the original studies that draw attention to the need for further high-quality cost-effectiveness analyses (CEAs).[19,21]

We identified 13 RCT-based CEAs of treatment approaches using SMT alone or in combination with other conservative treatments through existing systematic reviews and updated searches of Medline, the Cochrane database, the health economics evaluation database, and the Tufts CEA registry (See Table 1). Most trials were conducted in European healthcare settings where healthcare costs are much lower relative to the U.S. Only two of the existing studies took place in the U.S.[26,27] and only one assessed SMT delivered by chiropractors,[27] who deliver over 90% of SMT in the U.S.[28] Importantly, most of the existing RCT based CEAs have substantial missing data including quality-adjusted life year (QALY) outcomes, a broad measure of health recommended for CEAs, as well as other important healthcare utilization measures. Only four of the existing studies collected healthcare use and QALY data from over 80% of participants.[27,29-31] Further, only three CEAs[27,32,33] conducted analyses from both the societal (including lost productivity costs) and healthcare perspectives (as recommended by the Second Panel on Cost-effectiveness in Health in Medicine) to ensure findings are applicable to multiple audiences (e.g. policy makers, health-care systems).[34] In summary, there are still very few high quality RCT based CEAs of SMT for spine pain and even fewer have been performed in the U.S.

Table 1. RCT-based CEAs of SMT for Spinal Pain

Study (n)	Condition	Setting	Complete data	Cost-QALY ICER Results in 2020 US$ (Perspective)
Korthals de Bos (n=183)[29]	Acute Neck Pain (26% Chronic)	Netherlands	95%	Dominant over GP care (Soc) Dominant over ET (Soc)
Lewis (n=350)[32]	Chronic Neck Pain (23% Acute)	UK	73%	$6000 per QALY vs A&E (HC) Dominant over A&E (Soc)
Bosmans (n=146)[35]	Acute Neck Pain	Netherlands	62%	Dominant over BGA (Soc)
Lamb (n=599)[36]	Acute WAD	UK	69%	Dominated by Advice (HC)
UK Beam (n=1334)[30]	Chronic LBP (42% Acute)	UK	95%	$10,000 per QALY vs GP (HC)
Whitehurst (n=402)[37]	Acute LBP	UK	66%	$5000 per QALY vs BPM (HC)
Rivero-Arias (n=286)[33]	Chronic LBP (25% Acute)	UK	51%	$6000 per QALY vs Advice (HC) Dominant vs Advice (Soc)
Critchley (n=212)[38]	Chronic LBP	UK	70%	$2000 per QALY vs ET (HC) Dominated by PM (HC)
Williams (n=201)[39]	Acute LBP or Neck Pain	UK	54%	$8000 per QALY vs GP (HC)
Van Dongen (n=181)[40]	Chronic Neck Pain	Netherlands	62%	$22,000 per QALY vs ET (Soc)
Fritz (n=220)[26]	Acute LBP	US	70%	$36k per QALY vs UC (Soc)
Leininger (n=241)[27]	Chronic Neck Pain (Older adults)	US	93%	Dominant over ET (HC & Soc) Dominant when added to A&E (Soc) $80k per QALY when added to A&E (HC)
Aboagye (n=409)[31]	Chronic Neck or LBP (25% Acute)	Sweden	81%	Dominant when added to evidence-based advice (Soc)

WAD=whiplash associated disorders; GP=general practitioner care; ET=exercise therapy; A&E=advice & exercise; BGA=behavioral graded activity exercise; BPM=brief pain management; PM=pain management program; UC=usual care; Soc= Societal Perspective; HC=Healthcare Perspective; LBP=Low Back Pain

The objective for this project was to assess the cost-effectiveness of SMT using an individual participant data meta-analytic approach (IPDMA) that incorporates clinical outcomes, health care use, and lost productivity data from eight similar RCTs conducted in the U.S. by members of our research team. Combined analyses of economic data are rarely possible due to differences in resource utilization outcomes, costs, and healthcare settings.[41] Additionally, individual clinical trials rarely include a sufficient number of participants to detect important differences in economic outcomes. This project represented a unique opportunity to potentially combine clinical and economic data collected in eight randomized clinical trials using an IPDMA approach as there was substantial overlap of assessed treatments and consistency in treatment and data collection protocols. In addition, I participated in the conduct and analysis for a number of the included trials and had access to individual level data from all eight trials. Additional data from trials assessing the cost-effectiveness of SMT was not sought, due to differences in treatment comparisons and healthcare settings (see Table 1). An IPDMA approach has many advantages over traditional meta-analysis including the ability to conduct standardized within-study analyses, account for missing data at the individual level, and investigate potential sub-group effects at the participant level which may account for heterogeneity in estimates across studies.[42]

Study Objectives

Our primary objective was to estimate the incremental cost-effectiveness of spinal manipulation, exercise therapy, and self-management for spinal pain from both societal and healthcare perspectives using quality-adjusted life years (QALYs), pain intensity, and disability as effectiveness measures. We analyzed cost and clinical outcome data collected as part of eight randomized clinical trials performed in the U.S. using an IPDMA approach. The eight randomized clinical trials used similar methods, collected similar clinical outcome, healthcare utilization, and work productivity data, and included different combinations of SMT, exercise therapy, or self-management for spinal pain.

Methods

We used an IPDMA approach to evaluate costs and effects of spinal manipulation, exercise therapy, and self-management (i.e. home exercise & advice) for spinal pain using data from eight randomized clinical trials. Each of the included trials obtained written consent from participants who were 18 years of age or older, and written patient assent and parent consent from participants 12-17 years of age. Six of the clinical trials were funded by the U.S. Department of Health and Human Services Health Resources and Services Administration[43-48] and one was funded by the National Institute of Health's National Center for Complementary and Integrative Health.[49] Seven of the trials are registered on clinicaltrials.gov (one trial[50] was initiated prior to its existence). A protocol outlining our detailed methods was published.[51] Table 2 provides an overview of trial populations and interventions.

Table 2. Clinical trial populations and interventions

	Population			Interventions		
	Condition	**Sample**	**Age**	**Group 1**	**Group 2**	**Group 3**
Pre-dates CT.gov[50]	Chronic neck pain	191	20-65	SMT+ET	ET	SMT
NCT00269360[45]	Chronic neck pain	270	18-65	SMT+ET	ET	HEA
NCT00269308[47]	Chronic neck pain	241	65+	SMT+HEA	ET+HEA	HEA
NCT00029770[49]	Acute neck pain	272	18-65	SMT	HEA	Medication
NCT00269347[44]	Chronic low back pain	301	18-65	SMT	ET	HEA
NCT00269321[48]	Chronic low back pain	240	65+	SMT+HEA	ET+HEA	HEA
NCT00494065[43]	Chronic back-related leg pain	192	21+	SMT+HEA	SC	-
NCT01096628[46]	Chronic low back pain	184	12-18	SMT+ET	ET	-

CNP=chronic neck pain; ANP=acute neck pain; CLBP=chronic low back pain; BRLP=back related leg pain; SMT=spinal manipulation therapy; ET=exercise therapy; HEA=home exercise and advice

Settings and participants

All of the clinical trials were performed within a university-affiliated research clinic in the Minneapolis, MN metropolitan region. Six of the clinical trials were performed exclusively in MN[44,45,47-50] and two were multi-center studies with additional sites in Portland, OR[46] or Davenport, IA.[43] Participants had commonly recognized sub-groups of spinal pain including acute or chronic neck pain, chronic low back pain, and back-related leg pain (Table 1). Five of the clinical trials included adults (18-65 years), two trials included older adults (65 years and older), and one trial focused on adolescents (12-18 years). All eight trials recruited participants from the general population primarily through mass mailings. Other recruitment strategies included advertisement in newspapers, social media, television, radio, and community posters.

Inclusion/Exclusion Criteria

In all eight of the clinical trials, participants were required to have self-reported spinal pain severity ≥3/10 for inclusion. Other inclusion criteria common to the eight clinical trials were a stable medication plan and no ongoing spinal treatment prior to enrollment. Common exclusion criteria included current or pending litigation, inability to read and comprehend English, substance abuse, history of surgical spinal fusion, progressive neurological deficits, or contraindications to study treatments.

Interventions

Spinal manipulation was included as an intervention in all eight trials. Supervised exercise therapy was provided in six trials and a self-management intervention focusing on home exercises and advice was also provided in six of the trials.

Spinal manipulation therapy (SMT) was delivered by licensed chiropractors over an 11-12 week intervention period in all eight trials. The treating chiropractor determined the frequency of SMT visits in six of the eight studies. The mean frequency of SMT visits ranged from 10 to 20 across the eight trials with most trials reporting a mean visit frequency between 15 and 20. SMT consisted of high velocity, low amplitude manipulation, with an option to use low velocity, variable amplitude mobilization as indicated. Brief soft tissue work (up to five minutes) and heat therapy were allowed to facilitate the manual treatment, if necessary, which is typical in clinical practice.

Supervised exercise therapy (ET) was delivered by licensed chiropractors, physical therapists or exercise therapists over an 11-12 week period in six trials. Five studies[44,45,47,48,50] included 20 one-hour visits of one-on-one supervised exercise therapy and one trial[46] included 8 to 16, 45-minute visits with the number of visits individualized based on patient response and needs. Participants completed a combination of stretching and strengthening exercises emphasizing a high number of repetitions with progressions in challenge and/or resistance over time. Exercises were tailored for each participant's abilities and could include the use of labile surfaces in addition to balance and coordination exercises. Participants also completed a light aerobic warm-up (up to 10 minutes) in all of the clinical trials.

Home exercise and advice (HEA) was delivered by licensed chiropractors or exercise therapists in six trials.[43-48] Participants attended two to four one-hour visits where they were given information on their prognosis, self-care advice, and home exercise instruction. Home exercises typically included a combination of self-mobilization, stretching and strengthening exercises specific to the individual's condition and ability.

Each RCT included SMT, ET, or HEA either alone or in combination with one of the other treatments. A maximum of three treatment approaches were included and compared in each trial. No trial assessed all possible treatment strategies (See Table 2). We compared the following treatment approaches which assessed the impact of SMT in more than a single trial:

1. SMT vs HEA
2. SMT+HEA vs HEA
3. ET vs SMT
4. SMT+ET vs ET

CEAs comparing other treatment combinations will be reported in separate publications (i.e. ET vs HEA, ET+HEA vs HEA, SMT vs Medication, HEA vs Medication).

<u>Perspective, Time Horizon & Discount Rate</u>

We adopted a societal perspective for the primary analysis including all healthcare costs regardless of payer (third-party insurers, patient out-of-pocket costs) in addition to time and transportation costs associated with healthcare use and lost productivity costs for both paid and unpaid labor related to spinal pain. We excluded future earnings and consumption costs since interventions for spinal pain are not expected to impact mortality. In addition to the societal perspective, we adopted a healthcare perspective including only healthcare costs.[34] A summary of resources included in the healthcare and societal perspectives is provided in Table 3. We did not include a patient perspective, as patient level costs vary considerably by health insurance plan in the U.S. and we do not have access to this data for trial participants. All eight clinical trials collected clinical outcome and healthcare utilization data for one year, which was the time horizon for the cost-effectiveness evaluation. No discounting (diminishing future costs and health effects to represent present value) was applied.

Outcomes

In all trials, clinical and cost outcomes were collected by self-report at multiple time points over a one year period with similar timing (4, 12, 26, and 52 weeks). All eight trials collected clinical outcomes including pain, disability, quality of life, and work absenteeism.

Clinical outcomes

QALYs (a metric combining quality and quantity of life) were constructed for all eight trials, using the SF6D, collected in seven trials, and the EQ5D-3L, collected in six trials. The SF6D is derived from 11 items within the Medical Outcomes Study Short Form 36-item Health Survey (SF-36) and includes six dimensions of health, each with 4-6 different levels.[52] We used U.S. preferences for individual SF6D health states obtained via discrete choice experimentation, which are similar to UK values elicited with standard gamble methods.[53] In addition, QALYs were estimated using the EuroQol 5D-3L (EQ5D-3L) as a sensitivity analysis. The EQ5D-3L measures health across five dimensions, each with three possible levels. Preferences for EQ5D-3L health states were determined using published values from a representative sample of the U.S. population elicited by time trade-off methods.[54] Finally, one study of adolescents [27] assessed health related quality of life using the pediatric quality of life inventory (PedsQL) which has recently been mapped to the EQ5D in a UK adolescent population.[55]

Self-reported pain intensity was measured using the 11-box numerical rating scale (NRS) and was the primary outcome in each of the eight trials. The NRS is a reliable and valid outcome measure for individuals with spinal pain and is recommended as a core outcome domain by both the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials group and the NIH task force on research standards for chronic low back pain.[56,57]

Disability was measured with reliable and valid measures commonly used in spine pain research: the Neck Disability Index (four trials)[58,59] and Roland-Morris Disability Questionnaire (four trials).[60] Standardized mean differences were used for disability analyses to provide a uniform scale for meta-analysis of outcomes measured with different scales. The standardized mean difference reports the size of the treatment effect relative to the amount of variability between participants in the same treatment group within each study.[61] A standardized mean difference of one equates to a treatment effect that is the size of one standard deviation across studies.

Cost outcomes

Direct Healthcare Costs: Healthcare utilization outcomes collected include the number of provider visits by specialty, types of services provided, and medication use. The number of provider visits and medication use were collected using standardized self-report questionnaires in all eight trials, and more detailed information regarding the types of services provided (e.g. MRI, injections) was collected by phone interviews in five of the trials. A list of procedures and corresponding Current Procedural Terminology (CPT)/ Healthcare Common Procedure Coding System (HCPCS) codes was compiled and unit costs for each procedure were determined using Medicare's national allowable payment. Unit costs for non-covered services under Medicare (such as acupuncture) were determined using Medicare's published relative value unit for the corresponding CPT code. Unit costs for medication were determined using the average cost per prescription day from Medicare's prescription drug profiles public use file. All unit cost estimates were converted to 2020 U.S. dollars using the Centers for Medicare and Medicaid Services Personal Health Care Expenditure deflator to account for inflation.[34]

Productivity Costs: A human capital approach including lost productivity costs for both paid and unpaid labor (such as retirees or homemakers) was used.[62] Lost work productivity due to absenteeism was collected using a modified question from the U.S. National Health Interview Survey (seven trials).[63] Participants reported the number of days in the past month they were unable to carry out their daily work (in or away from home) due to spine pain. We valued each day as eight hours of reduced productivity using age specific U.S. national pre-tax median hourly wage rates plus fringe benefits.[34]

Time & Transportation Costs: Time and transportation costs associated with healthcare utilization were included using an opportunity cost approach (valuing resources according to their best alternative use). A standardized time unit for each procedure was multiplied by the age specific U.S. national post-tax median wage rate plus fringe benefits. Healthcare related transportation costs were estimated using average distance and transportation time estimates for medical care in the U.S. as reported in the National Household Travel Survey.[64] Transportation time was valued using age-specific national post-tax median wage rates plus fringe benefits.[34] The U.S. Internal Revenue Service's standard mileage deduction rate for operating an automobile was used to value transportation costs.

Table 3. Cost components included in the societal and healthcare perspectives

Cost component	Perspective	
	Healthcare	Societal
Formal healthcare sector		
Paid for by third-party payers	X	X
Paid for by patients	X	X
Informal healthcare sector		
Patient time	-	X
Transportation costs	-	X
Non-healthcare sector		
Productivity costs (paid and unpaid labor)	-	X

Analyses

Effectiveness Analyses: We used time weighted averages over the one-year time horizon using linear interpolation to determine mean clinical outcomes. Differences in outcomes were analyzed using linear regression with the baseline measure of the outcome included as a covariate.

Cost Outcomes Analyses: Cost data for healthcare and medication use, time and transportation, and lost productivity were analyzed using generalized linear models with a gamma distribution and identity link to model mean costs over the one year time horizon.[65]

Cost-effectiveness Analyses: We ranked treatments by mean outcome and determined the incremental cost-effectiveness ratio (ICER) by dividing incremental costs by incremental effects. We did not calculate ICERs for treatments which were dominated (more expensive, less effective); however, we reported uncertainty of cost and effect differences for dominated interventions.[66] Bias-corrected bootstrap confidence intervals were calculated using 5000 samples taken with replacement with the subject as the unit of observation. Bootstrapped cost-effect pairs were plotted on the cost-effectiveness plane to graphically display uncertainty surrounding the ICER.[67] We used cost-effectiveness acceptability curves (graphical display of uncertainty that an intervention is cost-effective at different willingness to pay thresholds for one year of perfect health) to determine the probability each treatment is cost-effective based on a range of recommended willingness to pay thresholds for a QALY within the U.S.[68] Additionally, we conducted net monetary benefit analyses to display confidence intervals over a large range of willingness to pay thresholds (the amount of money a decision maker would be willing to pay for one year of full health given a fixed budget).[69]

Missing Data: Missing clinical outcome and cost data were imputed separately for each treatment group using multiple imputation (Procedure MI in STATA). For each study, ten imputed data sets were created using a multivariate normal model for clinical outcomes and predictive mean matching for costs.[70] The imputation models included clinical outcomes in addition to baseline covariates associated with missing data.

Individual Participant Data Meta-analysis (IPDMA): We used a two-stage approach for IPDMA and followed recommended guidelines for standard and IPDMA analyses.[42,71,72]

Stage One: First, for each perspective (societal, healthcare) and comparison (e.g. SMT vs HEA), we identified trials for possible meta-analysis. Next, we conducted individual trial estimates for differences in effectiveness, costs, and incremental cost-effectiveness.

Stage Two: We combined studies using random effects models to produce pooled estimates. Prior to pooling, we visually inspected individual trial estimates of effectiveness and costs using forest plots and determined the amount of statistical heterogeneity using the I^2 statistic. In addition, we inspected ICERs and cost-effectiveness acceptability curves from each individual study to ensure pooled results were clinically appropriate (i.e. not pooling results from studies where ICERs or acceptability curves are drastically different). When ICERs or cost-effectiveness acceptability curves were not similar, we reported the individual trial cost-effectiveness results.

A limited number of sub-group analyses were planned (age, pain location, pain duration), but could not be completed due to a limited number of subjects within each sub-group for each comparison.

Results

We included data from 1803 participants across eight randomized trials. Complete clinical outcome and cost data was available for 1488 (83%) of participants. Results are presented by treatment comparison below (Tables 4-7). ICERs and cost-effectiveness acceptability curves varied substantially between studies, thus we reported findings from the individual trials. Figures detailing the uncertainty of ICER estimates on the cost-effectiveness plane for all outcomes, net monetary benefit findings for QALY outcomes, and cost-effectiveness acceptability curves for pain and disability reduction are displayed in the appendix.

SMT vs HEA

Two trials with 383 participants included data for this comparison, one included adults with acute neck pain and the other included adults with chronic low back pain. Complete cost and clinical outcome data was available for 295 (77%) participants. ICERs and cost-effectiveness acceptability curves were substantially different by trial, so cost-effectiveness outcomes were not pooled (e.g. ICERs below $44k/QALY for acute neck pain, but not calculated due to SMT having higher costs and lower QALYs for chronic back pain). Differences in clinical outcomes over the one-year time horizon were small and not statistically significant across studies. Clinical outcomes favored SMT over HEA for adults with acute neck pain, and HEA over SMT for adults with chronic back pain. Societal and healthcare costs were higher for SMT compared to HEA, and differences in healthcare costs were statistically significant in both trials. On average, societal costs were $611 higher for adults with acute neck pain (95% CI -$1243 to $2396) and $82 higher for adults with chronic back pain (-$2577 to $2291). Healthcare costs were $262 higher for adults with acute neck pain (95% CI $138 to $437) and $311 higher for adults with chronic back pain (95% CI $158 to $461).

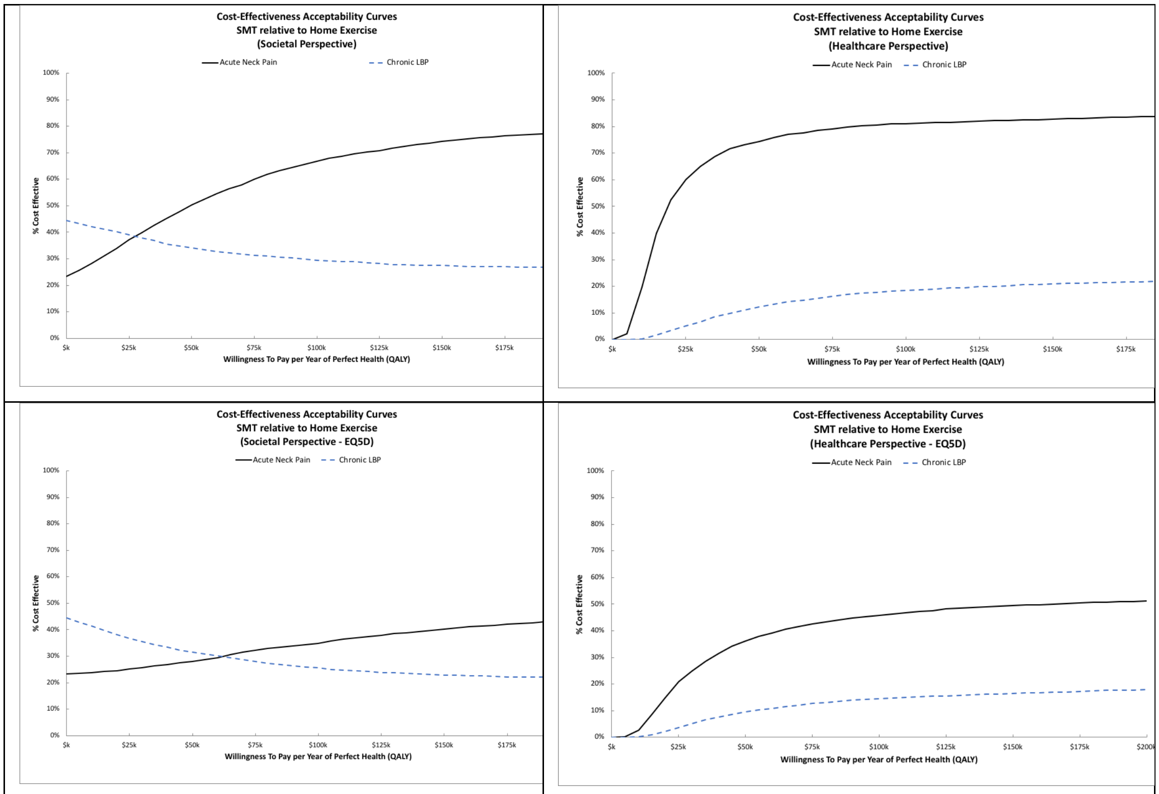
The individual trial ICER estimates and cost-effectiveness acceptability curves varied substantially. For adults with acute neck pain, SMT costs more and was more effective on average. ICERs were $44k/QALY from the societal perspective and $19k/QALY from the healthcare perspective. Sensitivity analyses assessing differences in QALYs using the EQ5D instead of the SF6D resulted in smaller QALY differences (mean difference of 0.002 QALYs) and higher ICERs ($305k/QALY for societal perspective; $131k/QALY for healthcare perspective). Figure 1 shows cost-effectiveness acceptability curves for SMT relative to HEA across perspectives and QALY outcomes. For acute neck pain, the probability SMT is cost-effective relative to HEA is near 70% for the societal perspective and 80% for the healthcare perspective at willingness to pay (WTP) thresholds of $100k/QALY and higher. In the sensitivity analyses using EQ5D QALYs, the probability of cost-effectiveness decreases to roughly 40% for the societal perspective and 50% for the healthcare perspective at WTP thresholds of $100k/QALY and higher. For adults with chronic back pain, SMT cost more and was less effective than HEA across perspectives and outcomes with probabilities of cost-effectiveness that were below 50% for a wide range of willingness to pay thresholds.

Table 4. Cost-effectiveness results for Spinal Manipulation Therapy relative to Home Exercise and Advice

	# trials	# subjects	Δ Societal Costs (95% CI)†	I^2	Δ Healthcare Costs (95% CI) †	I^2	Δ Outcome (95%CI) †	I^2	ICER (Societal)	ICER (Healthcare)
QALYs (SF6D)	2	383	$422 (-$1064 to $1836)	0%	$286 ($187 to $437)	0%	0.003 (-0.014 to 0.020)	34%	--	--
ANP	--	182	$611 (-$1243 to $2396)	--	$262 ($138 to $437)	--	0.014 (-0.011 to 0.039)	--	$43,614/ QALY	$18,747/ QALY
CLBP	--	201	$82 (-$2577 to $2291)	--	$311 ($158 to $461)	--	-0.008 (-0.031 to 0.017)	--	HEA Dominant‡	HEA Dominant‡
QALYs (EQ5D)	2	383	$422 (-$1064 to $1836)	0%	$286 ($187 to $437)	0%	-0.003 (-0.018 to 0.013)	0%	--	--
ANP	--	182	$611 (-$1243 to $2396)	--	$262 ($138 to $437)	--	0.002 (-0.018 to 0.022)	--	$305,300/ QALY	$131,230/ QALY
CLBP	--	201	$82 (-$2577 to $2291)	--	$311 ($158 to $461)	--	-0.010 (-0.034 to 0.013)	--	HEA Dominant‡	HEA Dominant‡
Pain reduction	2	383	$422 (-$1064 to $1836)	0%	$286 ($187 to $437)	0%	0.06 (-0.28 to 0.35)	0%	--	--
ANP	--	182	$611 (-$1243 to $2396)	--	$262 ($138 to $437)	--	0.15 (-0.31 to 0.62)	--	$4,070	$1,749
CLBP	--	201	$82 (-$2577 to $2291)	--	$311 ($158 to $461)	--	-0.03 (-0.52 to 0.40)	--	HEA Dominant‡	HEA Dominant‡
Disability reduction (SMD)	2	383	$422 (-$1064 to $1836)	0%	$286 ($187 to $437)	0%	-0.07 (-0.27 to 0.10)	0%	--	--
ANP	--	182	$611 (-$1243 to $2396)	--	$262 ($138 to $437)	--	0.03 (-0.24 to 0.29)	--	$20,354	$8,749
CLBP	--	201	$82 (-$2577 to $2291)	--	$311 ($158 to $461)	--	-0.16 (-0.44 to 0.07)	--	HEA Dominant‡	HEA Dominant‡

† Bias-corrected bootstrap confidence intervals; ‡ Dominant = lower mean costs and better mean outcomes; ICER = Incremental cost-effectiveness ratio; QALY = quality adjusted life year; ANP = acute neck pain trial in adults; CLBP = chronic low back pain trial in adults

Figure 1. Cost-effectiveness acceptability curves for Spinal Manipulation Therapy relative to Home Exercise and Advice.



The top row displays findings from the primary analysis. The bottom row displays findings from the sensitivity analysis using EQ5D for QALYs. The societal perspective is shown in the left column and the healthcare perspective is shown in the right column.

<u>SMT+HEA vs HEA</u>

Three trials with 512 participants included data for this comparison. One trial included adults with back-related leg pain, the second assessed older adults with chronic low back pain, and the third included older adults with chronic neck pain. Complete cost and clinical outcome data was available for 445 (87%) participants. Cost-effectiveness outcomes were not pooled due to important differences in estimated ICERs and cost-effectiveness acceptability curves between studies (e.g. Adding SMT to HEA resulted in lower costs and higher QALYs in back-related leg pain, but higher costs and lower QALYs in older adults with chronic back pain). Differences in clinical outcomes were small and generally not statistically significant across studies. Across all three studies, clinical outcomes favored adding SMT to HEA, with the exception of QALYs for older adults with chronic low back pain. The only statistically significant finding favored adding SMT to HEA for reducing pain severity in older adults with chronic neck pain. Pooled differences in pain and disability reduction across studies were statistically significant, but small in magnitude with a mean difference in pain reduction of 4 percentage points (0.41 on a 0-10 scale) and a standardized mean difference in disability reduction of 0.19. Differences in costs varied by population and perspective. Both societal and healthcare costs were significantly lower when adding SMT to HEA for adults with back-related leg pain (mean difference of $4918 lower for societal perspective and $1804 lower for healthcare perspective). Healthcare costs were significantly higher for older adults with chronic neck ($724 higher) and low back pain ($1022 higher). Societal costs were not significantly different in the two trials with older adults and were lower when adding SMT to HEA for chronic neck pain ($541 lower), but higher for chronic low back pain ($949 higher).

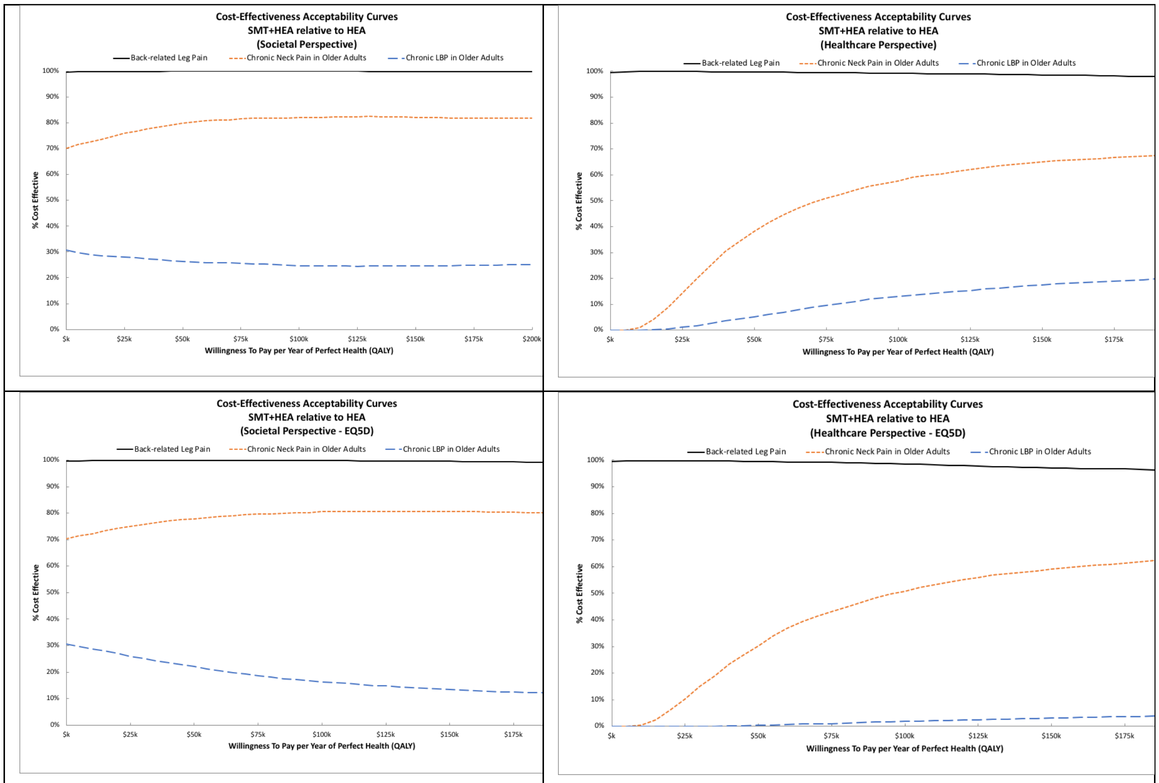
ICER estimates and cost-effectiveness acceptability curves varied by trial. For adults with back-related leg pain, adding SMT to HEA costs less and was more effective across all outcomes and perspectives. For older adults with chronic neck pain, adding SMT to HEA cost less and was more effective from the societal perspective. Costs for adding SMT to HEA were higher from the healthcare perspective resulting in ICERs ranging from $80k to $91k per QALY. For older adults with chronic low back pain, adding SMT to HEA cost more and was less effective in terms of QALYs (i.e. dominated). Figure 2 shows cost-effectiveness acceptability curves for adding SMT to HEA. For adults with back-related leg pain, adding SMT to HEA has a very high probability of cost-effectiveness across perspectives and willingness to pay thresholds. For older adults with chronic low back pain, there is a low probability (<30%) that adding SMT to HEA is cost-effective across perspectives and WTP thresholds. For older adults with chronic neck pain, the probability that adding SMT to HEA is cost-effective is above 70% regardless of WTP threshold for the societal perspective. For the healthcare perspective, the probability of cost-effectiveness plateaus at around 60% for WTP thresholds above $100k/QALY. Sensitivity analyses using EQ5D QALYs had similar findings across all three trials.

Table 5. Cost-effectiveness results for adding Spinal Manipulation Therapy to Home Exercise and Advice

	# trials	# subjects	Δ Societal Costs (95% CI)†	I²	Δ Healthcare Costs (95% CI) †	I²	Δ Outcome (95%CI) †	I²	ICER (Societal)	ICER (Healthcare)
QALYs (SF6D)	3	512	-$1382 (-$3574 to $182)	56%	$194 (-$591 to $427)	79%	0.008 (-0.006 to 0.023)	0%	--	--
BRLP	--	192	-$4918 (-$9325 to -$1312)	--	-$1804 (-$3556 to -$356)	--	0.018 (-0.004 to 0.044)	--	SMT+HEA Dominant‡	SMT+HEA Dominant‡
SLBP	--	161	$949 (-$3390 to $5032)	--	$1022 ($413 to $2369)	--	-0.008 (-0.037 to 0.019)	--	HEA Dominant‡	HEA Dominant‡
SNP	--	159	-$541 (-$3015 to $1604)	--	$724 ($324 to $1651)	--	0.009 (-0.018 to 0.034)	--	SMT+HEA Dominant‡	$80,497/QALY
QALYs (EQ5D)	3	512	-$1382 (-$3574 to $182)	56%	$194 (-$591 to $427)	79%	0.002 (-0.013 to 0.014)	39%	--	--
BRLP	--	192	-$4918 (-$9325 to -$1312)	--	-$1804 (-$3556 to -$356)	--	0.015 (-0.011 to 0.043)	--	SMT+HEA Dominant‡	SMT+HEA Dominant‡
SLBP	--	161	$949 (-$3390 to $5032)	--	$1022 ($413 to $2369)	--	-0.013 (-0.036 to 0.005)	--	HEA Dominant‡	HEA Dominant‡
SNP	--	159	-$541 (-$3015 to $1604)	--	$724 ($324 to $1651)	--	0.008 (-0.015 to 0.031)	--	SMT+HEA Dominant‡	$90,560/QALY
Pain reduction	3	512	-$1382 (-$3574 to $182)	56%	$194 (-$591 to $427)	79%	0.41 (0.15 to 0.68)	0%	--	--
BRLP	--	192	-$4918 (-$9325 to -$1312)	--	-$1804 (-$3556 to -$356)	--	0.48 (-0.002 to 0.95)	--	SMT+HEA Dominant‡	SMT+HEA Dominant‡
SLBP	--	161	$949 (-$3390 to $5032)	--	$1022 ($413 to $2369)	--	0.15 (-0.32 to 0.66)	--	$6326	$6811
SNP	--	159	-$541 (-$3015 to $1604)	--	$724 ($324 to $1651)	--	0.56 (0.12 to 1.00)	--	SMT+HEA Dominant‡	$1294
Disability reduction (SMD)	3	512	-$1382 (-$3574 to $182)	56%	$194 (-$591 to $427)	79%	0.19 (0.04 to 0.37)	0%	--	--
BRLP	--	192	-$4918 (-$9325 to -$1312)	--	-$1804 (-$3556 to -$356)	--	0.24 (-0.02 to 0.50)	--	SMT+HEA Dominant‡	SMT+HEA Dominant‡
SLBP	--	161	$949 (-$3390 to $5032)	--	$1022 ($413 to $2369)	--	0.09 (-0.22 to 0.40)	--	$10,544	$11,352
SNP	--	159	-$541 (-$3015 to $1604)	--	$724 ($324 to $1651)	--	0.24 (-0.05 to 0.56)	--	SMT+HEA Dominant‡	$3,018

† Bias-corrected bootstrap confidence intervals; ‡ Dominant = lower mean costs and better mean outcomes; ICER = Incremental cost-effectiveness ratio; QALY = quality adjusted life year; BRLP = back-related leg pain trial in adults; SLBP = chronic low back pain trial in older adults (seniors); SNP = chronic neck pain trial in older adults (seniors)

Figure 2. Cost-effectiveness acceptability curves for adding Spinal Manipulation Therapy to Home Exercise and Advice



The top row displays findings from the primary analysis. The bottom row displays findings from the sensitivity analysis using EQ5D for QALYs. The societal perspective is shown in the left column and the healthcare perspective is shown in the right column.

ET vs SMT

Four trials with 650 participants included data for this comparison. Two trials focused on chronic back pain and the other two focused on neck pain. The population was limited to older adults in one of the chronic back and chronic neck pain trials. Complete cost and clinical outcome data was available for 551 (85%) participants. Cost-effectiveness outcomes were not pooled due to clinical heterogeneity in estimated ICERs and cost-effectiveness acceptability curves between studies (ICERs for ET relative to SMT were below $29k/QALY in two studies, but ET was dominated with higher costs and lower QALYs in two studies). Differences in clinical outcomes were small and generally not statistically significant across studies. Differences in clinical outcomes consistently favored ET for chronic neck pain, with a significant improvement in pain reduction (mean difference 0.61; 95% CI 0.01 to 1.13). For older adults with chronic neck pain, differences in clinical outcomes consistently favored SMT, but were not significant. Differences in clinical outcomes for the two chronic back pain studies did not consistently favor one treatment over the other. ET consistently resulted in higher costs across trials from both the societal and healthcare perspectives, with most differences being statistically significant. Societal costs were over $2000 higher with ET for chronic back pain and chronic neck pain in older adults. Differences in societal costs were lower and not statistically significant for chronic neck pain ($524) and chronic back pain in older adults ($433). Healthcare costs were significantly higher for ET relative to SMT across trials with differences ranging from $1394 in older adults with chronic neck pain to $1965 for chronic back pain.

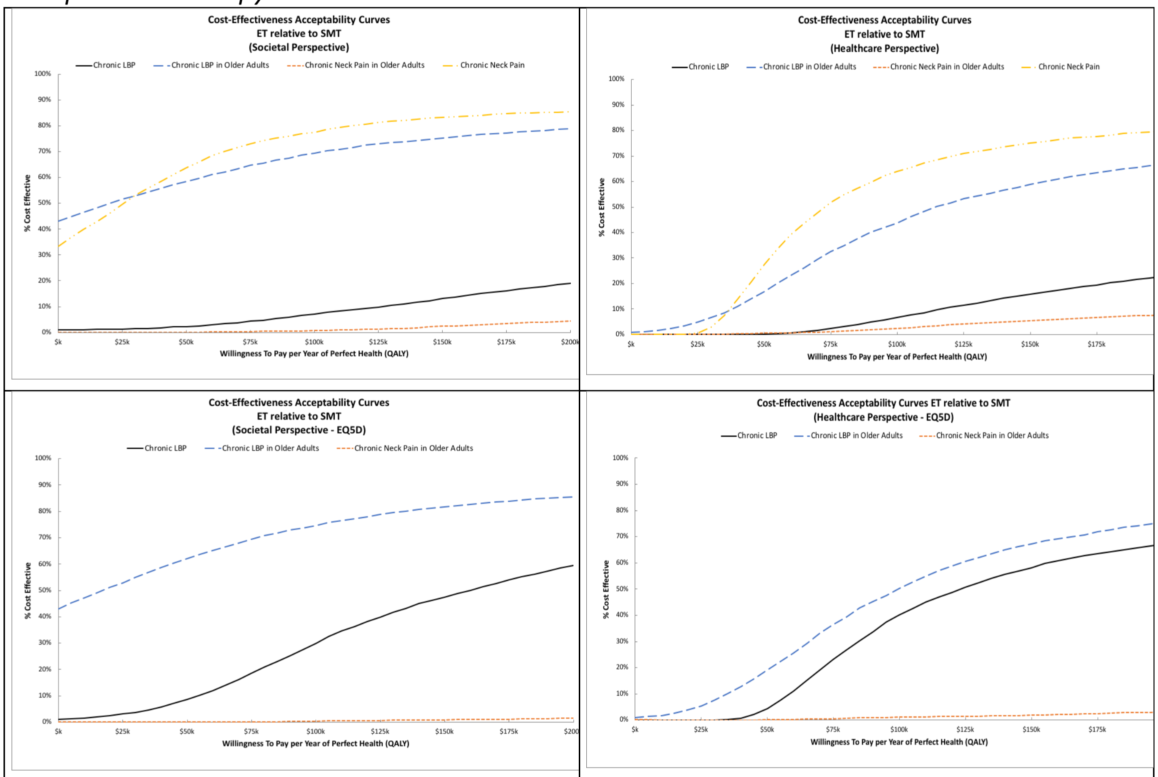
ICER estimates and cost-effectiveness acceptability curves varied by trial. For adults with chronic back pain, ET resulted in higher costs and lower QALYs than SMT across perspectives. The sensitivity analyses using EQ5D QALYs favored ET over SMT, resulting in ICERs of $156k/QALY for the societal perspective and $123k/QALY for the healthcare perspective. Findings for older adults with chronic back pain were more consistent, with ET consistently resulting in higher costs and QALYs with ICERs below $30k/QALY from the societal perspective and below $120k/QALY from the healthcare perspective. For adults with chronic neck pain, ET had higher costs and greater QALYs with ICERs near $22k/QALY from the societal perspective and $69k/QALY from the healthcare perspective. EQ5D QALY estimates were not available from this trial. For older adults with chronic neck pain, ET resulted in higher costs and lower QALYs across both perspectives. Figure 3 displays the cost-effectiveness acceptability curves for ET relative to SMT. The probability of cost-effectiveness for ET relative to SMT was low (<20%) across WTP thresholds and perspectives for adults with chronic back pain and older adults with chronic neck pain. The probability of cost-effectiveness for ET in adults with chronic back pain increased in the sensitivity analyses using EQ5D QALYs. For older adults with chronic back pain, the probability of cost-effectiveness for ET was near 70% for WTP thresholds of $100k/QALY and higher from the societal perspective and near 60% for thresholds of $150k/QALY and higher from the healthcare perspective. The sensitivity analysis with EQ5D QALYs had little impact on results from this trial. For adults with chronic neck pain, the probability of cost-effectiveness was near 80% for WTP thresholds of $100k/QALY and higher from the societal perspective and thresholds of $150k/QALY and higher from the healthcare perspective.

Table 6. Cost-effectiveness results for Exercise Therapy relative to Spinal Manipulation Therapy

	# trials	# subjects	Δ Societal Costs (95% CI)†	I^2	Δ Healthcare Costs (95% CI) †	I^2	Δ Outcome (95%CI) †	I^2	ICER (Societal)	ICER (Healthcare)
QALYs (SF6D)	4	650	$1915 ($1093 to $3225)	0%	$1746 ($1668 to $1999)	73%	0.004 (-0.011 to 0.016)	12%	--	--
CLBP	--	200	$2501 ($388 to $4551)	--	$1965 ($1788 to $2127)	--	-0.001 (-0.028 to 0.022)	--	SMT Dominant‡	SMT Dominant‡
CNP I	--	127	$524 (-$2164 to $2966)	--	$1647 ($1548 to $1756)	--	0.024 (-0.010 to 0.058)	--	$21,827/ QALY	$68,643/ QALY
SLBP	--	161	$433 (-$3192 to $4191)	--	$1769 ($317 to $3358)	--	0.015 (-0.013 to 0.044)	--	$28,849/ QALY	$117,926/ QALY
SNP	--	162	$2235 ($771 to $3458)	--	$1394 ($573 to $1816)	--	-0.010 (-0.033 to 0.013)	--	SMT Dominant‡	SMT Dominant‡
QALYs (EQ5D)	3	523							--	--
CLBP	--	200	$2501 ($388 to $4551)	--	$1965 ($1788 to $2127)	--	0.016 (-0.011 to 0.042)	--	$156,310/ QALY	$122,825/ QALY
SLBP	--	161	$433 (-$3192 to $4191)	--	$1769 ($317 to $3358)	--	0.019 (-0.005 to 0.045)	--	$22,776/ QALY	$93,100/ QALY
SNP	--	162	$2235 ($771 to $3458)	--	$1394 ($573 to $1816)	--	-0.015 (-0.037 to 0.008)	--	SMT Dominant‡	SMT Dominant‡
Pain reduction	4	650	$1915 ($1093 to $3225)	0%	$1746 ($1668 to $1999)	73%	0.05 (-0.20 to 0.29)	68%	--	--
CLBP	--	200	$2501 ($388 to $4551)	--	$1965 ($1788 to $2127)	--	0.26 (-0.19 to 0.70)	--	$9,619	$7,558
CNP I	--	127	$524 (-$2164 to $2966)	--	$1647 ($1548 to $1756)	--	0.61 (0.01 to 1.13)	--	$859	$2,701
SLBP	--	161	$433 (-$3192 to $4191)	--	$1769 ($317 to $3358)	--	-0.19 (-0.67 to 0.30)	--	SMT Dominant‡	SMT Dominant‡
SNP	--	162	$2235 ($771 to $3458)	--	$1394 ($573 to $1816)	--	-0.40 (-0.85 to 0.05)	--	SMT Dominant‡	SMT Dominant‡
Disability reduction (SMD)	4	650	$1915 ($1093 to $3225)	0%	$1746 ($1668 to $1999)	73%	0.05 (-0.11 to 0.21)	51%	--	--
CLBP	--	200	$2501 ($388 to $4551)	--	$1965 ($1788 to $2127)	--	0.19 (-0.09 to 0.48)	--	$13,163	$10,343
CNP I	--	127	$524 (-$2164 to $2966)	--	$1647 ($1548 to $1756)	--	0.21 (-0.12 to 0.56)	--	$2,494	$7,845
SLBP	--	161	$433 (-$3192 to $4191)	--	$1769 ($317 to $3358)	--	0.08 (-0.26 to 0.40)	--	$5,410	$22,112
SNP	--	162	$2235 ($771 to $3458)	--	$1394 ($573 to $1816)	--	-0.28 (-0.59 to 0.01)	--	SMT Dominant‡	SMT Dominant‡

† Bias-corrected bootstrap confidence intervals; ‡ Dominant = lower mean costs and better mean outcomes; ICER = Incremental cost-effectiveness ratio; QALY = quality adjusted life year; CLBP = chronic low back pain trial in adults; CNP I = first chronic neck pain trial in adults; SLBP = chronic low back pain trial in older adults (seniors); SNP = chronic neck pain trial in older adults (seniors)

Figure 3. Cost-effectiveness acceptability curves for Exercise Therapy relative to Spinal Manipulation Therapy



The top row displays findings from the primary analysis. The bottom row displays findings from the sensitivity analysis using EQ5D for QALYs. The societal perspective is shown in the left column and the healthcare perspective is shown in the right column.

SMT+ET vs ET

Two trials with 365 participants included data for this comparison. One trial included adolescents with chronic low back pain and the other included adults with chronic neck pain. Complete cost and clinical outcome data was available for 273 (88%) participants. Cost-effectiveness outcomes were not pooled due to clinical heterogeneity in estimated ICERs and cost-effectiveness acceptability curves between studies (e.g. ICERs for societal perspective using EQ5D near \$35k/QALY for adolescents with chronic back pain and \$150k/QALY for adults with chronic neck pain). QALYs in the adolescent trial were only available from the EQ5D. For adolescents with chronic back pain, adding SMT to ET resulted in mean pain reduction of 0.75 (95% CI 0.30 to 1.23) and a standardized mean disability reduction of 0.29 (95% CI 0.02 to 0.59). Differences in other clinical outcomes were small and not statistically significant within the individual trials and pooled analyses. All differences in clinical outcomes favored the addition of SMT to ET with the exception of pain reduction for adults with chronic neck pain (mean difference -0.09; 95%CI -0.57 to 0.39). Societal and healthcare costs were higher for the addition of SMT to ET in both trials. For adolescents with chronic back pain, societal costs were $354 higher (95% CI $210 to $483) and healthcare costs were $280 higher (95% CI $167 to $389). For adults with chronic neck pain, societal costs were $460 higher (95% CI -$2884 to $3421) and healthcare costs were $187 higher (-$435 to $543).

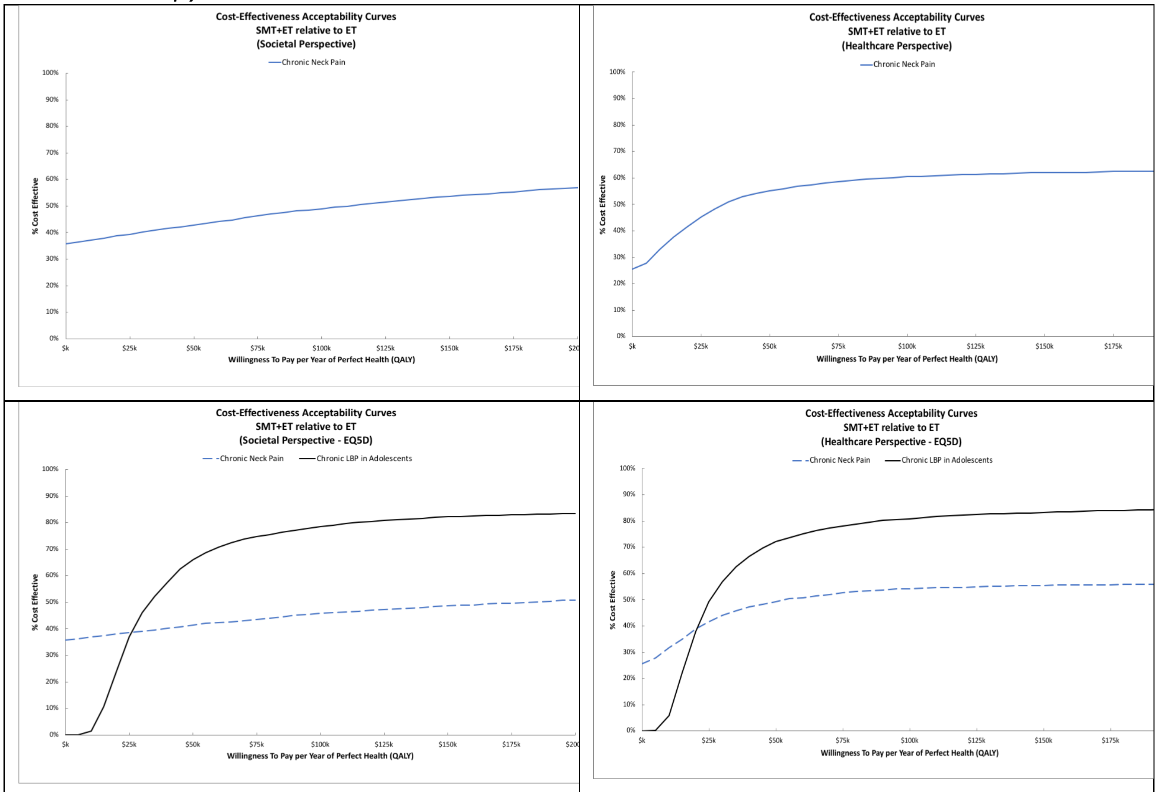
ICER estimates and cost-effectiveness acceptability curves varied by trial. For adults with chronic neck pain, adding SMT to ET resulted in higher costs and QALYs with ICERs of $77k/QALY from the societal perspective and $31k/QALY from the healthcare perspective. QALY gains were lower in the sensitivity analysis using EQ5D, resulting in larger ICERs of $153k/QALY for the societal perspective and $62k/QALY from the healthcare perspective. For adolescents with chronic back pain, adding SMT to ET also resulted in higher costs and QALYs with ICERs of $35k/QALY from the societal perspective and $28k/QALY from the healthcare perspective. Figure 4 displays the cost-effectiveness acceptability curves for adding SMT to ET. For adults with chronic neck pain, the probability of cost-effectiveness is near 50% across perspectives for WTP thresholds above $100k/QALY. The sensitivity analyses using EQ5D QALYs had minimal impact on these findings. For adolescents with chronic back pain, the probability adding SMT to ET is cost-effective is above 70% for WTP thresholds above $50k/QALY across perspectives.

Table 7. Cost-effectiveness results for adding Spinal Manipulation Therapy to Exercise Therapy

	# trials	# subjects	Δ Societal Costs (95% CI)†	I^2	Δ Healthcare Costs (95% CI) †	I^2	Δ Outcome (95%CI) †	I^2	ICER (Societal)	ICER (Healthcare)
QALYs (SF6D)										
CNP II	--	180	$460 (-$2884 to $3421)	--	$187 (-$435 to $543)	--	0.006 (-0.019 to 0.031)	--	$76,642/ QALY	$31,091/ QALY
QALYs (EQ5D)	2	365	$354 (-$842 to $1249)	0%	$277 ($22 to $382)	6%	0.003 (-0.024 to 0.033)	0%	--	--
ALBP	--	185	$354 ($210 to $483)	--	$280 ($167 to $389)	--	0.010 (-0.009 to 0.028)	--	$35,356/ QALY	$27,981/ QALY
CNP II	--	180	$460 (-$2884 to $3421)	--	$187 (-$435 to $543)	--	0.003 (-0.024 to 0.033)	--	$153,282/ QALY	$62,180/ QALY
Pain reduction	2	365	$354 (-$842 to $1249)	0%	$277 ($22 to $382)	6%	0.33 (-0.02 to 0.67)	0%	--	--
ALBP	--	185	$354 ($210 to $483)	--	$280 ($167 to $389)	--	0.75 (0.30 to 1.23)	--	$472	$373
CNP II	--	180	$460 (-$2884 to $3421)	--	$187 (-$435 to $543)	--	-0.09 (-0.57 to 0.39)	--	ET Dominant‡	ET Dominant‡
Disability reduction (SMD)	2	365	$354 (-$842 to $1249)	0%	$277 ($22 to $382)	6%	0.23 (0.03 to 0.46)	1%	--	--
ALBP	--	185	$354 ($210 to $483)	--	$280 ($167 to $389)	--	0.29 (0.02 to 0.59)	--	$1,219	$965
CNP II	--	180	$460 (-$2884 to $3421)	--	$187 (-$435 to $543)	--	0.16 (-0.11 to 0.45)	--	$2,874	$1,166

† Bias-corrected bootstrap confidence intervals; ‡ Dominant = lower mean costs and better mean outcomes; ICER = Incremental cost-effectiveness ratio; QALY = quality adjusted life year; ALBP = chronic low back pain trial in adolescents; CNP II = second chronic neck pain trial in adults

Figure 4. Cost-effectiveness acceptability curves for adding Spinal Manipulation Therapy to Exercise Therapy



The top row displays findings from the primary analysis. The bottom row displays findings from the sensitivity analysis using EQ5D for QALYs. The societal perspective is shown in the left column and the healthcare perspective is shown in the right column.

Discussion

Summary of Findings

Our primary goal was to estimate the incremental cost-effectiveness of spinal manipulation, exercise therapy, and self-management for spinal pain using cost and clinical outcome data collected as part of eight randomized clinical trials performed in the U.S. with an individual patient data meta-analysis (IPDMA) approach. IPDMA of cost-effectiveness data are rarely possible due to differences in outcomes and settings across trials. Our project was promising as we had access to eight randomized clinical trials with similar methods, clinical and cost outcomes, treatment comparisons, and settings. Despite these similarities, estimates of cost-effectiveness and the uncertainty surrounding them varied considerably across trials preventing the pooling and meta-analysis of cost-effectiveness outcomes. In response, we reported cost-effectiveness findings by treatment comparison and trial with the following findings:

SMT vs HEA - For chronic back pain, SMT resulted in higher costs and worse health outcomes relative to HEA across all outcomes and perspectives and is unlikely to be cost-effective. For acute neck pain, SMT may be cost-effective relative to HEA depending on the outcome and perspective. SMT had higher costs and better outcomes on average, but differences in outcomes were small. QALY estimates varied considerably between the SF6D and EQ5D (SF6D: 0.014; EQ5D: 0.002) with ICERs of $19k to $44k per QALY using the SF6D and $131k to $305k per QALY using EQ5D. ICERs were more favorable for the healthcare perspective. Prior research has demonstrated that the EQ5D and SF6D are not interchangeable for neck pain patients due to differences in the domains assessed and number of response options.[73] The SF6D includes vitality as a health dimension and has more response options than the EQ5D, which allows for better distinction between health states and fewer ceiling effects. An assessment of the psychometric properties of the two QALY measures in older adults with chronic neck pain showed minor differences in responsiveness, but the SF6D had better reliability and known-group validity with less measurement error relative to the EQ5D. [74]

SMT+HEA vs HEA - Adding SMT to HEA resulted in lower costs and better health outcomes for back-related leg pain across all outcomes and perspectives and is very likely cost-effective. Adding SMT to HEA is also likely to be cost-effective for older adults with chronic neck pain. Adding SMT to HEA resulted in better health outcomes and lower societal costs. Healthcare costs were higher, but resulted in ICERs that were below $100k/QALY. For older adults with chronic back pain adding SMT to HEA is not likely cost-effective. Clinical outcomes did not favor adding SMT to HEA for QALYs, differences in pain and disability reduction were small, and costs were higher from both perspectives.

ET vs SMT – SMT is not likely cost-effective relative to ET for adults with chronic neck pain. ET consistently resulted in better outcomes and higher costs, with ICERs below $70k/QALY. However, for older adults with chronic neck pain, SMT is very likely cost-effective. SMT consistently resulted in lower costs and better outcomes with high probabilities (>90%) of cost-effectiveness across a wide range of WTP thresholds. For chronic back pain, SMT may be cost-effective compared to ET depending on the population, outcome, and perspective considered.

In adults with chronic back pain, costs were consistently higher for ET and QALY estimates varied considerably between the SF6D and EQ5D, resulting in ICERs that ranged from domination for SMT with the SF6D to as low as $122k/QALY for ET with the EQ5D. For older adults with chronic back pain, ET resulted in higher QALYs and costs with ICERs below $29k/QALY from the societal and $118k/QALY from the healthcare perspective. Results for pain reduction were less favorable with ET resulting in higher costs and less pain reduction.

SMT+ET vs ET - Adding SMT to ET results in higher costs and better health outcomes for adolescents with chronic back pain and is likely cost-effective. For adults with chronic neck pain, adding SMT to ET may be cost-effective. Adding SMT to ET resulted in higher costs and QALYs with ICERs below $77k/QALY with the SF6D and below $154k/QALY with the EQ5D. Results for pain reduction were less favorable with adding SMT to ET resulting in higher costs and less pain reduction.

Table 8 provides a high level summary of findings considering ICER results in relationship to potential willingness-to-pay thresholds for a QALY, the probability of cost-effectiveness across the range of willingness-to-pay thresholds, and the consistency of findings across perspectives and outcomes.

Table 8. High-level summary of findings

	SMT vs HEA	**SMT+HEA vs HEA**	**SMT vs ET**	**SMT+ET vs ET**
Chronic LBP	Not likely (adults)	Not likely (older adults)	Maybe (adults and older adults)	Likely (adolescents)
Chronic BRLP		Very likely (adults)		
Chronic NP		Likely (older adults)	Very Likely (older adults) Not likely (adults)	Maybe (adults)
Acute NP	Maybe (adults)			

Very likely = Dominant or ICERs below $50k/QALY; 80% or greater probability of cost-effectiveness at WTP thresholds above $100k/QALY; Consistent findings across outcomes/perspectives
Likely = Dominant or ICERs below $100k/QALY; 60% to 80% probability of cost-effectiveness at WTP thresholds above $100k/QALY; Findings mostly consistent across outcomes/perspectives
Maybe = ICERs between $100k and $200k/QALY; 40 to 60% probability of cost-effectiveness for WTP thresholds between $100k and $200k/QALY; Inconsistency across outcomes/perspectives
Not likely = Dominated or ICERs above $150k/QALY; 20 to 40% probability of cost-effectiveness for WTP thresholds between $100 and $200k/QALY; Findings mostly consistent across outcomes/perspectives
Very unlikely = Dominated or ICERs above $200k/QALY with less than 20% probability of cost-effectiveness for WTP thresholds below $200k/QALY; Consistent findings across outcomes/perspectives
BRLP = Back-related leg pain; **ET =** Supervised Exercise therapy – up to 20, one-hour visits; **HEA =** Home exercise and advice – 2 to 4, one-hour visits; **LBP =** Low back pain; **NP =** Neck pain; **SMT =** Spinal manipulation therapy – 15 to 20 visits

Strengths

This study has many important strengths. The use of data from randomized trials lowers the risk of selection bias impacting not only differences in clinical outcomes, but also subsequent healthcare use and costs. Multiple high-quality systematic reviews, including Cochrane reviews, have assessed the methods of the included trials as fair to high quality.[20,24,25,75-77] The amount of missing data was low with 83% of all participants providing complete cost and clinical outcome data. Only two of the assessed comparisons (SMT vs HEA and ET vs HEA) had greater than 20% of participants not providing complete data. The similarity between trials in treatment comparisons, treatment protocols, study settings, and data collection measures and methods is a major strength. We assessed cost-effectiveness from both the healthcare and societal perspective and included lost productivity costs for reduced work both in and outside of the home, which is important for valuing societal costs, but is not common for economic evaluations in the spine pain field. The inclusion of condition specific measures such as pain intensity and disability is also a strength as it allows for assessment of consistency in findings across outcomes.

Limitations

There are also a number of important limitations to consider when assessing our findings. Randomized clinical trials are often designed and powered to detect important differences in disease specific clinical outcomes that are most likely to be impacted by the treatments assessed (e.g. pain severity). Important measures for assessing cost-effectiveness include more general health measures like changes in QALYs, healthcare use, and missed work. These measures were collected alongside disease specific measures, but the trials were not powered to detect important differences in cost-effectiveness outcomes. Participants self-reported their use of healthcare and medications along with number of missed work days. We did not have access to administrative data for healthcare use or costs. While access to administrative data would have reduced potential measurement error for these variables, it is not without limitations due to the high variability in coverage and re-imbursement policies for healthcare procedures and providers across insurance products in the U.S. Costs for reduced productivity due to spinal pain included missed work in and outside of the home, but costs due to reduced productivity while still at work (i.e. presenteeism) were not included. This is an important limitation as costs due to reduced productivity while at work consistently account for a large proportion of total costs in spinal pain burden of illness studies.[9,78]

Comparisons to existing work

There are a number of published RCT-based cost-effectiveness analyses that have assessed SMT, ET, HEA, or combinations of these strategies (see Table 1). Most of the existing studies assessing these treatment comparisons were conducted in European healthcare settings where costs for healthcare are much lower than in the U.S. Published studies from the U.S. either compared the SMT approach to usual care for acute LBP or were included as part of this project. Published findings from our team on the cost-effectiveness of SMT in older adults with chronic neck pain have been updated in this project using 2020 cost estimates. Overall, the structure, number, and length of assessed programs varied considerably in existing studies. These studies have generally found SMT to be cost-effective, while the cost-effectiveness of exercise therapy approaches varied by trial, program format, and population.

One trial compared manual therapy (SMT) (up to 6, 45-minute visits) to a home exercise and advice intervention delivered by general practitioners for primarily chronic neck or back pain.[31] Manual therapy had lower healthcare costs, lower societal costs, and higher QALY gains compared to home exercise and advice. The probability that manual therapy is cost-effective relative to home exercise and advice was above 80% for a wide range of WTP thresholds.

Four trials compared manual therapy (SMT) and exercise interventions for neck pain. A trial by Korthals de Bos primarily included participants with acute or sub-acute neck pain (over 70% had pain for less than 12 weeks) and compared manual therapy (up to 6, 45-minute sessions) to physiotherapy (up to 12, 30 minute sessions; primarily exercise) and general practitioner care.[29] Manual treatment had lower healthcare and societal costs and better clinical outcomes compared to physiotherapy or general practitioner care for neck pain. The findings consistently favored manual therapy with little uncertainty as over 98% of the bootstrapped cost-effect estimates showed manual treatment resulting in lower costs and higher QALYs. A trial by Bosmans et al. included participants with subacute neck pain (pain duration between 4 and 12 weeks) and compared manual therapy (up to 6, 30-45 minute sessions) to a behavioral graded exercise approach (up to 18, 30-minute sessions).[35] Manual therapy resulted in significantly worse pain and disability outcomes, but differences in QALYs, healthcare, and societal costs were small and favored manual therapy. The uncertainty of cost-effectiveness findings for QALY analyses were not reported, but given the small differences in costs and QALYs, it's likely that the probability of cost-effectiveness would be near 50%, indicating that one approach is not clearly more cost-effective than the other. A trial by Van Dongen et al. compared manual therapy (up to 6, 30-60 minute sessions) to physiotherapy (up to 9, 30 minute sessions) for neck pain lasting between 2 and 52 weeks.[40] Manual therapy resulted in lower healthcare and societal costs and better clinical outcomes relative to physiotherapy, but differences in QALYs were small and the probabilities of cost-effectiveness were near 50% across a range of WTP thresholds, indicating that neither approach is cost-effective compared to the other. Finally, a trial by Lewis et al. compared the addition of either manual therapy or pulsed shortwave diathermy to an advice and exercise intervention with up to 7, 20-minute visits allowed for each approach.[32] Adding manual treatment to advice and exercise had the highest probability of being cost-effective compared to the other two approaches across all WTP thresholds from the societal perspective. For the healthcare perspective, adding manual therapy to advice and exercise had the highest probability of being cost-effective at WTP thresholds of $14k/QALY or higher.

Three trials compared manual therapy and exercise interventions for LBP. The UK BEAM trial included participants with acute or chronic LBP (~60% chronic) and compared an active education intervention in general practice to either a group exercise intervention that included cognitive behavioral principles (9, 60-minute classes), SMT (up to 8, 20-minute visits), or both exercise and SMT.[30] Compared to the active education intervention, both the SMT and exercise interventions resulted in higher healthcare costs and more QALYs, with ICERs below $19k/QALY. SMT had the highest probability of cost-effectiveness relative to the other treatments at WTP thresholds of $22k/QALY and higher. A trial by Rivero-Arias et al. compared the addition of a physiotherapy intervention including manual therapy and exercise instruction (up 6, 30-minute visits) to an active education intervention (1, 60-minute visit) for primarily chronic LBP (>75% with pain duration >12 weeks).[33] The manual therapy and exercise intervention led to higher healthcare costs and QALYs with an ICER less than $7k/QALY. The probability of physiotherapy being cost-effective was near 70% for WTP thresholds of $22k/QALY and higher. Total societal costs were lower for the manual treatment and exercise intervention. Finally, a trial by Critchley et al. compared a physiotherapy intervention of manual therapy and home exercise instruction (up to 12, 30-minute visits) to a low back stabilization group exercise program (8, 90-minute classes) or a pain management program that included education, exercises, and cognitive behavioral therapy approaches (8, 90-minute classes) for chronic LBP.[38] The pain management program had the lowest healthcare costs and highest QALYs gains. The manual therapy and home exercise intervention resulted in higher healthcare costs and QALYs relative to the exercise intervention with an ICER below $2500/QALY.

Implications for clinical practice and research

We report incremental cost-effectiveness ratios for three commonly used conservative interventions for managing neck or back pain. The cost-effectiveness of the interventions often varied by population and perspective. Unlike many European countries, there is no single entity responsible for healthcare coverage and payment decisions in the U.S. and the use of cost-effectiveness findings directly impacting policy decisions is limited.[79] Consensus does not exist on what threshold values of Dollars per QALY represent good value for healthcare services. Members from the Panel of Cost-effectiveness in Health and Medicine recommend using a range of thresholds from $50k/QALY to $200k/QALY to assess the value of healthcare strategies for promoting health.[80] These ranges coincide with recommendations from the World Health Organization for using two to three times the per capita annual income which would be $140k/QALY to $210k/QALY in the U.S.[80] Compared to home exercise and advice, ICERs for SMT were often below and ICERs for exercise therapy were frequently above recommended WTP thresholds. Given the fragmented nature of health insurance and healthcare in the U.S., findings from this study may be less relevant for individual patients and providers, who are faced with unique circumstances regarding availability, insurance coverage, and costs for spinal pain treatments.

While this study adds important information on the cost-effectiveness of SMT, exercise therapy, and home exercise and advice for spinal pain in the U.S., there is a need for additional studies assessing the cost-effectiveness of these approaches relative to other guideline recommended treatments for spine pain such as massage, acupuncture, mindfulness-based stress reduction, tai chi, yoga, and cognitive behavioral therapy approaches.[15,81] In addition, trials assessing the cost-effectiveness of common approaches in higher risk populations with more impactful pain and higher resource use (e.g. radiating arm or leg pain, high-impact chronic pain) are needed. Finally, future studies need to address reduced productivity while at work (i.e. presenteeism) in addition to missed work, as reduced productivity while at work accounts for a substantial portion of the societal burden due to spinal pain.

Conclusions

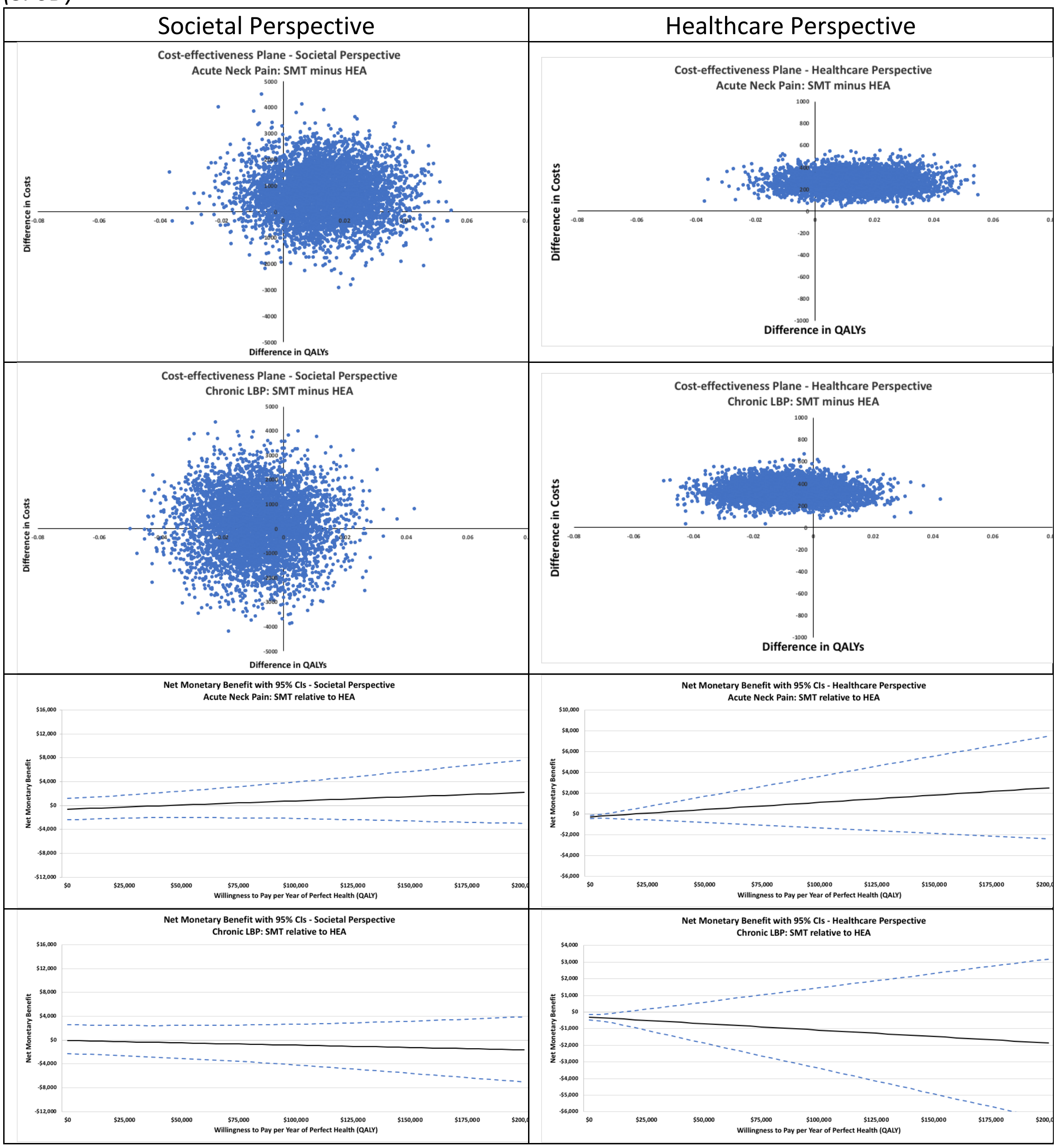
When compared with or added to home exercise and advice interventions, cost-effectiveness findings were favorable for using SMT for acute neck pain (may be cost-effective), chronic neck pain in older adults (likely cost-effective), and chronic back-related leg pain (very likely cost-effective). However, SMT was not likely cost-effective relative to home exercise approaches for chronic back pain in adults or older adults. When compared with exercise therapy approaches, SMT may be cost-effective for adults and older adults with chronic back pain and was very likely cost-effective for older adults with chronic neck pain. For adults with chronic neck pain, SMT is not likely cost-effective relative to ET, but may be cost-effective when added to ET depending on outcome. Adding SMT to ET is likely cost-effective for adolescents with chronic back pain.

Appendix materials

<u>SMT vs HEA Figures</u>

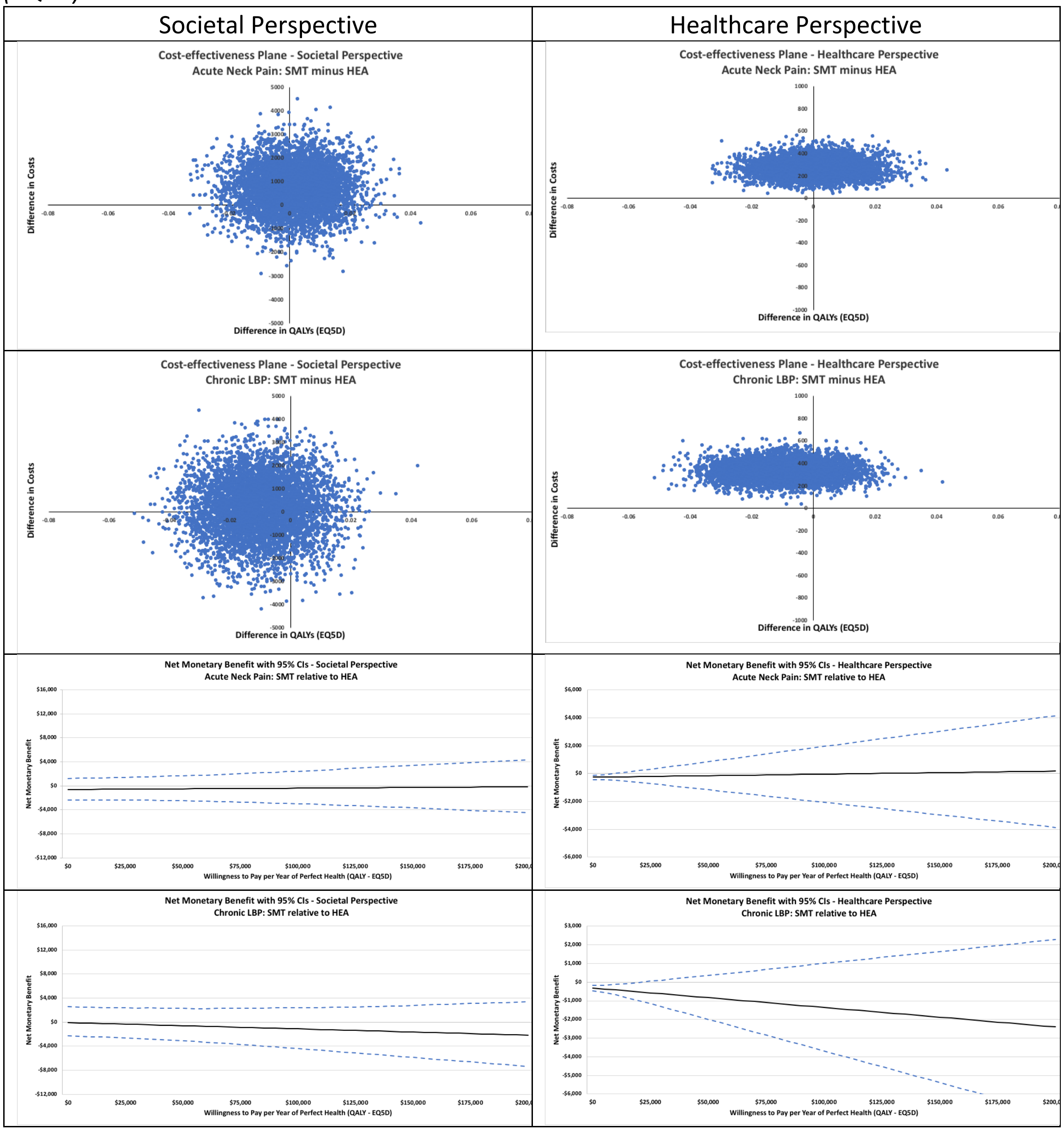
QALYs (SF6D)

Appendix Figure 1. SMT vs HEA Cost-effectiveness planes and net monetary benefit – QALYs (SF6D)



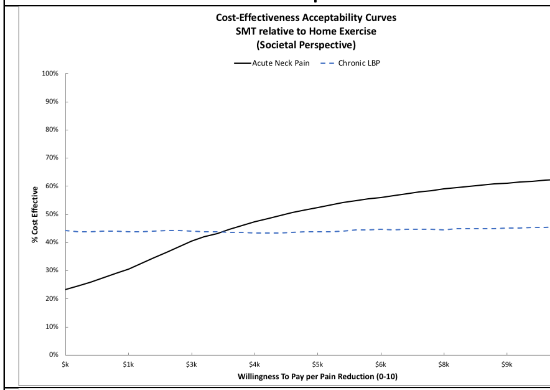
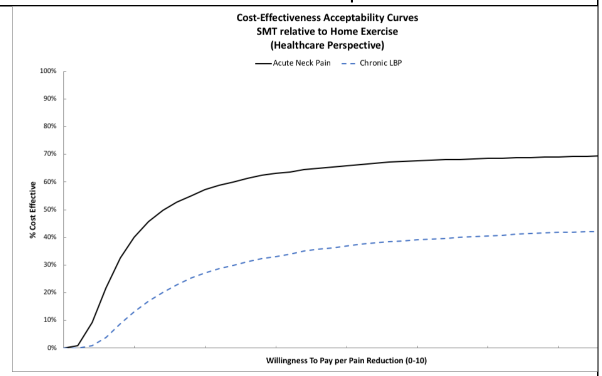
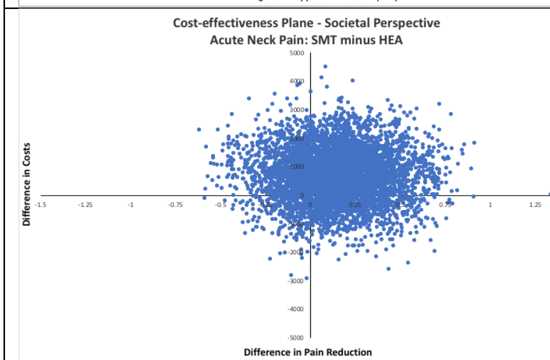
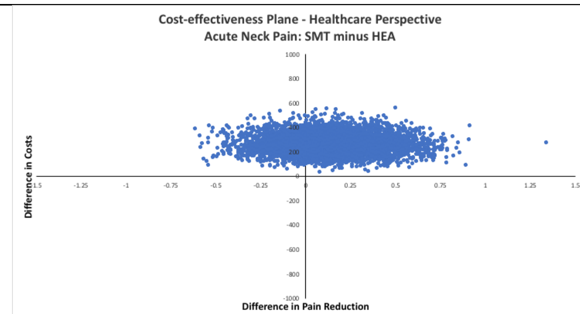
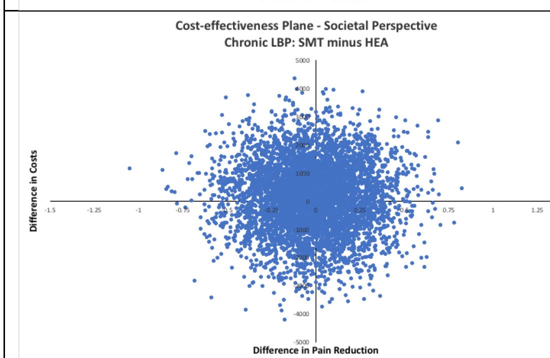
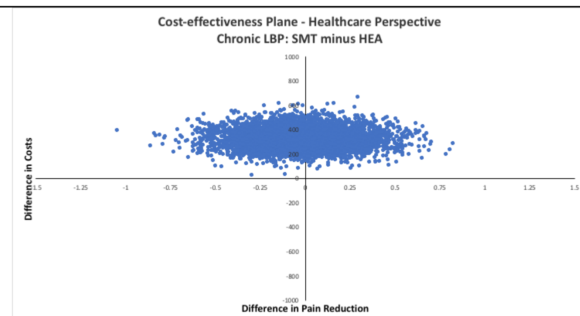
QALYs (EQ5D)

Appendix Figure 2. SMT vs HEA Cost-effectiveness planes and net monetary benefit – QALYs (EQ5D)



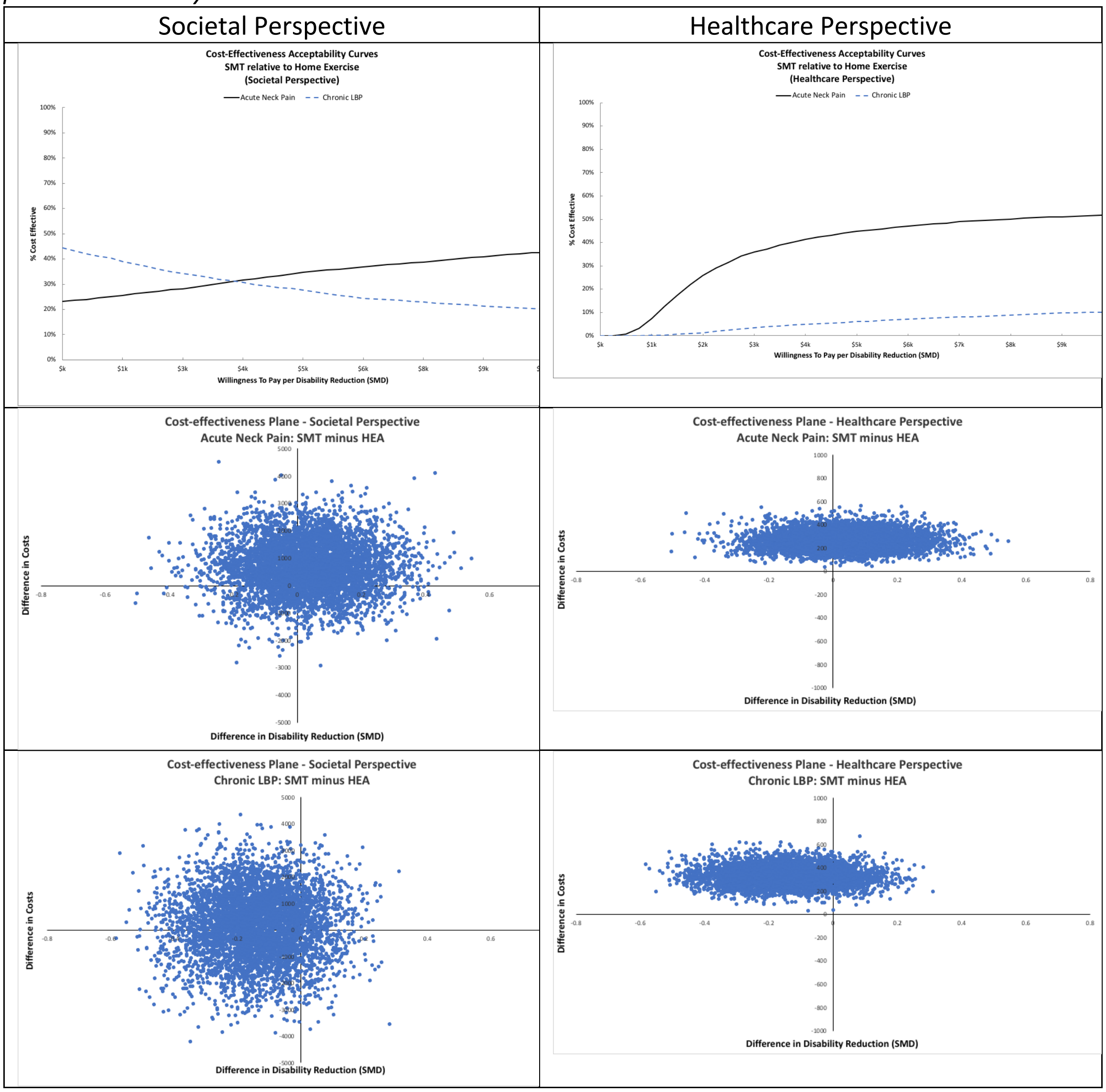
Pain Reduction

Appendix Figure 3. SMT vs HEA Cost-effectiveness acceptability curves and cost-effectiveness planes - pain reduction

Societal Perspective	Healthcare Perspective
	
	
	

Disability Reduction

Appendix Figure 4. SMT vs HEA Cost-effectiveness acceptability curves and cost-effectiveness planes – disability reduction



SMT + HEA vs HEA Figures

QALYs (SF6D)

Appendix Figure 5. SMT+HEA vs HEA Cost-effectiveness planes – QALYs (SF6D)

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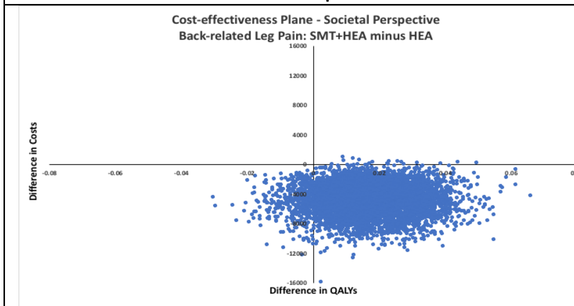
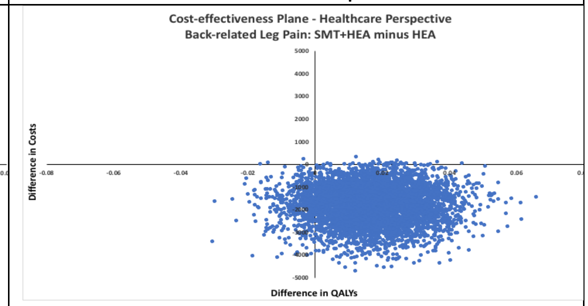
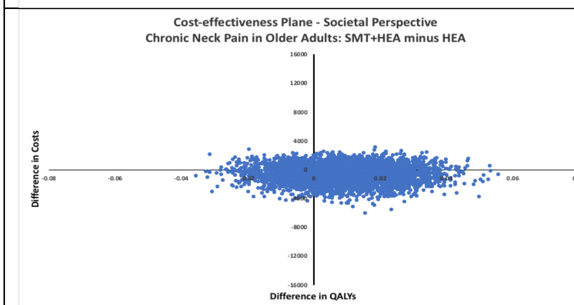
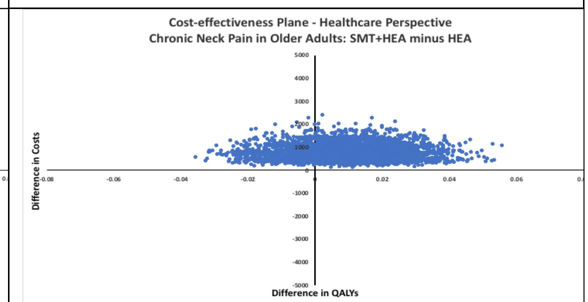
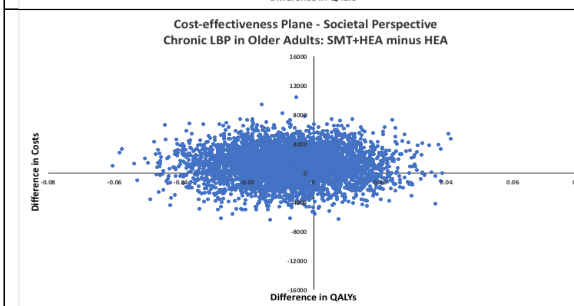
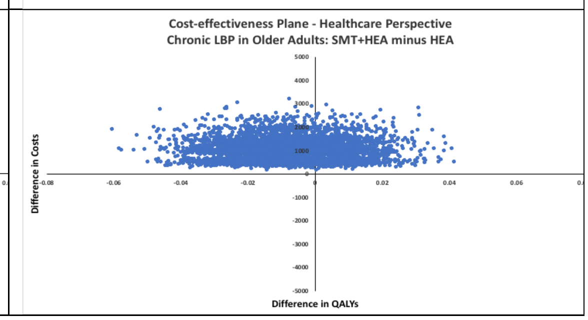
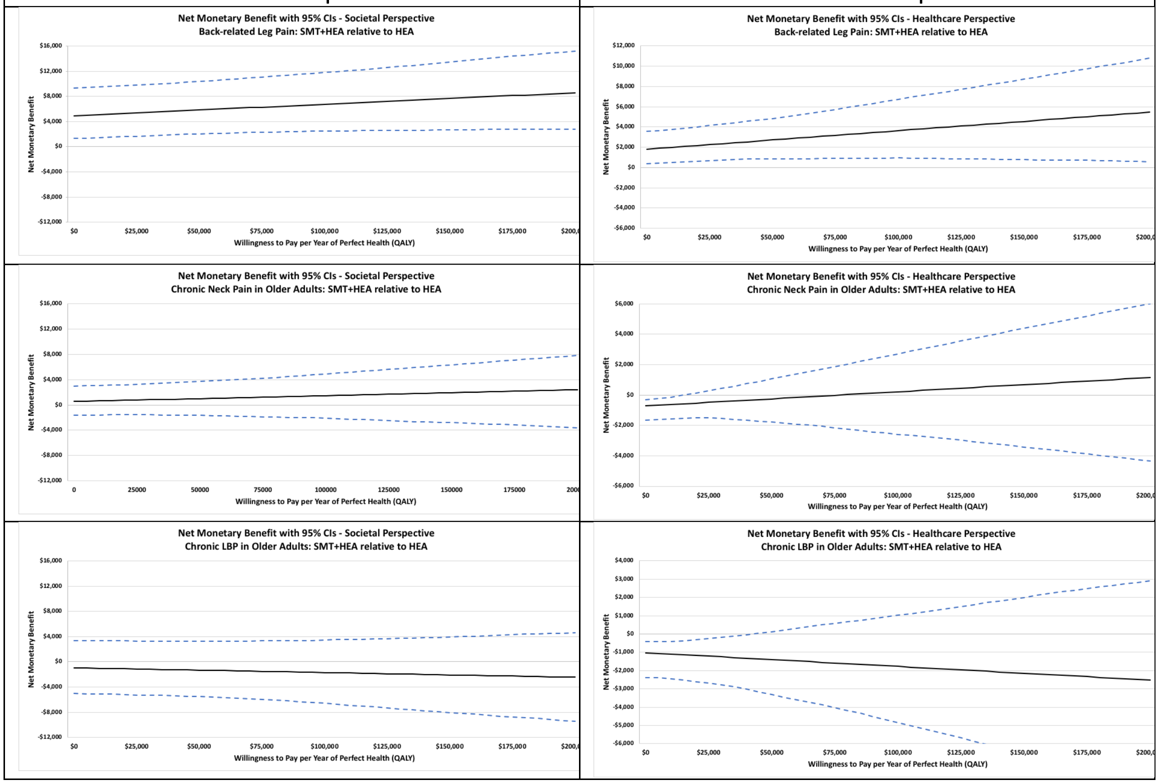
	
	
	

QALYs (SF6D)

Appendix Figure 6. SMT+HEA vs HEA Net monetary benefit – QALYs (SF6D)

Societal Perspective	Healthcare Perspective



QALYs (EQ5D)

Appendix Figure 7. SMT+HEA vs HEA Cost-effectiveness planes – QALYs (EQ5D)

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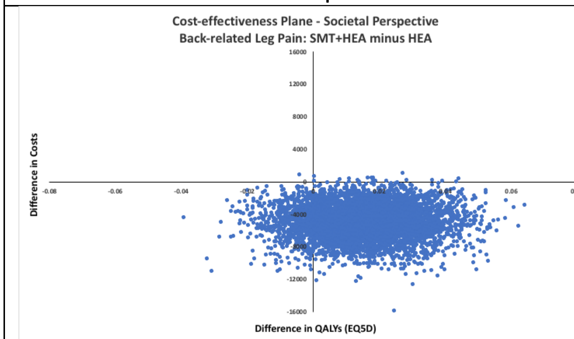
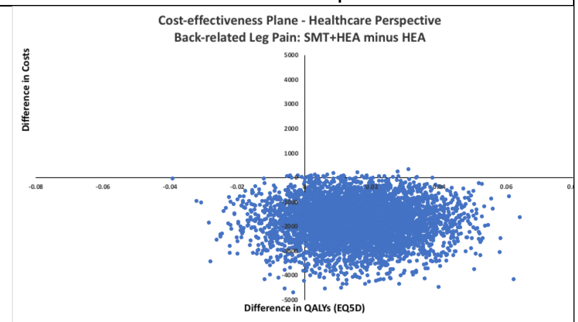
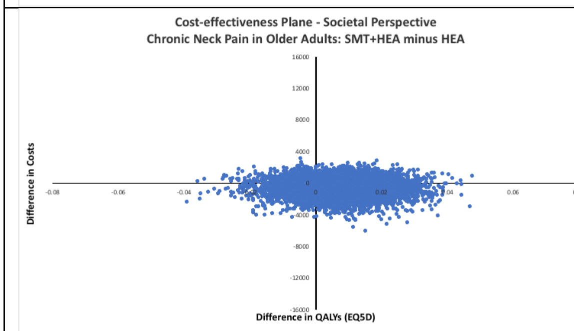
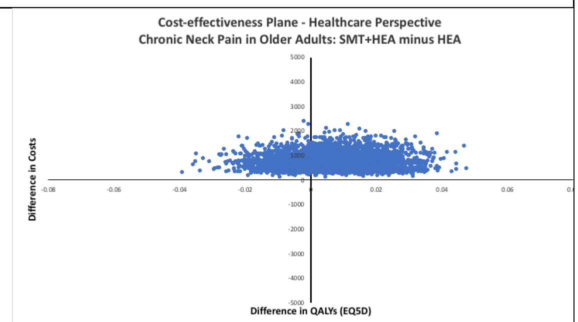
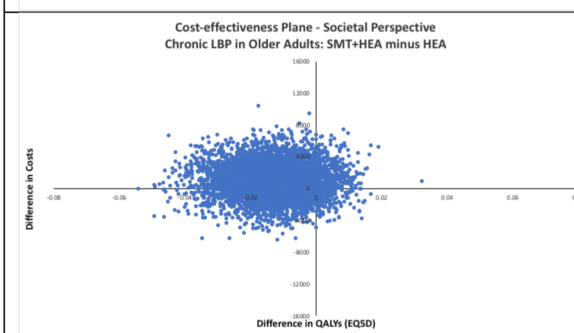
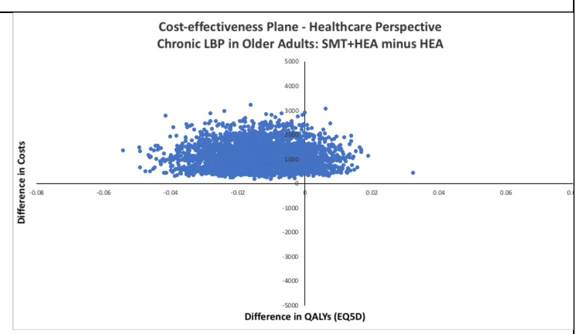
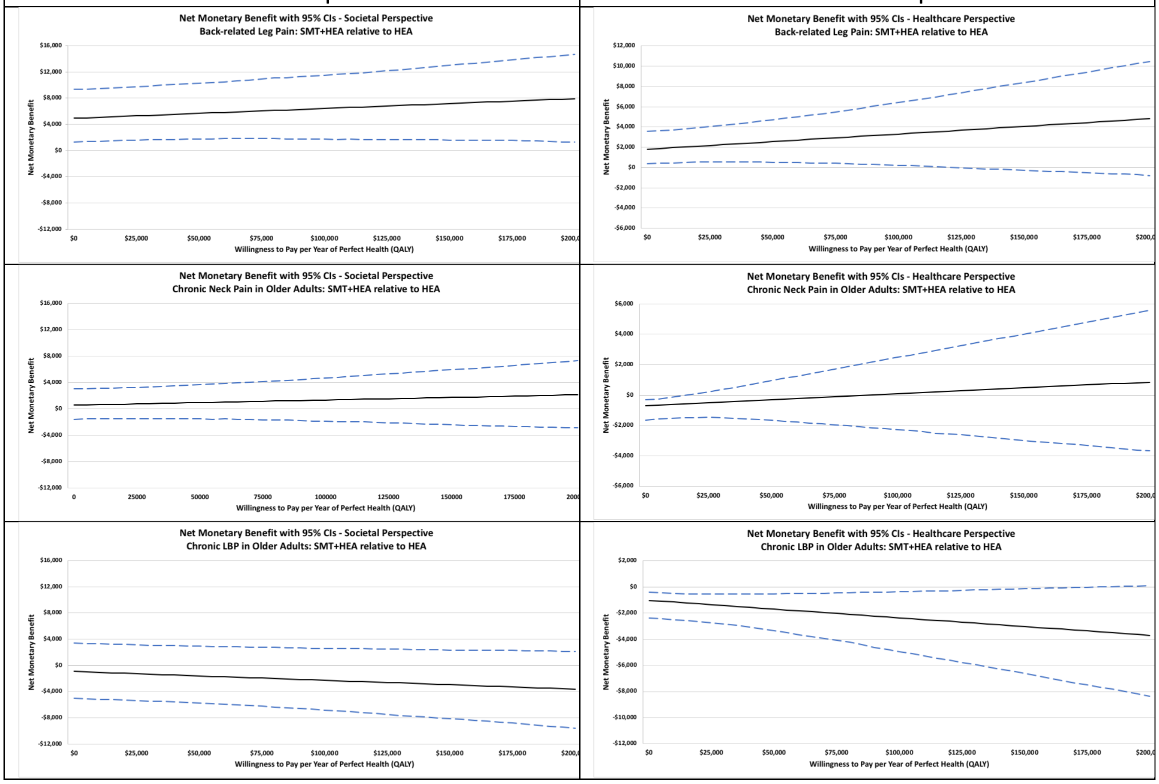
	
	
	

QALYs (EQ5D)

Appendix Figure 8. SMT+HEA vs HEA Net monetary benefit – QALYs (EQ5D)

Societal Perspective	Healthcare Perspective



Pain Reduction

Appendix Figure 9. SMT+HEA vs HEA Cost-effectiveness acceptability curves and cost-effectiveness planes – pain reduction

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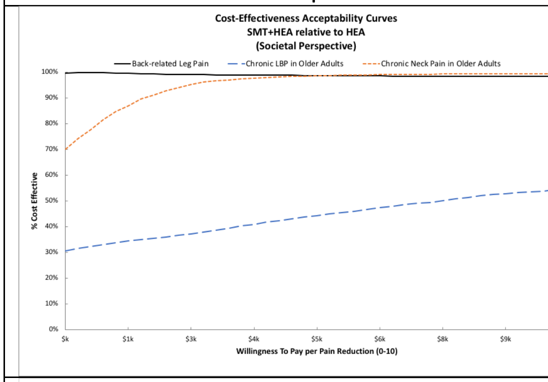

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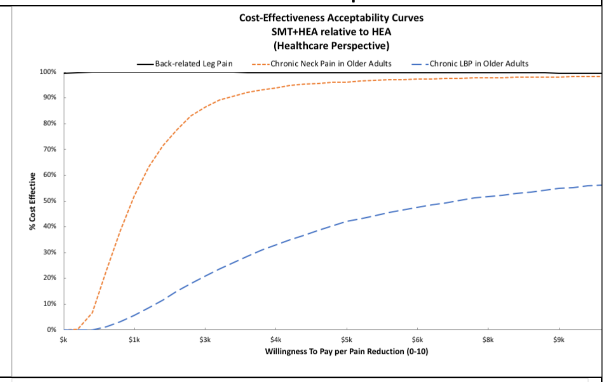

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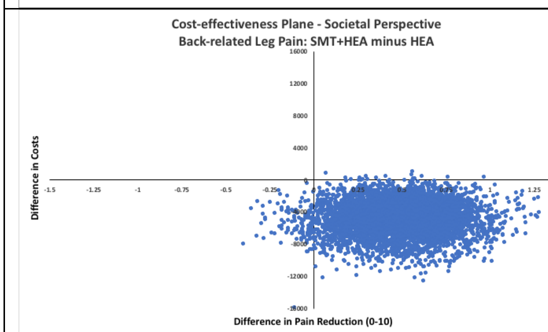

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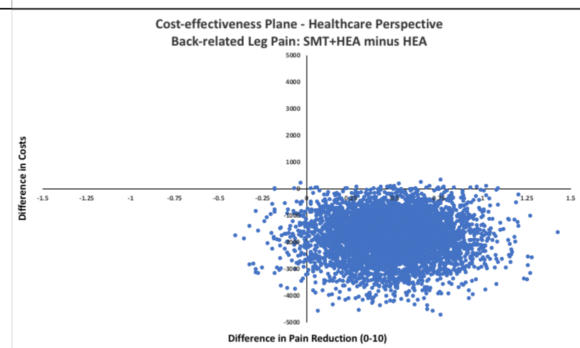

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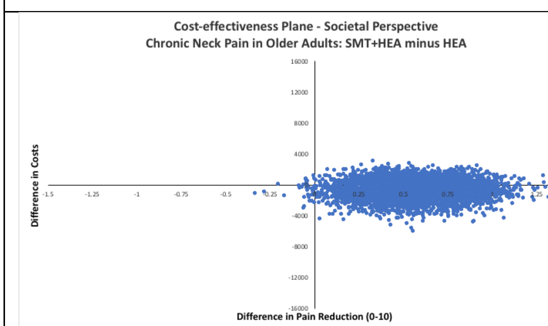

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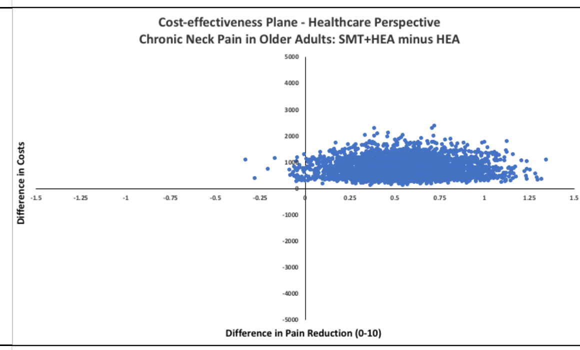

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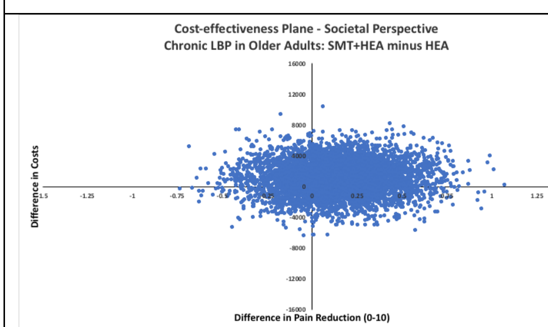

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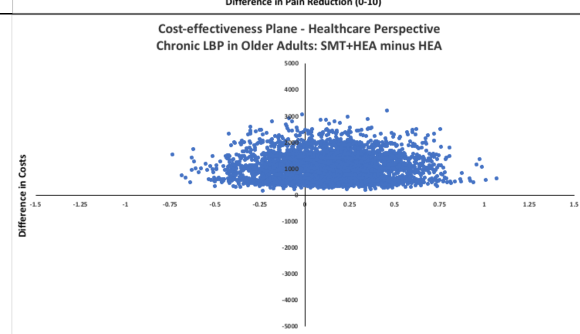

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Disability Reduction

Appendix Figure 10. SMT+HEA vs HEA Cost-effectiveness acceptability curves and cost-effectiveness planes – disability reduction

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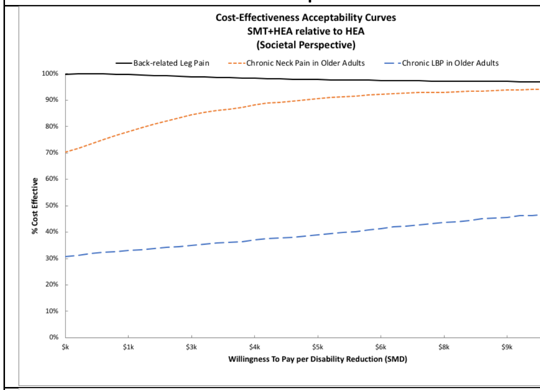
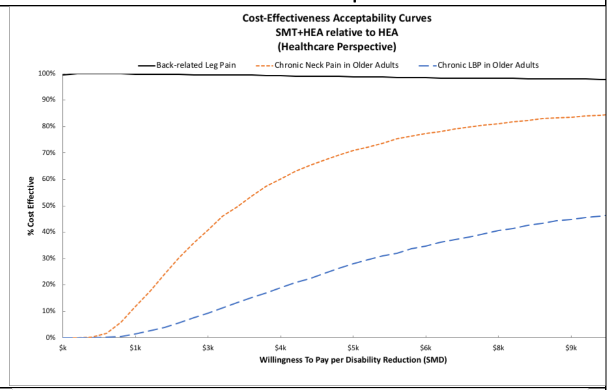
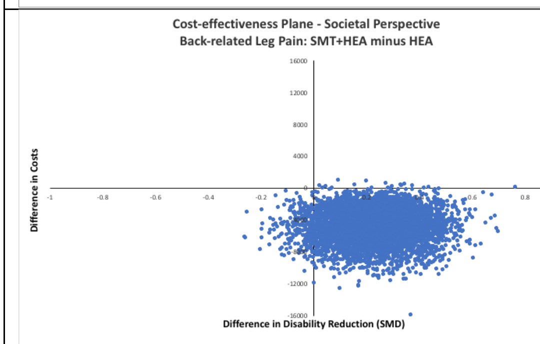
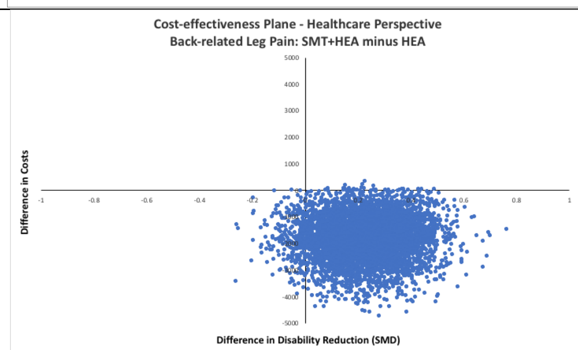
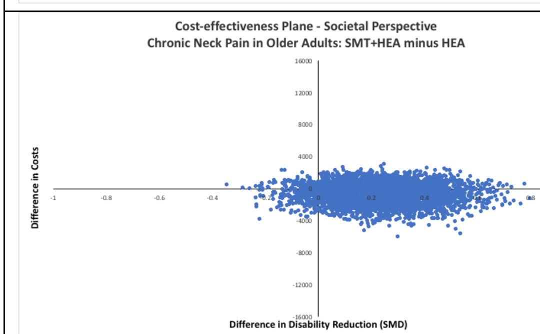
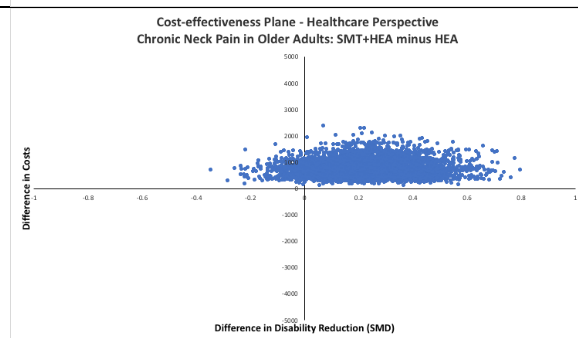
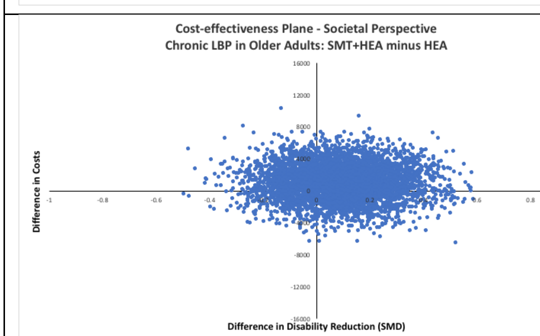
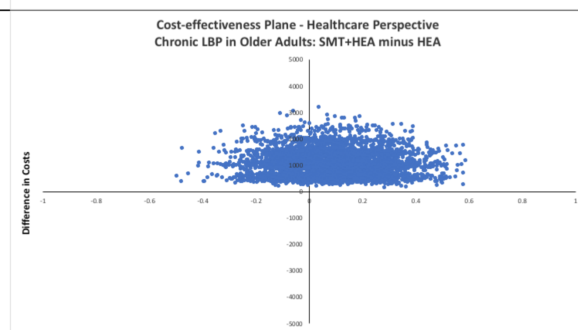
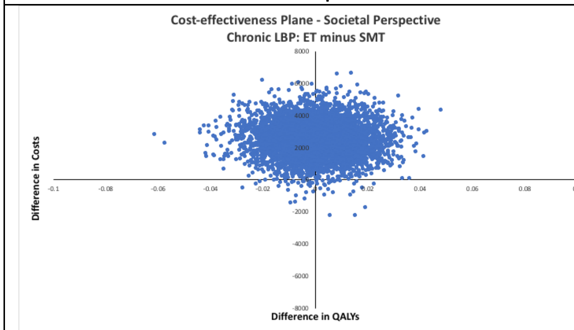
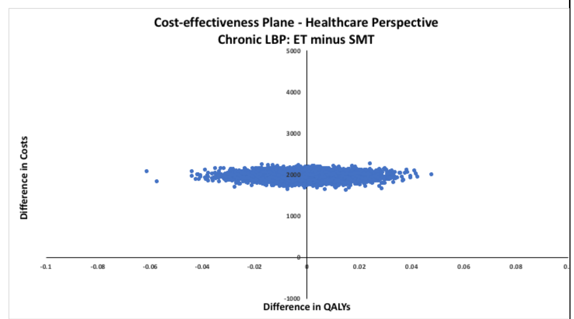
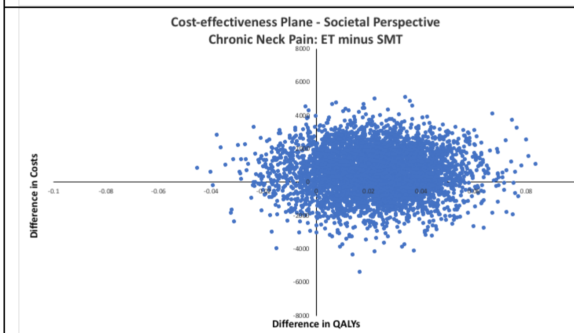
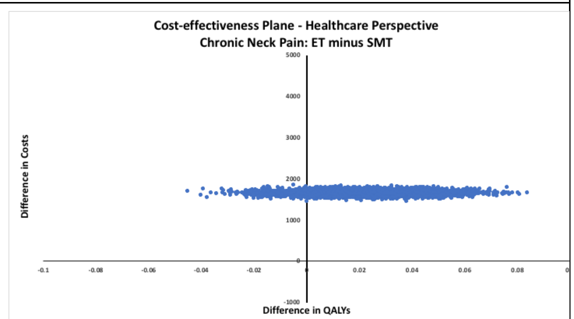
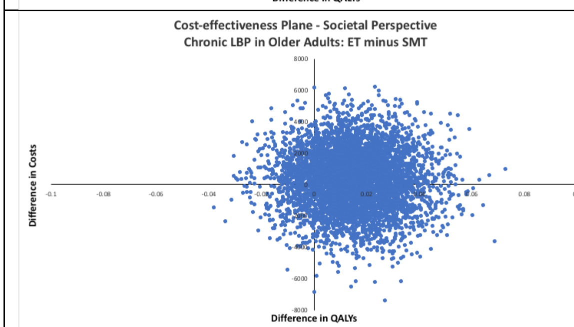
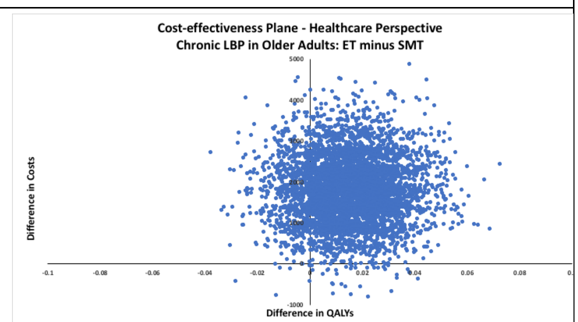
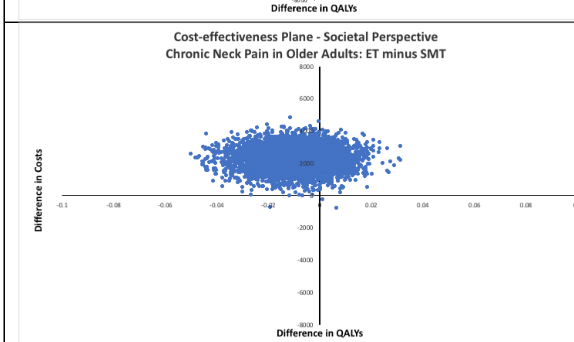
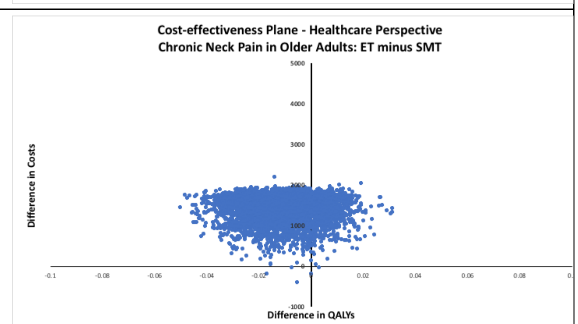
	
	
	
	

ET vs SMT Figures

QALYs (SF6D)

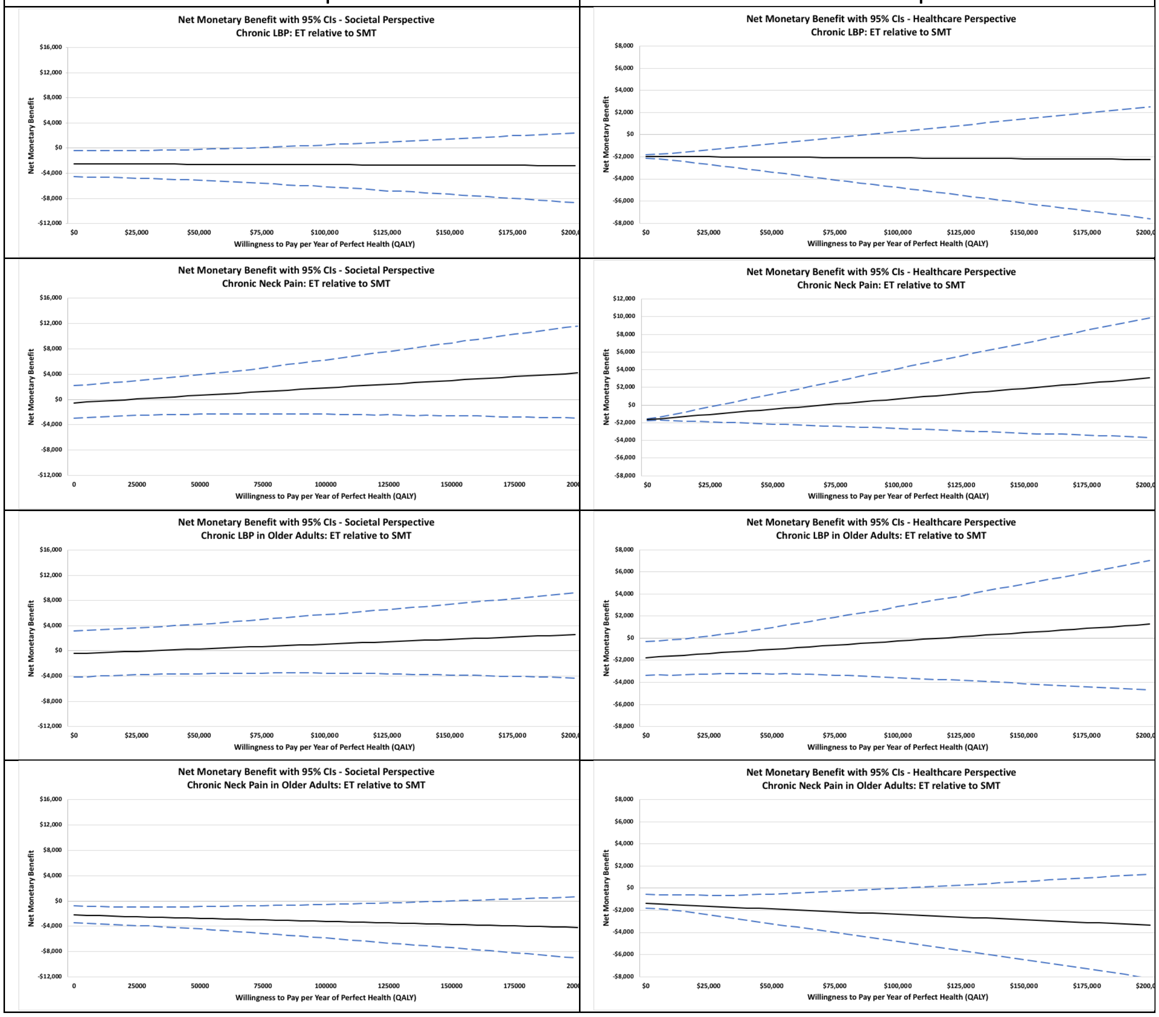
Appendix Figure 11. ET vs SMT Cost-effectiveness planes - QALYs (SF6D)

Societal Perspective	Healthcare Perspective
	
	
	
	

QALYs (SF6D)

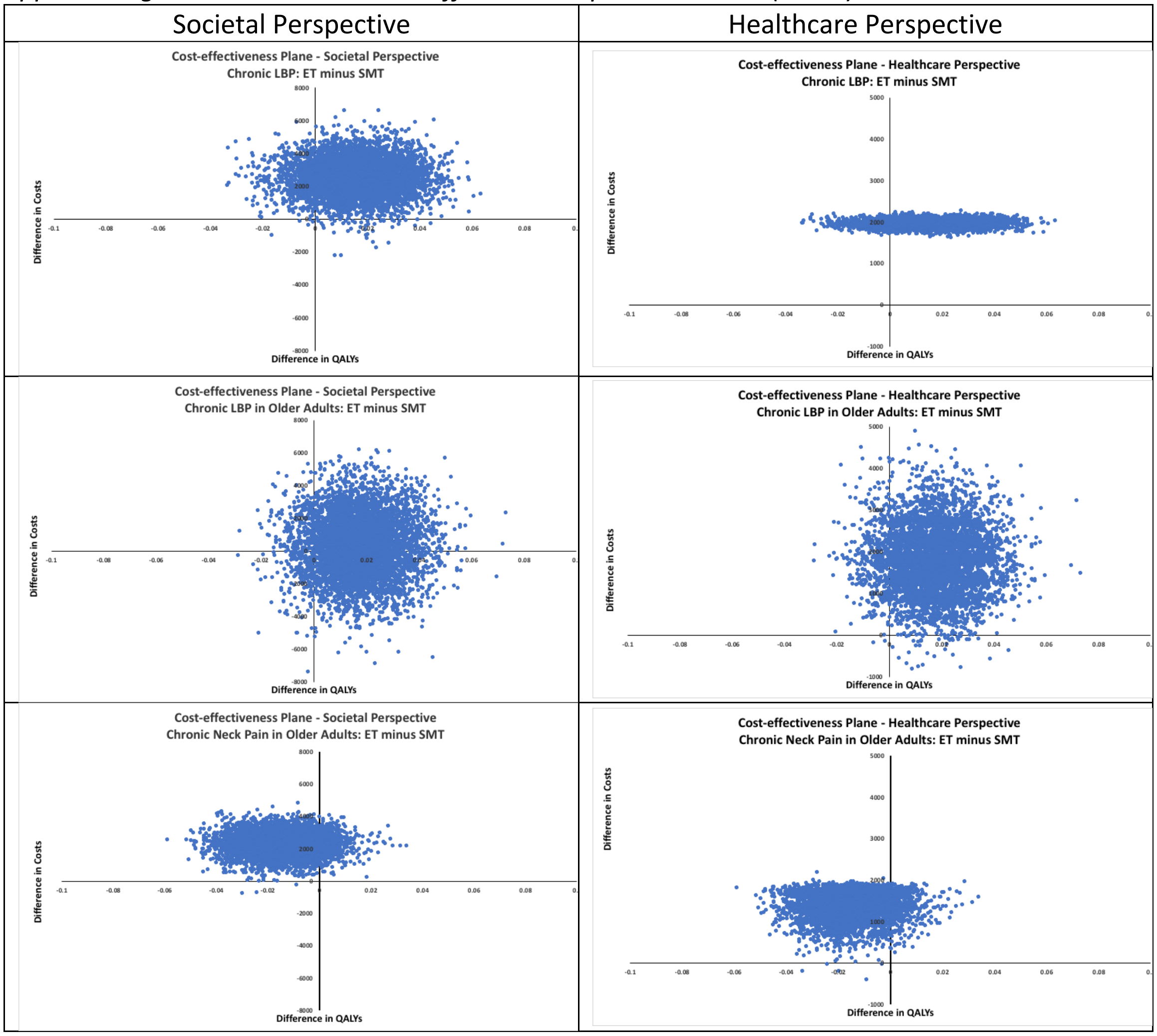
Appendix Figure 12. ET vs SMT Net monetary benefit - QALYs (SF6D)

Societal Perspective	Healthcare Perspective



QALYs (EQ5D)

Appendix Figure 13. ET vs SMT Cost-effectiveness planes - QALYs (EQ5D)



QALYs (EQ5D)

Appendix Figure 14. ET vs SMT Net monetary benefit - QALYs (EQ5D)

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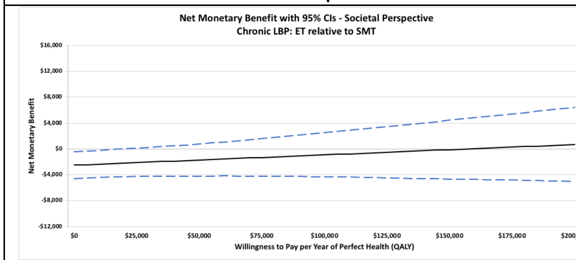
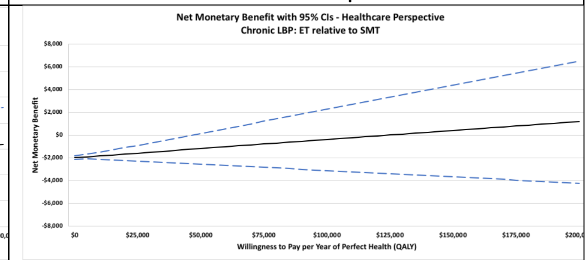
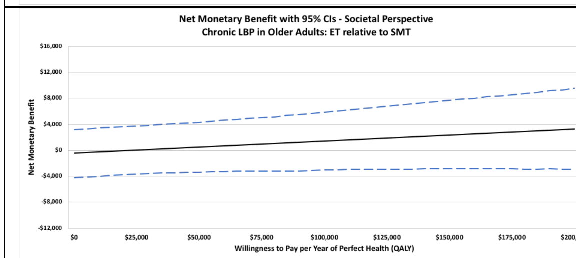
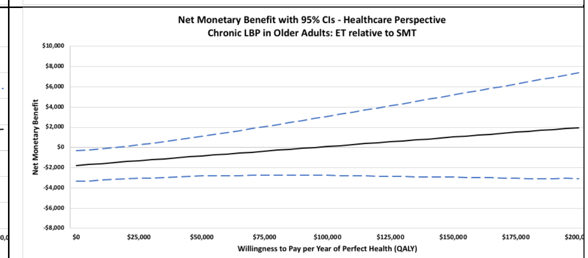
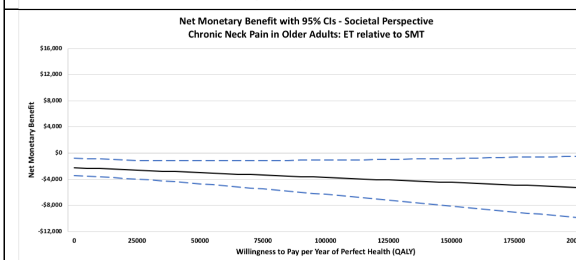
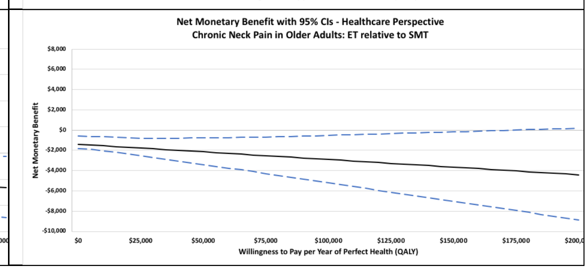
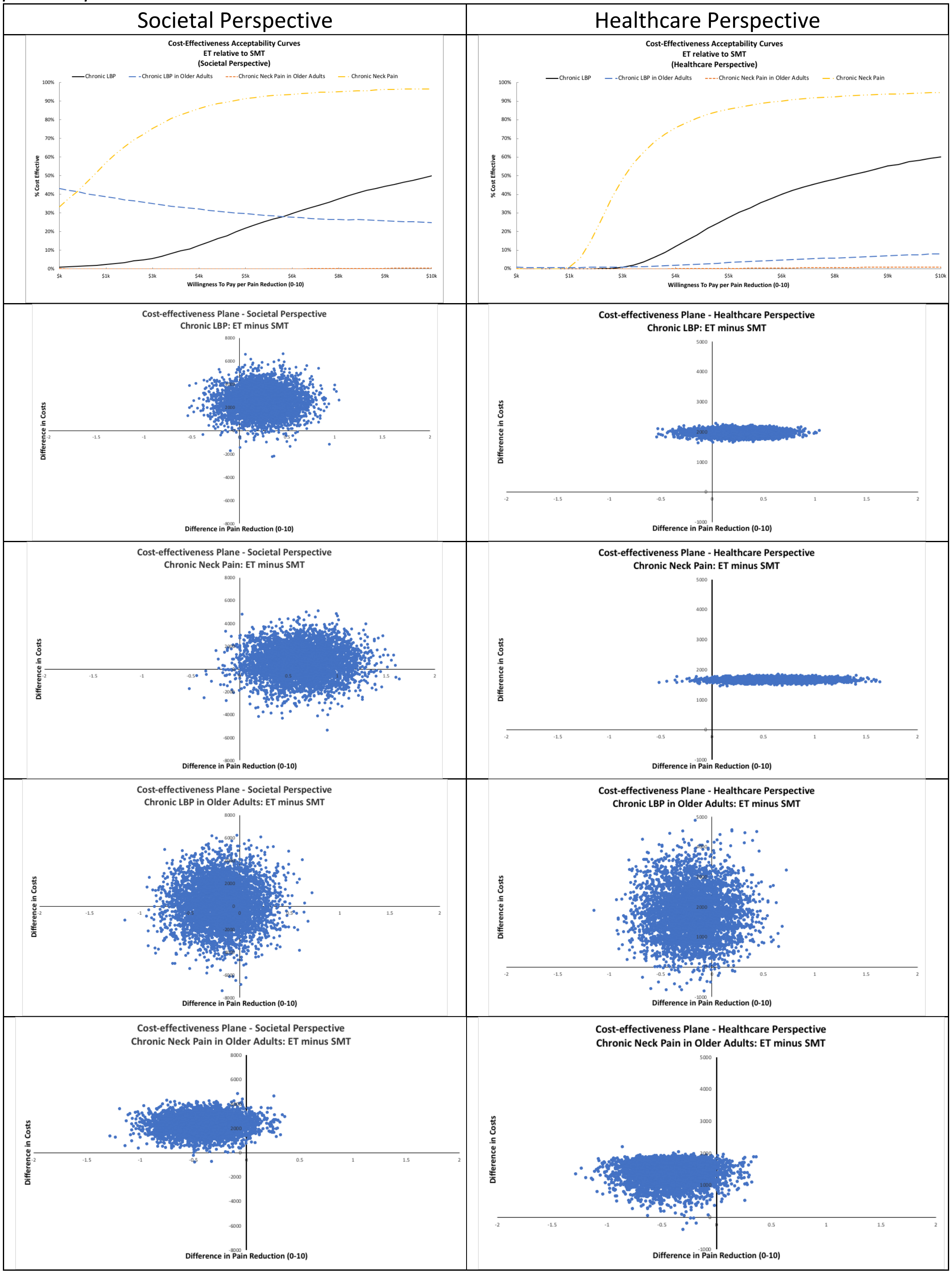
	
	
	

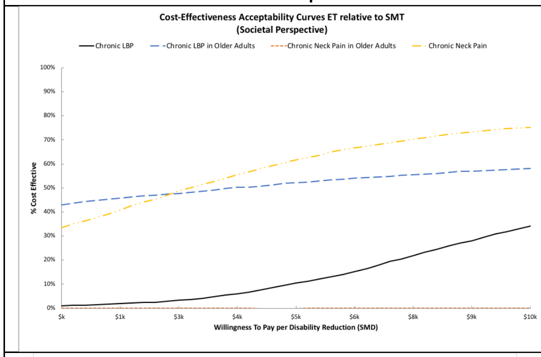
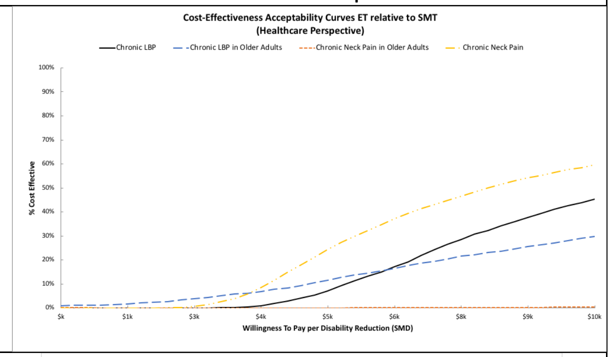
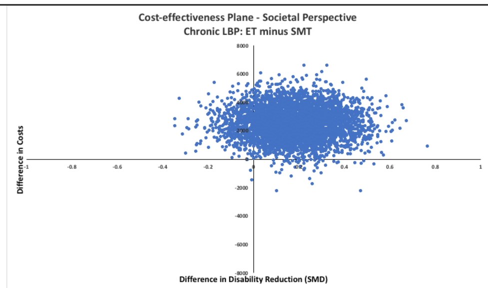
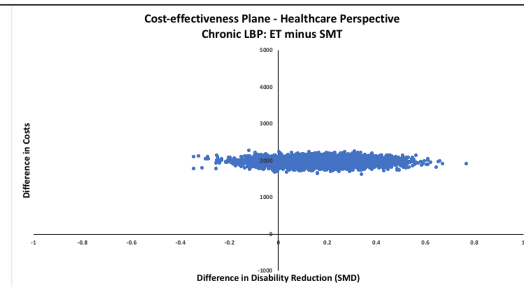
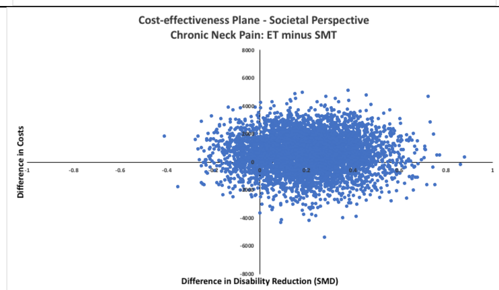
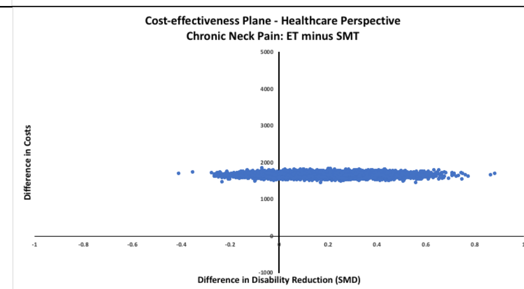
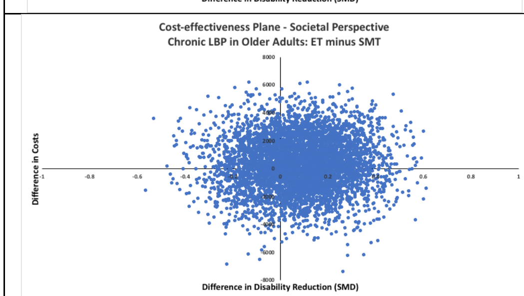
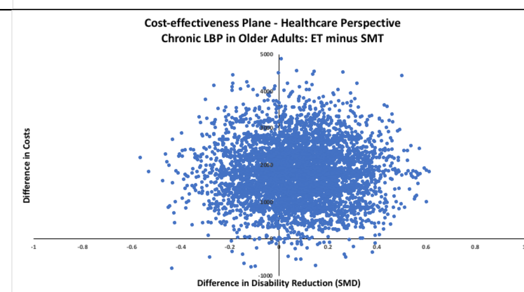
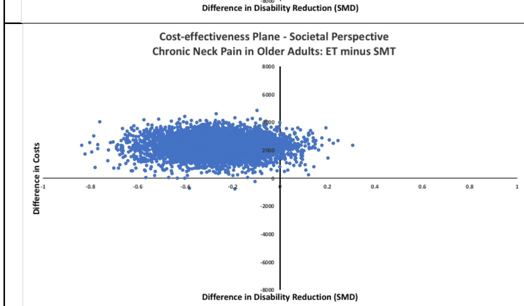
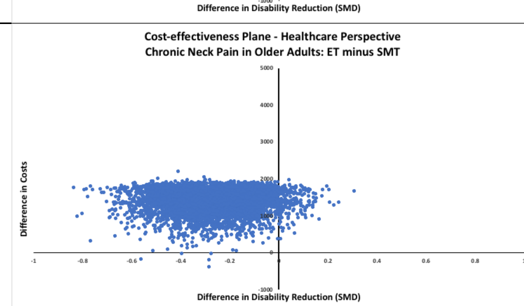
Pain Reduction

Appendix Figure 15. ET vs SMT Cost-effectiveness acceptability curves and cost-effectiveness planes - pain reduction



Disability Reduction

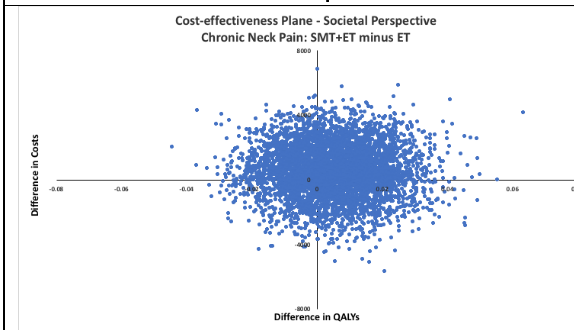
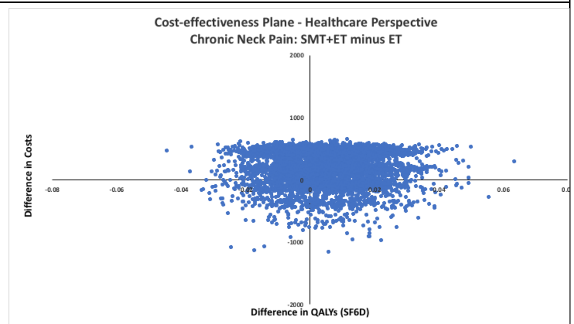
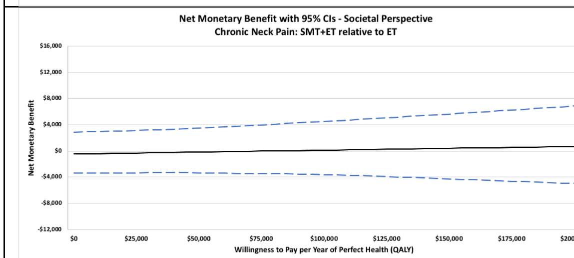
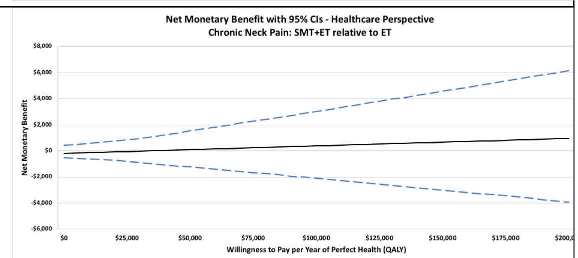
Appendix Figure 16. ET vs SMT Cost-effectiveness acceptability curves and cost-effectiveness planes - disability reduction

Societal Perspective	Healthcare Perspective
	
	
	
	
	

SMT+ET vs ET Figures

QALYs (SF6D)

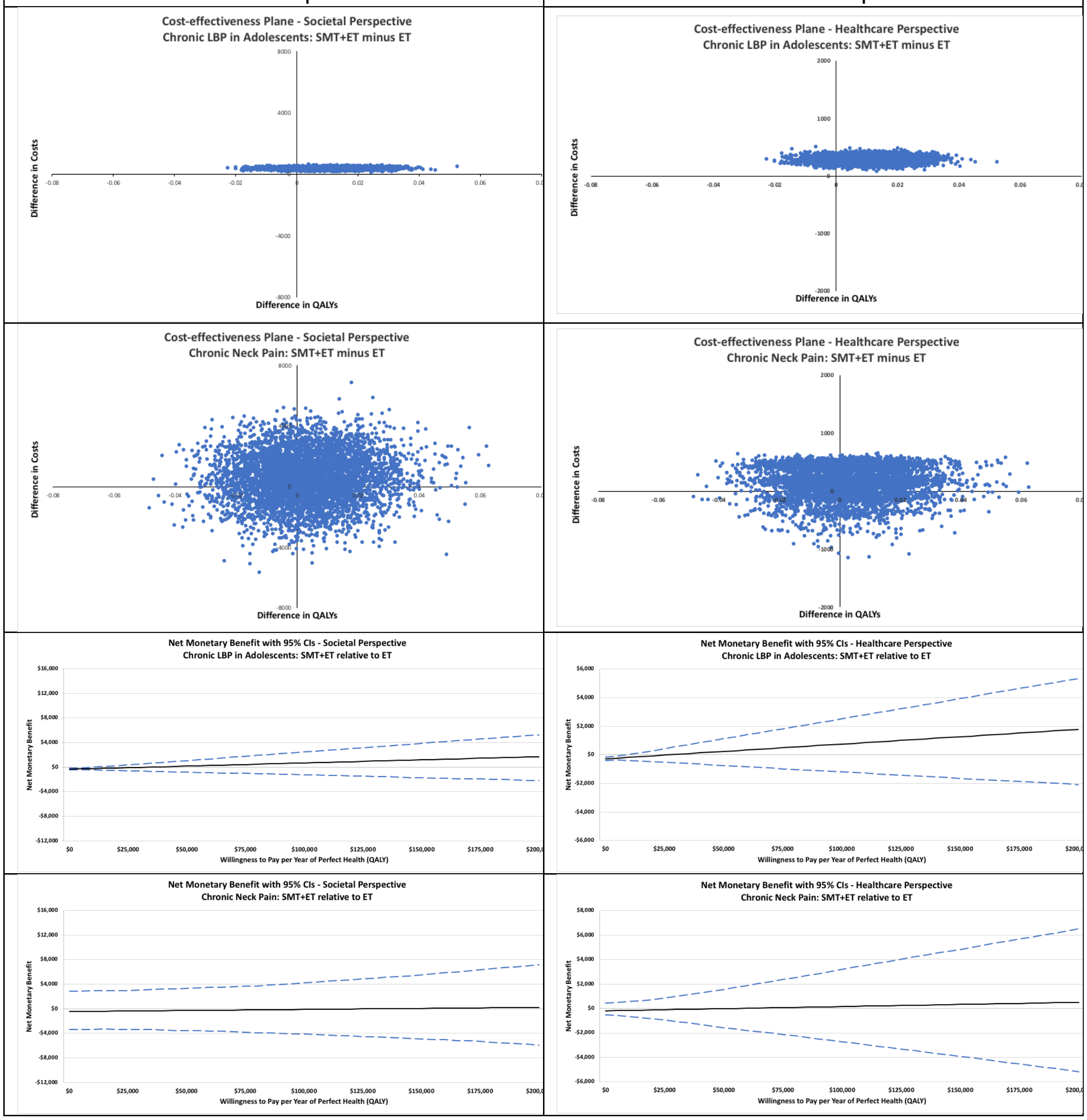
Appendix Figure 17. SMT+ET vs ET Cost-effectiveness planes and net monetary benefit - QALYs (SF6D)

Societal Perspective	Healthcare Perspective
	
	

QALYs (EQ5D)

Appendix Figure 18. SMT+ET vs ET Cost-effectiveness planes and net monetary benefit - QALYs (EQ5D)

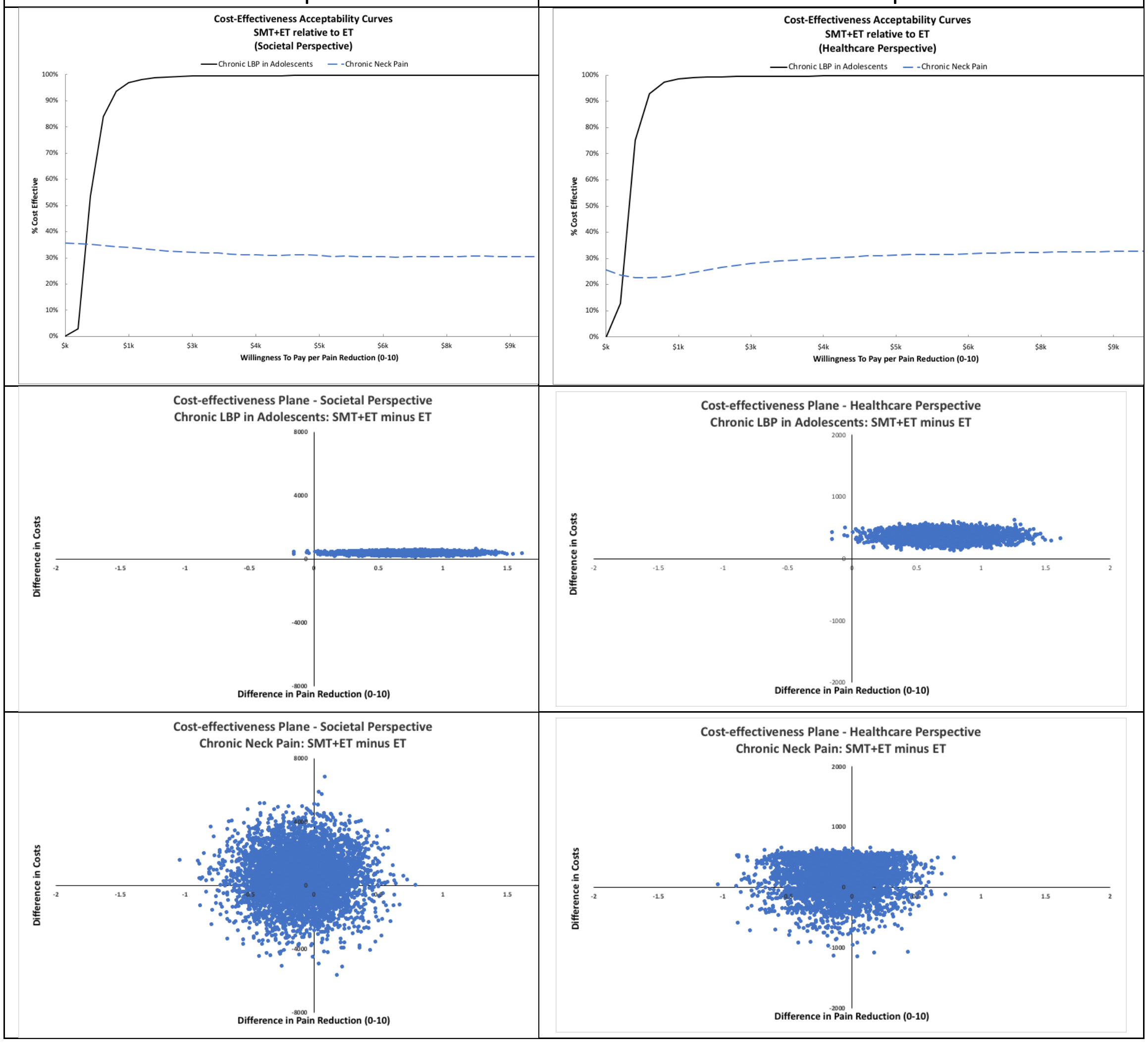
Societal Perspective	Healthcare Perspective



Pain Reduction

Appendix Figure 19. SMT+ET vs ET Cost-effectiveness acceptability curves and cost-effectiveness planes - pain reduction

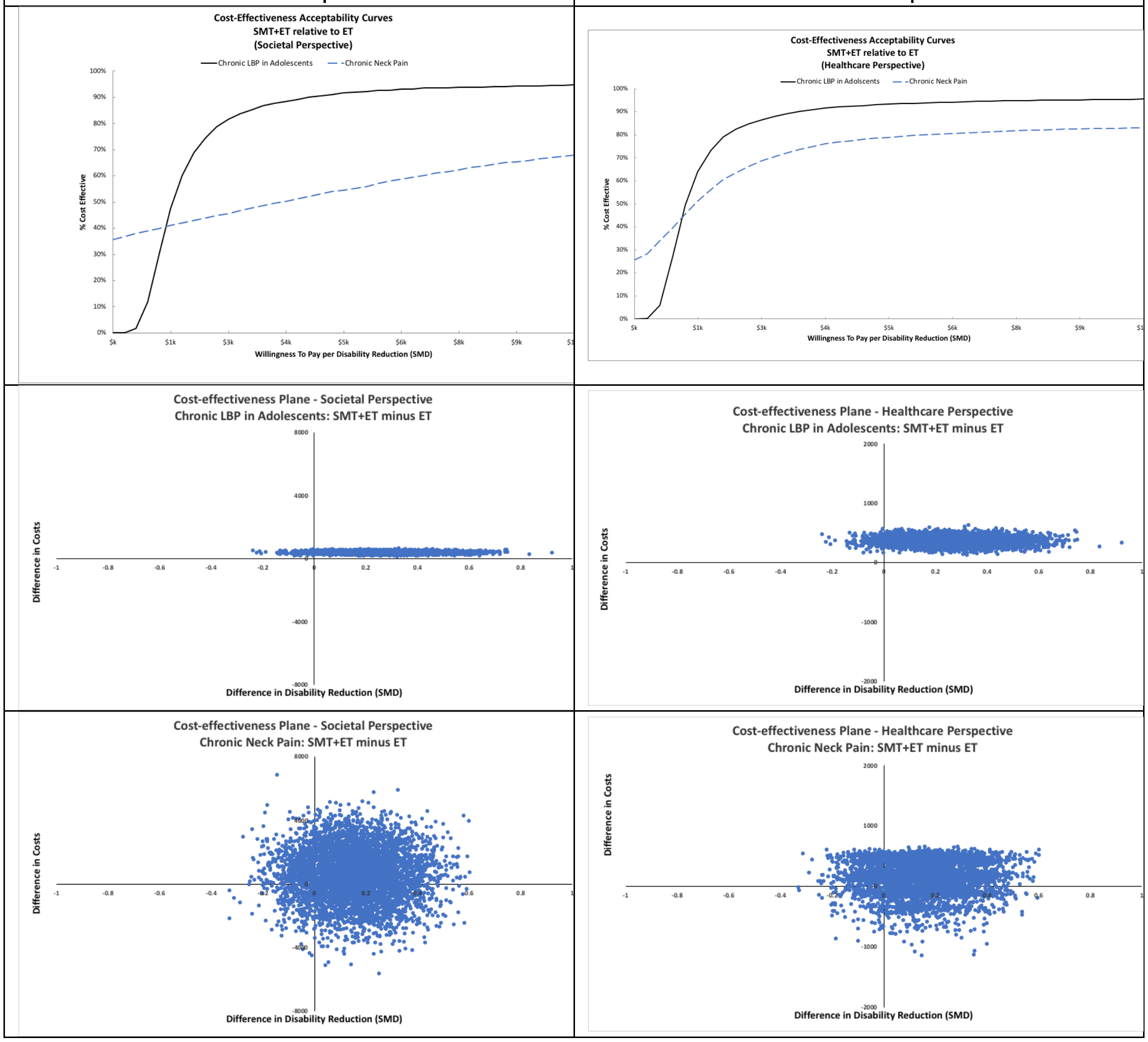
Societal Perspective	Healthcare Perspective



Disability Reduction

Appendix Figure 20. SMT+ET vs ET Cost-effectiveness acceptability curves and cost-effectiveness planes - disability reduction

Societal Perspective	Healthcare Perspective



Aim 2 paper: How well do participants in clinical trials represent the U.S. population with chronic neck or back pain?

Background

Randomized clinical trials (RCTs) are recognized as the gold standard study design for assessing treatment effectiveness. However, generalizability issues are common among RCTs and include the ability to recruit a representative population, reliance on protocolized interventions, limitations in the number of treatments assessed, and a limited time horizon for assessing effects.[82,83] A key component of generalizability is the trial patient population and how representative they are of the population that will receive the treatment in clinical practice.[84] The final trial population is shaped by the sampling or recruitment plan (e.g. recruit from secondary clinics or general population), inclusion and exclusion criteria (e.g. exclusion of patients with comorbidities), individuals' compliance with trial procedures prior to randomization, their preferences for treatment (must be willing to accept all treatments under study), and their willingness to comply with the extensive data collection that is inherent with RCTs. These limitations can theoretically be minimized through pragmatic RCTs which recruit participants from the general population, use broad inclusion and limited exclusion criteria, use common treatment alternatives, and mimic treatment delivery in "real world" healthcare settings.[85]

The representativeness of RCT populations is an important issue which potentially limits the ability of RCT findings to influence clinical practice and policy. If RCT populations demonstrate important differences from the general population, researchers can use this information to design better sampling and recruitment strategies to reach under-represented populations. In addition, the relationship between factors on which the populations differ and study outcomes can be explored to better estimate the potential impact on external validity. Differences in the RCT and general population only impact the external validity of the study if the treatment effects noted in the RCT are modified by the variable of interest. For instance, if the populations differ in terms of household income, but treatment effects are not influenced by household income, then the external validity of RCT findings are not compromised.[86] On the other hand, if RCT populations are shown to be representative of the general population, arguments against their external validity can be better addressed, and their findings may be more easily adopted into clinical practice and public policy. Currently, there are no analyses assessing the representativeness of populations enrolled in RCTs for spinal pain with respect to the broader U.S. spine pain population. The clinical course for back pain intensity has been shown to be similar in RCTs and observational studies; however, analyses comparing the demographic and clinical characteristics of the general U.S. spine pain population to individuals participating in clinical trials or observational studies are lacking.[87]

The purpose of this project is to evaluate the generalizability of chronic spinal pain RCT populations by comparing demographic and clinical characteristics to the U.S. spine pain population using data from national health and healthcare surveys.

Methods

We compared trial participants' socio-demographic characteristics, clinical features and healthcare utilization to a representative sample of a) U.S. adults with chronic spine pain and b) U.S. adults with chronic spine pain receiving chiropractic care using secondary data from the National Health Interview Survey (NHIS) and Medical Expenditure Panel Survey (MEPS). In addition, we assessed demographic and clinical predictors of chiropractic use in U.S. adults with chronic spinal pain using NHIS and MEPS data.

<u>Populations</u>

We compared RCT enrollees with chronic spinal pain, 1,444 participants in eight clinical trials[43-50], to a representative sample of the US population with chronic spinal pain from the NHIS and MEPS. Previous research has found differences in demographic and clinical characteristics in adults with low back and neck pain receiving complementary and integrative care, including chiropractic care.[17,88] Since all clinical trials included chiropractic spinal manipulation, we also completed analyses limiting the NHIS and MEPS samples to individuals receiving care from a chiropractor in the past year. We used a sample of eight clinical trials that collected similar sociodemographic and clinical characteristics and measured them consistently. Individual patient data from the trials was available as they were used for the economic analyses in Aim 1.

RCT inclusion/exclusion criteria, setting, and recruitment methods: We included participants from eight clinical trials conducted between 1994 and 2012. We included adults 18 or older with weekly, persistent, mechanical, non-specific neck or low back pain, with or without radiating extremity symptoms, lasting 12 weeks or longer. All trials required self-reported pain severity to be ≥3/10. Individual trial inclusion criteria for age were 12-18,[46] 18-65,[44,45] 20-65,[50] 21 or older,[43] or 65 and older.[47,48] Other standard inclusion criteria included having a stable medication plan and no ongoing spinal treatment at the time of enrollment. Common exclusion criteria included pregnancy, current or pending litigation, the inability to read or comprehend English, substance abuse, history of surgical spinal fusion, progressive neurological deficits, inflammatory spinal arthropathies, spinal fractures, metastatic disease, blood clotting disorders, and severe disabling health problems (e.g., organ failure). All of the clinical trials were performed within a university-affiliated research clinic in the Minneapolis, MN metropolitan region. Five of the clinical trials were performed exclusively in MN and two were multi-center studies with additional sites in Portland, OR[46] or Davenport, IA.[43] All trials recruited participants from the general population primarily through mass mailings. Other recruitment strategies included advertisement in newspapers, social media, television, radio, and community posters.

NHIS & MEPS: We used data from the NHIS accessed through the IPUMS NHIS database.[89] The NHIS is an annual, cross-sectional, in-person household survey used to monitor the health of US citizens.[90] Approximately 35,000 to 40,000 households including 75,000 to 100,000 individuals are interviewed annually with a response rate of 80-90%. NHIS uses a complex sampling design representative of the US civilian noninstitutionalized population with oversampling of Black, Hispanic, and Asian populations. We pooled data from the 2001-2010 NHIS resulting in a total of 883,541 observations. The majority of trial activities were conducted between 2001 and 2010 which is why these years were used for defining the U.S. sample. The NHIS is also the sampling frame for the MEPS. MEPS collects data on health services utilization and costs in addition to health status and socio-demographic characteristics. Approximately 12,000 to 15,000 households with 32,000 to 37,000 individuals complete the MEPS on an annual basis with response rates ranging between 58-71%. MEPS uses an overlapping panel design with five rounds of interviews occurring over a two and a half year period to capture longitudinal changes in health and expenditures. We used data from the 2002-2010 MEPS resulting in 309,620 observations. MEPS data from 2001 had a survey design that differed substantially from 2002-

2010 data and was omitted (e.g. non-compatible primary sampling units and independent variance strata).

Measures

Chronic Spine Pain and Chiropractic Use Variables: For NHIS, we identified individuals with functional limitations (e.g. difficulty shopping, participating in social activities, walking, etc.) due to a neck or back problem that lasted at least 3 months from the IPUMS NHIS database using the variable FLBACKC (See Appendix Table 1). NHIS also collects information on the types of health care providers seen in the past 12 months. We used the chiropractic use variable (SAWCHIR) to identify individuals with chronic spine pain receiving chiropractic care. For MEPS, we identified individuals with healthcare expenditures for spine problems in at least 2 of the 5 interviews over the 2.5 years the MEPS is administered. We used the Clinical Classification Code 205 within the Medical Conditions File to identify individuals with healthcare visits for spondylosis, intervertebral disc disorders, or other back problems. The number of office visits to a chiropractor (MEPS variable CHIROVISIT) was used to identify individuals with chronic spine problems receiving chiropractic care.

Demographic and health characteristics: We selected socio-demographic and clinical characteristics based on the minimal data set recommendations from the NIH's task force on research standards for chronic low back pain,[57] in addition to availability of comparable measures within the trials and NHIS or MEPS. We included the following socio-demographic variables: sex, race (White, Black, Alaskan Native or American Indian, Asian or Pacific Islander, multiple races, other race), ethnicity (Hispanic or not Hispanic), employment (yes or no), education (less than high school, school, some college, Associate or Technical school degree, Bachelor degree, Post-graduate or professional degree), and household income ($0-$35k, $35k-$75k, $75k+). Clinical measures included a body mass index indicator of weight (underweight: <18.5, healthy weight: 18.5-24.9, overweight: 25-29.9, obese: 30 or more), duration of neck or back problem (1 year or less, 1-5 years, 5-10 years, over 10 years), presence of radiating leg or arm pain, diabetes, current smoker, current alcohol use, the SF-12 physical component summary score (constructed so a normative score for U.S. population is 50 with standard deviation of 10), the SF-12 mental component summary score (constructed so a normative score for U.S. population is 50 with standard deviation of 10), and quality of life scores. Quality-adjusted life years (QALYs) were derived using the SF6D scoring system for describing health states using SF-12 data from MEPS and SF-36 data from the clinical trials. We calculated QALYs using weights from a study assessing U.S. preferences for SF6D health states with discrete choice experiments.[53] SF-12 and SF6D measures were obtained using MEPS data. All other socio-demographic and clinical characteristics were obtained using NHIS data. Details on NHIS and MEPS variables used for the analysis are provided in Appendix Table 1.

Analysis

All analyses used NHIS and MEPS data from survey respondents with no missing items for our chosen sociodemographic and clinical measures. The analysis consisted of four stages. First, we calculated point estimates (i.e. means, proportions), standard errors and confidence intervals for socio-demographic and clinical characteristics in both clinical trial and national survey participants with chronic spine pain. Sampling weight variables provided by MEPS and NHIS were used to account for the unequal probability of selection and were divided by the number of years used for the analyses as recommended by IPUMS.[91] We used design variables (e.g. strata and primary sampling unit) to account for the stratification and clustering of the complex multi-stage survey design. Standard errors for MEPS and NHIS data were estimated using the Taylor-series linearization method. [92] Second, we assessed differences between trial and U.S. spine populations using independent t-tests for means and z-tests for proportions. Third, we conducted multivariable logistic regression to assess differences in socio-demographic and clinical characteristics based on chiropractic use in the U.S. population with chronic spine pain using NHIS data. The outcome was chiropractic use and predictors were socio-demographic and clinical characteristics. Characteristics not included in all ten years of NHIS data were excluded from this analysis (i.e. history of arthritis or depression). Differences in chiropractic use base on the SF-12 and QALYs were assessed using multivariate logistic regression adjusted for age, gender, race, and ethnicity from MEPS. Finally, we compared trial participants to the U.S. population with chronic spine pain that reported chiropractic use with independent t-tests for means and z-tests for proportions. The magnitude of differences was depicted using effect sizes. We used Cohen's h to calculate effect sizes for differences in proportions ($|2 * (arcsin\sqrt{P_1}) - 2 * (arcsin\sqrt{P_2})|$) and standardized mean differences to calculate effect sizes for differences in means ($\left|\frac{mean\ difference}{standard\ deviation\ in\ NHIS\ or\ MEPS\ sample}\right|$).[93] We used Cohen's suggested definitions for interpretating effect size changes (Small = 0.20; Medium = 0.50; Large = 0.80).[93] We used Stata 13.1 for all analyses which uses the svy commands to account for the complex sample design of the NHIS and MEPS (i.e., unequal probability of selection, clustering, and stratification).

Results

Trial participants relative to the US population

Table 9 presents socio-demographic and clinical characteristics for the U.S. and clinical trial populations. The analytic sample from the NHIS included 15,312 adults with functional limitations due to a persistent neck or back problem, the MEPS sample included 12,679 adults with chronic spine-related healthcare expenditures, and the clinical trials included 1,444 adults with chronic neck or back pain. The NHIS and MEPS samples were representative of approximately 11.5 and 15.6 million U.S. adults, respectively. The difference in samples between NHIS and MEPS is due to differences in how chronic spine pain was defined between the two data sources (functional limitation due to a back or neck problem in NHIS and multiple healthcare visits over 2.5-year period for back or neck condition in MEPS). The clinical trials had a higher percentage of older adults relative to the U.S. population due to the inclusion of two trials that focused solely on older adults.[47,48] The percentage of females in the trials was larger relative to the U.S. population with chronic spinal pain. For other socio-demographic characteristics a number of important differences were observed. There was a higher percentage of White participants in the clinical trials and fewer Black, Asian or Pacific Islander, and Hispanic participants. A higher proportion of trial participants were employed, earned a Bachelor's, post-graduate, or professional degree, and had higher household incomes. For clinical characteristics, there were a higher percentage of trial participants with a healthy weight, a shorter duration of pain, and no radiating arm or leg pain, diabetes, or smoking. Trial participants reported a higher level of physical and mental health relative to the U.S. population according to the SF-12 in addition to higher quality-adjusted life years. There were no differences in alcohol use. Most differences were small in magnitude. Differences in age, ethnicity, income, and mental health were small to medium in magnitude and differences in education, employment, and smoking status had medium effect sizes.

Table 9. U.S. Population with chronic spine pain using NHIS and MEPS relative to trial participants

	U.S. Population		Trial Population			Trial – US		
	% or Mean (SD)	SE	% or Mean (SD)	SE	Obs	Diff	P-value	Effect Size
Age†								
18 to 30	10.6%	0.004	7.0%	0.007	101	-3.6%	<0.001	0.13
31 to 50	38.8%	0.005	32.8%	0.012	473	-6.0%	<0.001	0.13
51 to 64	30.0%	0.005	23.5%	0.011	339	-6.6%	<0.001	0.15
65 to 84	18.5%	0.004	35.9%	0.013	518	17.3%	<0.001	0.40
85 and above	2.1%	0.001	0.8%	0.002	12	-1.2%	0.0013	0.11
Sex†								
Male	44.4%	0.005	40.7%	0.013	588			
Female	55.6%	0.005	59.3%	0.013	856	3.6%	0.009	0.07
Race†								
White	86.3%	0.004	94.9%	0.006	1368	8.5%	<0.001	0.30
Black/African-American	9.6%	0.003	2.3%	0.004	33	-7.3%	<0.001	0.33
Alaskan Native, or American Indian	1.4%	0.001	0.9%	0.002	13	-0.5%	0.15	0.05
Asian or Pacific Islander	2.0%	0.001	1.2%	0.003	17	-0.8%	0.039	0.06
Other Race	0.4%	0.001	0.7%	0.002	10	0.3%	0.14	0.04
Multiple Race	0.3%	0.001	0.1%	0.001	1	-0.2%	0.13	0.05
Ethnicity†								
Not Hispanic	90.7%	0.003	98.7%	0.003	1419			
Hispanic	9.3%	0.003	1.3%	0.003	19	-8.0%	<0.001	0.39
Employment†*18-64 years old*								
Not Employed	44.8%	0.007	19.9%	0.013	178			
Employed	55.2%	0.007	80.1%	0.013	716	24.9%	<0.001	0.54
65 years or older								
Not Employed	89.9%	0.006	80.4%	0.017	426			
Employed	10.1%	0.006	19.6%	0.017	104	9.6%	<0.001	0.27
Education†								
Less than high school	20.9%	0.004	1.7%	0.003	24	-19.3%	<0.001	0.69
High school	31.5%	0.005	20.4%	0.011	291	-11.1%	<0.001	0.25
College, no degree	19.8%	0.004	21.5%	0.011	306	1.7%	0.13	0.04
Associate or technical school	10.9%	0.003	11.9%	0.009	170	1.0%	0.26	0.03
Bachelor's	10.8%	0.003	28.6%	0.012	407	17.8%	<0.001	0.46
Post-graduate or professional	6.1%	0.002	15.9%	0.010	227	9.9%	<0.001	0.32
Household Income†								
$0 - $34,999	47.7%	0.006	29.5%	0.013	353	-18.2%	<0.001	0.38
$35,000 - $74,999	31.5%	0.005	45.8%	0.014	548	14.3%	<0.001	0.29
$75,000+	20.8%	0.005	24.7%	0.012	296	3.9%	0.002	0.09
Body Mass Index†								
Underweight	0.9%	0.001	0.6%	0.002	8	-0.3%	0.17	0.03
Healthy weight	28.0%	0.005	31.9%	0.012	461	3.9%	0.002	0.09
Overweight	35.8%	0.005	36.4%	0.013	526	0.6%	0.65	0.01

Obese	35.2%	0.005	31.1%	0.012	449	-4.2%	0.002	0.09
Duration†								
1 year or less	9.9%	0.003	21.0%	0.011	296	11.2%	<0.001	0.31
1 to 5 years	27.3%	0.004	32.8%	0.013	461	5.4%	<0.001	0.12
5 to 10 years	22.0%	0.004	18.8%	0.010	265	-3.1%	0.007	0.08
Over 10 years	40.8%	0.005	27.4%	0.012	385	-13.4%	<0.001	0.28
Radiating pain†								
No	46.8%	0.005	60.0%	0.013	866			
Yes	53.2%	0.005	40.0%	0.013	578	-13.2%	<0.001	0.27
Diabetes†								
No	87.0%	0.003	93.8%	0.006	1355			
Yes	13.0%	0.003	6.2%	0.006	89	-6.8%	<0.001	0.23
Smoking†								
No	68.7%	0.005	90.3%	0.008	1304			
Yes	31.3%	0.005	9.7%	0.008	140	-21.6%	<0.001	0.55
Alcohol Use†								
No	39.5%	0.005	41.5%	0.014	521			
Yes	60.5%	0.005	58.5%	0.014	735	-2.0%	0.18	0.04
SF-12/36 PCS*	40.5 (13.0)	0.196	43.0 (8.1)	0.216	1424	2.5	<0.001	0.19
SF-12/36 MCS*	48.2 (11.5)	0.154	53.5 (9.1)	0.241	1424	5.3	<0.001	0.46
QALYs*	0.69 (0.21)	0.003	0.76 (0.13)	0.004	1414	0.07	<0.001	0.33

† Data from NHIS using 15,312 observations representative of 11,473,330 U.S. adults.
*Data from MEPS using 12,679 observations representative of 15,604,791 U.S. adults.

Chiropractic use in U.S. population

Table 10 displays the results of the multivariable logistic regression estimating the odds of chiropractic use for U.S. adults with chronic spine pain based on socio-demographic and clinical characteristics using NHIS data. The odds of chiropractic use did not differ based on sex, ethnicity, body mass index, or the presence of diabetes. The odds of chiropractic use was significantly lower for adults from the southern U.S. Relative to young adults (18 to 30 years old), adults over the age of 50 have a lower odds of chiropractic use. For race, Black and Asian or Pacific Islander adults have a lower odds of chiropractic use compared to White adults, but no other significant racial differences were noted. For socio-economic status measures, the odds of chiropractic use significantly increased based on employment (compared to unemployed), higher education levels (compared to no high school degree), and higher household incomes (compared to household incomes <$35,000). Adults with a pain duration over a year had lower odds of chiropractic use relative to those with a pain duration less than a year. The odds of chiropractic use also increased for those with radiating pain, headaches, alcohol users, and non-smokers. Table 11 displays the results of the multivariable logistic regression estimating the odds of chiropractic use for U.S. adults with chronic spine pain based on socio-demographic and clinical characteristics using MEPS data. The odds of chiropractic use were lower for adults 85 and older relative to younger adults (18 to 30 years old). For race and ethnicity, the odds of chiropractic use were lower for Black, Asian or Pacific Islander, and Hispanic adults. For overall physical and mental health, the odds of chiropractic use were increased for adults in the top three quartiles for physical health, the top two quartiles for mental health, and the middle two quartiles for quality-adjusted life years compared to those in the lowest quartile.

Table 10. Odds of chiropractic use in U.S. Population with chronic spine pain using NHIS

	OR	95% CI		OR	95% CI
Region of U.S.			Body Mass Index		
Northeast	1.00	Reference	Underweight	0.76	(0.45 to 1.27)
Midwest	1.02	(0.86 to 1.21)	Healthy weight	1.00	Reference
South	0.64***	(0.54 to 0.75)	Overweight	0.96	(0.84 to 1.09)
West	1.06	(0.90 to 1.26)	Obese	0.89	(0.78 to 1.03)
Age			Duration		
18 to 30	1.00	Reference	1 year or less	1.00	Reference
31 to 50	0.88	(0.75 to 1.03)	1 to 5 years	0.74***	(0.62 to 0.88)
51 to 64	0.70***	(0.58 to 0.83)	5 to 10 years	0.61***	(0.50 to 0.73)
65 to 84	0.69***	(0.56 to 0.85)	Over 10 years	0.63***	(0.54 to 0.75)
85 and above	0.45***	(0.29 to 0.70)	Radiating pain		
Sex			No	1.00	Reference
Male	1.00	Reference	Yes	1.18***	(1.08 to 1.31)
Female	1.00	(0.90 to 1.11)	Headache		
Race			No	1.00	Reference
White	1.00	Reference	Yes	1.12*	(1.01 to 1.25)
Black/African-American	0.81*	(0.68 to 0.96)	Diabetes		
Alaskan Native, or American Indian	0.83	(0.55 to 1.26)	No	1.00	Reference
Asian or Pacific Islander	0.68*	(0.48 to 0.97)	Yes	0.89	(0.76 to 1.05)
Other Race	0.60	(0.33 to 1.10)	Smoking		
Multiple Race	0.43	(0.17 to 1.06)	No	1.00	Reference
Ethnicity			Yes	0.69***	(0.61 to 0.78)
Not Hispanic	1.00	Reference	Alcohol Use		
Hispanic	0.85	(0.72 to 1.02)	No	1.00	Reference
Employment			Yes	1.16**	(1.04 to 1.29)
Not Employed	1.00	Reference	Household Income		
Employed	1.36***	(1.21 to 1.52)	$0 - $34,999	1.00	Reference
Education			$35,000 - $74,999	1.17**	(1.04 to 1.32)
Less than high school	1.00	Reference	$75,000+	1.19*	(1.02 to 1.39)
High school	1.20*	(1.02 to 1.40)			
College, no degree	1.41***	(1.21 to 1.66)			
Associate or technical school	1.39**	(1.13 to 1.70)			
Bachelor's	1.26*	(1.02 to 1.55)			
Post-graduate or professional	1.30*	(1.02 to 1.65)			

*P≤0.05, **P≤0.01, ***P≤0.001

Data from NHIS using 15,312 observations representative of 11,473,330 U.S. adults.

Table 11. Odds of chiropractic use in U.S. Population with chronic spine pain using MEPS

	OR	95% CI		OR	95% CI
Age			SF-12/36 PCS		
18 to 30	1.00	Reference	Quartile 1	1.00	Reference
31 to 50	1.04	(0.83 to 1.29)	Quartile 2	1.39**	(1.10 to 1.76)
51 to 64	1.03	(0.83 to 1.29)	Quartile 3	2.15***	(1.61 to 2.89)
65 to 84	0.87	(0.68 to 1.11)	Quartile 4	2.88***	(2.10 to 3.94)
85 and above	0.41**	(0.22 to 0.75)	SF-12/36 MCS		
Sex			Quartile 1	1.00	Reference
Male	1.00	Reference	Quartile 2	1.08	(0.87 to 1.35)
Female	1.22***	(1.09 to 1.36)	Quartile 3	1.36*	(1.07 to 1.74)
Race			Quartile 4	1.47**	(1.11 to 1.94)
White	1.00	Reference	QALYs		
Black/African-American	0.27***	(0.21 to 0.34)	Quartile 1	1.00	Reference
Alaskan Native, or American Indian	0.57	(0.29 to 1.12)	Quartile 2	1.34*	(1.05 to 1.71)
Asian	0.59**	(0.42 to 0.84)	Quartile 3	1.40*	(1.03 to 1.90)
Other Race	0.58	(0.19 to 1.76)	Quartile 4	1.32	(0.93 to 1.88)
Multiple Race	1.02	(0.66 to 1.57)			
Ethnicity					
Not Hispanic	1.00	Reference			
Hispanic	0.37***	(0.30 to 0.46)			

*P≤0.05, **P≤0.01, ***P≤0.001
*Data from MEPS using 12,679 observations representative of 15,604,791 U.S. adults.

Trial participants relative to the US population visiting a chiropractor

Table 12 compares trial participants to the U.S. population with chronic spine pain and chiropractic use since all of the clinical trials included spinal manipulation, a treatment most commonly delivered by chiropractors in the U.S. Trial participants were still more likely to be older, female, and White, and less likely to be Black or Hispanic relative to the US population seeing a chiropractor. Socioeconomic status indicators such as employment, education, and household income were also higher among trial participants. For clinical characteristics, trial participants had a shorter pain duration, less radiating arm or leg pain, diabetes, smoking or alcohol use. Overall physical health was lower in trial participants, mental health was higher, and there were no differences in quality-adjusted life years. Most differences were small in magnitude apart from small to medium differences in ethnicity and smoking and medium differences in age and education.

Table 12. U.S. Population with chronic spine pain who visited a chiropractor from NHIS & MEPS relative to trial participants

	U.S. Population who visited a chiropractor	Trial Population	Trial – U.S.

	% or Mean (SD)	SE	% or Mean (SD)	SE	Obs	Diff	P-value	Effect Size
Age†								
18 to 30	13.7%	0.008	7.0%	0.007	101	-6.7%	<0.001	0.22
31 to 50	44.7%	0.011	32.8%	0.012	473	-12.0%	<0.001	0.24
51 to 64	26.3%	0.009	23.5%	0.011	339	-2.8%	0.057	0.06
65 to 84	14.2%	0.007	35.9%	0.013	518	21.7%	<0.001	0.51
85 and above	1.1%	0.002	0.8%	0.002	12	0.3%	0.41	0.03
Sex†								
Male	44.1%	0.011	40.7%	0.013	588			
Female	55.9%	0.011	59.3%	0.013	856	3.4%	0.048	0.07
Race†								
White	89.0%	0.006	94.9%	0.006	1368	5.8%	<0.001	0.22
Black/African-American	7.6%	0.005	2.3%	0.004	33	-5.3%	<0.001	0.25
Alaskan Native, or American Indian	1.2%	0.002	0.9%	0.002	13	-0.3%	0.46	0.03
Asian or Pacific Islander	1.8%	0.003	1.2%	0.003	17	-0.6%	0.13	0.05
Other Race	0.3%	0.001	0.7%	0.002	10	0.4%	0.026	0.06
Multiple Race	0.2%	0.001	0.1%	0.001	1	-0.1%	0.35	0.03
Ethnicity†								
Not Hispanic	91.3%	0.006	98.7%	0.003	1419			
Hispanic	8.7%	0.006	1.3%	0.003	19	-7.3%	<0.001	0.37
Employment†*18-64 years old*								
Not Employed	34.6%	0.013	19.9%	0.013	178			
Employed	65.4%	0.013	80.1%	0.013	716	14.6%	<0.001	0.33
65 years or older								
Not Employed	85.1%	0.018	80.4%	0.017	426			
Employed	14.9%	0.018	19.6%	0.017	104	4.7%	0.07	0.12
Education†								
Less than high school	14.2%	0.008	1.7%	0.003	24	-12.5%	<0.001	0.51
High school	29.6%	0.010	20.4%	0.011	291	-9.2%	<0.001	0.21
College, no degree	23.0%	0.009	21.5%	0.011	306	-1.5%	0.28	0.04
Associate or technical school	13.0%	0.008	11.9%	0.009	170	-1.1%	0.34	0.03
Bachelor's	12.8%	0.008	28.6%	0.012	407	15.7%	<0.001	0.40
Post-graduate or professional	7.3%	0.006	15.9%	0.010	227	8.6%	<0.001	0.27
Household Income†								
$0 - $34,999	38.6%	0.011	29.5%	0.013	353	-9.1%	<0.001	0.19
$35,000 - $74,999	35.2%	0.011	45.8%	0.014	548	10.6%	<0.001	0.22
$75,000+	26.2%	0.011	24.7%	0.012	296	-1.5%	0.38	0.03
Body Mass Index†								
Underweight	0.7%	0.002	0.6%	0.002	8	-0.1%	0.63	0.01
Healthy weight	30.0%	0.010	31.9%	0.012	461	2.0%	0.22	0.04
Overweight	36.5%	0.011	36.4%	0.013	526	-0.1%	0.96	0.00
Obese	32.8%	0.010	31.1%	0.012	449	-1.7%	0.28	0.04
Duration†								
1 year or less	13.9%	0.008	21.0%	0.011	296	7.1%	<0.001	0.19

1 to 5 years	29.2%	0.010	32.8%	0.013	461	3.6%	0.028	0.08
5 to 10 years	19.9%	0.009	18.8%	0.010	265	-1.1%	0.42	0.03
Over 10 years	37.0%	0.010	27.4%	0.012	385	-9.6%	<0.001	0.21
Radiating pain†								
No	46.6%	0.011	60.0%	0.013	866			
Yes	53.4%	0.011	40.0%	0.013	578	-13.3%	<0.001	0.27
Diabetes†								
No	90.4%	0.006	93.8%	0.006	1355			
Yes	9.6%	0.006	6.2%	0.006	89	-3.4%	<0.001	0.13
Smoking†								
No	73.7%	0.010	90.3%	0.008	1304			
Yes	26.3%	0.010	9.7%	0.008	140	-16.6%	<0.001	0.44
Alcohol Use†								
No	31.7%	0.010	41.5%	0.014	521			
Yes	68.3%	0.010	58.5%	0.014	735	-9.8%	<0.001	0.20
SF-12/36 PCS*	44.9 (11.7)	0.323	43.0 (8.1)	0.216	1424	-1.9	<0.001	0.16
SF-12/36 MCS*	50.4 (10.0)	0.284	53.5 (9.1)	0.241	1424	3.1	<0.001	0.31
QALYs*	0.762 (0.17)	0.005	0.760 (0.13)	0.004	1414	0.002	0.70	0.01
† Data from NHIS using 3006 observations representative of 2,315,852 U.S. adults. *Data from MEPS using 2870 observations representative of 4,194,660 U.S. adults.								

Discussion

Summary of findings

We identified important differences between clinical trial participants and the general U.S. population with chronic spine pain. The clinical trials had an over-representation of White, non-Hispanic, employed participants with higher household incomes relative to the general US population with chronic spinal pain. Trial participants also had shorter pain duration, less radiating pain, fewer co-morbid conditions, worse physical health, and better mental health. All of the clinical trials included spinal manipulation, a common modality used by chiropractors in the U.S. The odds of chiropractic use in the U.S. are lower for older adults, Black or Asian/Pacific Islander adults, the unemployed, those with less education, lower household income, a longer duration of pain, and a history of smoking. In addition, the odds of chiropractic use also decreased for those with lower physical or mental health. Despite these differences in demographic and health characteristics of the U.S. population using chiropractic care, there were similar important differences compared to clinical trial participants when limiting the U.S. population to adults with chronic spinal pain who visited a chiropractor in the past year. Most of the differences identified had small effect sizes, with small to medium or medium effect sizes noted for age, ethnicity, employment, income, education, smoking status, and mental health.

Strengths & Limitations

This study has important strengths and weaknesses. First, the use of individual participant data from multiple clinical trials measuring similar demographic and health characteristics that could be combined and compared to national survey measures is an important strength. Existing studies pooling individual participant data from spine pain trials have noted substantial heterogeneity between studies in the demographic and health characteristics collected with sex and age being the only two characteristics consistently collected and reported.[94] For example, the IPDMA by Patel et al. included 19 randomized trials with 9328 participants, but important baseline characteristics such as race, ethnicity, smoking status, and body mass index were reported by less than 1/3 of trials.[95] Another strength of this study was the use of nationally representative surveys where demographic and health characteristics of adults with chronic spine pain were available. In addition to these strengths, this project also has important limitations. The clinical trial data used for this project was limited to a readily available sample of trials conducted by one research group with most participants recruited from a single geographic location. This limitation can potentially impact the generalizability of findings if spine pain trials conducted by other groups included a more diverse sample of participants who are more representative of the population of interest. In addition, health characteristics were self-reported and are subject to potential recall bias. Health characteristics were self-reported in the clinical trials and national health surveys, so any potential misclassifications would not be expected to have a differential impact. Finally there was slight differences in time periods between the data sources used (NHIS: 2001-2010; MEPS: 2002-2010; Trials: Majority 2000-2010, one trial from 1994-1997 and one trial from 2010-2013).

Comparisons to other research

This is the first study comparing demographic and clinical characteristics of participants in clinical trials for spinal pain to the U.S. population. However, there are a number of individual patient data meta-analyses (IPDMA) of spinal pain treatments that provide a summary of the typical population in clinical trials for spine pain, including trials within and outside of the U.S. [94-96] The broader set of international clinical trials for spine pain have similar demographic characteristics to the set of eight trials used for this analysis in terms of sex (~55% female), race and ethnicity (90% White, non-Hispanic), employment (51-75% employed), and education (68% low/middle education). Clinical characteristics such as duration of spine pain (20% <1 year) and the presence of leg pain (59%) were also similar. One area with a notable difference compared to existing IPDMA trials is that participants in the trials used for this project reported better overall mental health as indicated by higher scores on the SF-36 mental component summary (53.5 in the 8 trials vs 45 in existing IPDMAs). It's unclear why this difference exists as the inclusion/exclusion criteria for the eight trials included in the study are similar to the trials included in the IPDMAs (e.g. exclude individuals with severe comorbid conditions, substance abuse).

Findings for predictors of chiropractic care in U.S. adults with chronic spine pain are generally consistent with prior studies including studies assessing predictors of complementary and integrative healthcare use, which includes chiropractic.[17,97] Previous studies have identified that the use of chiropractic care is less likely among racial and ethnic minorities, those with less education, without employment, and with more co-morbid non-musculoskeletal conditions including depression, heart disease, and diabetes.[28,98,99] This study builds on prior work by confirming these findings using surveys representative of the U.S. population over a decade (2001 to 2010). One finding that differed from prior work is the decreased use of chiropractic for those with lower mental health scores. A random sample of chiropractors from 5 geographically distinct regions across the U.S. (and one site in Canada) noted that individuals seeking chiropractic care reported significantly lower mental health relative to patients seeking care from medical providers.[100] The results from the study by Coulter et al. are also at odds with other studies using national survey data which report a lower prevalence of mental health conditions (e.g. depression) for individuals that use chiropractic services.[98]

Implications for Clinical Practice

The findings from this study raise important questions for clinical practice. The primary goal for clinical trials is to provide answers for important clinical questions that can be easily translated into practice. The important differences between trial participants and the U.S. population with chronic spinal pain raises questions regarding how findings from the trials may generalize to inform clinical practice. So long as the typical patients being seen by a provider reflect the populations included within the trials (e.g. predominantly white, educated, employed, with few comorbidities) the findings from the clinical trials will readily translate. For populations under-represented in clinical trials, the findings may still be relevant, so long as the treatment effects are not modified by characteristics within the population. Research investigating effect modification of spinal pain treatments is an emerging field as clinical trials are not typically powered for such analyses and IPDMA have limitations due to inconsistent availability and measurement of potential modifying factors.

Three recent IPDMAs assessed potential treatment effect modifiers of non-invasive and non-pharmacological treatments such as spinal manipulation and exercise for low back pain. Patel et al. included 19 acute or chronic low-back pain trials (n=9328) and grouped treatments into broad categories which included both active physical treatments (e.g., exercise, graded activity) and passive physical treatments (e.g., spinal manipulation, acupuncture, physiotherapy).[95] They noted younger individuals with worse disability, physical health status, and less psychological distress were more likely to benefit from passive physical treatments including spinal manipulation. No effect modifiers were noted for active physical treatments. De Zoete et al. included 21 chronic low-back pain trials (n=4223) to assess potential effect modifiers of spinal manipulation relative recommended treatments, non-recommended treatments, or sham interventions.[96] Sufficient data were available for only one of the planned comparisons: spinal manipulation vs other recommended therapies (e.g., exercise, medication, psychological treatment). The authors noted small moderating effects for duration of pain with durations <1 year favoring spinal manipulation relative to other recommended treatments, with similar effects for those with longer durations. No other consistent moderating effects were noted including education and employment. Some of the planned modifiers had a limited amount of data for analysis(e.g. analyses of race/ethnicity included 64 or fewer non-white individuals). Hayden et al. included 27 chronic low-back pain trials (n=3514) and compared exercise interventions to any non-exercise treatment (e.g., no treatment, usual care, advice/education, spinal manipulation, psychological therapy).[94] The authors noted that the absence of heavy physical demands at work, lower body mass index, and medication use for low back pain (LBP) were potential effect modifiers favoring exercise interventions. Education and employment did not have a moderating effect on exercise interventions. We found differences in some of these effect modifying characteristics in the current study. Relative to the U.S. population with chronic spine pain, the clinical trial populations had an over-representation of individuals with shorter pain durations (less than 1 year), better physical health, and better mental health. Effect modification studies have shown that individuals with shorter pain durations and better mental health show a larger benefit with spinal manipulation and those with better physical health have less benefit relative to other treatments.

In addition to IPDMA studies assessing potential effect modifiers, we also searched Pubmed and Google Scholar for RCTs assessing the impact of spinal manipulation or exercise in underserved populations and identified one trial that compared yoga, physical therapy, and education for chronic LBP in an underserved population.[101] This study noted significant differences favoring exercise over education for pain reduction and medication use, but not disability. This trial is comparable to a trial included in this project which compared supervised exercise therapy to home exercise and advice from chronic back pain and found no differences between groups in pain reduction, disability, or medication use.[44] The education intervention used in the trial by Saper et al. was less intensive than the home exercise and advice intervention, which along with the differences in population may potentially explain the differences in findings between the two studies. We did not identify any RCTs assessing spinal manipulation in underserved populations.

Implications for Research

Although greater attention has been devoted to increasing the diversity and representativeness of clinical trial participants, many trials still fall short. Inclusion of minorities in NIH-funded clinical trials has increased over the past 25 years (from 2.8% to 11.1%), but minorities are still widely underrepresented. [102] Representation of Hispanic and Black patients in clinical trials for pain treatments are 2 to 3.5 times lower relative to census estimates.[103,104] This under-representation is especially troubling given the known disparities in health outcomes for underserved populations. Among individuals with chronic pain, Black Americans and individuals in the lowest wealth quartile report more pain related disability.[105] Further, high impact chronic pain, pain that limits life activities or work on most days, is twice as prevalent among those with low income.[105]

A number of factors that contribute to the low participation of underserved populations in clinical research have been identified including low research literacy, lack of culturally relevant information in the consent process, and distrust of researchers, including fears that participation will worsen their health status, expose them to unnecessary risks, lead to a loss of privacy or confidentiality, and result in stigmatization.[106,107] Further, the burden of clinical research participation is often a significant barrier as the transportation, financial, and time demands are greater than routine clinical care.[106] In addition, biases among those who recruit and screen for clinical trials is a barrier, as individuals from underserved communities can be viewed as less than ideal candidates, due to potential compliance concerns for attending study visits and complying with treatment and data collection protocols.[108]

To enact change, spine pain researchers will need to embrace key community-based approaches that have shown promise for increasing participation of underrepresented populations. These approaches are becoming common in many health research fields, but are used infrequently in pain research.[109-111] Successful strategies are often multilevel, engage the community throughout the research process, and address concerns at the participant, provider, and community level, including issues of trust.[109] Strategies that have been used successfully by others include engaging key community members in trial protocols and implementation early and often within the life cycle of the project, the use of patient navigators to help reduce the complexity of participation, pilot testing of recruitment approaches, placing enrollment and treatment sites within underserved communities to reduce travel burden, and the use of flexible appointment times to reduce work or childcare barriers to participation.[109,112]

Conclusions

This project assessed the generalizability of randomized trial populations participating in research assessing spinal manipulation for chronic spinal pain. The clinical trials had an under-representation of individuals from underserved communities with lower percentages of racial and ethnic minorities, less educated, and unemployed relative to the U.S. population with spine pain. While the odds of chiropractic use in the U.S. are lower for individuals from underserved communities, the trial populations also under-represented these populations relative to U.S. adults with chronic spine pain who visit a chiropractor.

Appendix Materials

Appendix Table 1. NHIS and MEPS variables

Source	Variable Name	Description
IPUMS NHIS	AGE	Age in years since their last birthday
	SEX	Indicates whether the person was male or female
	RACEA	Racial background using the pre-1997 Office of Management and Budget's (OMB's) Statistical Policy Directive No. 15.
	HISPETH	Hispanic/Spanish/Latino origin or ancestry based on the origin of a parent, grandparent, or some far-removed ancestor.
	EDUC	Highest level of schooling completed
	EMPSTAT	Employment status in the last 1-2 weeks
	INCFAM97ON2	Total household income using categories introduced in 2007
	BMICALC	Calculated body mass index
	SAWCHIR	Identifies individuals who had seen or talked to a chiropractor during the past 12 months
	DIABETICEV	Identifies individuals who had ever been diagnosed with "diabetes or sugar diabetes" by a doctor or other health professional
	LEGPAIN3MO	Identifies individuals who had low back pain that "spread down either leg to areas below the knees" during the past three months
	ALCSTAT1	Identifies individuals who had at least 12 drinks of any type of alcoholic beverage in their lifetime
	SMOKESTATUS2	Identifies current smoking status as every day, some days, unknown frequency, former smoker, and never smoked.
	FLBACKC	Indicates whether adults who have at least a little difficulty with one or more functional activities due to a back or neck problem have a chronic back or neck problem
	FLBACKNO/ FLBACKTP	Duration of back or neck problem causing at least a little difficulty with one or more functional activities
MEPS	CCC0DEX	Aggregation of ICD-9-CM condition codes into clinically meaningful categories that group similar conditions
	PCS42	Physical Component Summary of the SF-12 Version 2
	MCS42	Mental Component Summary of the SF-12 Version 2
	CHIROVISIT	Number of office based visits to a chiropractor
	ADDAYA42	Limitations in moderate activities during a typical day (used to construct SF6D)
	ADPWLM42	Limitations in kind of work and other activities due to physical health in past four weeks (used to construct SF6D)
	ADMALS42	Accomplished less than would like due to mental problems in the past four weeks (used to construct SF6D)
	ADSOCA42	Physical health or emotional problems interfered with social activities during the past four weeks (used to construct SF6D)
	ADPAIN42	Pain interfered with normal work outside the home and housework during past four weeks (used to construct SF6D)

	ADDOWN42	Felt downhearted and depressed during past four weeks (used to construct SF6D)
	ADNRGY42	Had a lot of energy during the past four weeks (used to construct SF6D)

Aim 3 paper: Cost-effectiveness of common treatments including spinal manipulation for chronic neck or back pain: development and findings from a decision model

Background

Trial-based cost-effectiveness analyses (CEAs), where economic outcomes are collected alongside clinical outcome data in randomized clinical trials, have increased in frequency over the past few decades and have been used to inform policy decisions based on both effectiveness and efficiency across the world.[79] While trial-based CEAs have many important strengths, there are also limitations including the number of treatments evaluated in the trial (usually two or three strategies), the limited trial time horizon, and the difficulty of incorporating additional evidence from prior RCTs or other study designs into the analysis.[34] Incorporating information from multiple RCTs, as well as other information sources, into a decision analytic model is a recommended framework for overcoming the inherent limitations in trial-based CEAs. Decision models allow for the synthesis of evidence from multiple study designs to best address the question of interest.

Decision models are an ideal framework for assessing the benefits, harms, and costs of treatments for back or neck pain as there are a large number of potential treatment options to consider, many with similar clinical effects.[113,114] A 2019 systematic review identified 21 studies using decision analysis models to assess treatment strategies for non-specific low back pain (LBP) or sciatica, one of the most disabling presentations of LBP.[115] Importantly, none of the existing studies evaluated SMT as a first-line approach. SMT was included in some models as a second-line approach[116] or as one of many potential conservative treatment options grouped together as a single comparator to surgical interventions.[117,118] The authors noted that current decision models for back pain poorly represent the clinical course and impact of LBP and sciatica on daily activities and functioning. More attention is needed for choosing health states and time horizons that reflect the impact of the condition and evaluated treatments. The authors also noted that the overall quality of existing modeling studies is poor and that future studies should follow recommendations for good research practices in modeling.[34,119] Common limitations of existing studies include inadequate time horizons, inappropriate use of utility data, calculation errors, lack of clearly defined methods, and limited consideration for the impact of model assumptions and uncertainty on overall results and their generalizability.[115]

Through searches of Medline, the health economics evaluation database, and the Tufts cost-effectiveness analysis registry, we identified three existing decision models that evaluated SMT as a first-line approach for neck or back pain (See Table 1).[120-122] A modeling study by Herman et al. assessed the cost-effectiveness of non-pharmacologic interventions (including SMT) for chronic LBP.[120] The authors used data from 10 large randomized trials including 17 different therapies to estimate transition probabilities between 4 health states representing the morbidity of chronic back pain over a one year period (i.e. no pain, low-impact, moderate-impact, or high-impact chronic pain). However, the model did not include health states to capture potential harms associated with common treatments for back pain. In addition, findings from the model are difficult to interpret as the authors included separate cost-effectiveness estimates for similar forms of treatment without a clear explanation. For example, the authors report five separate societal cost estimates for SMT relative to usual care that vary from -$818 to $513 and five separate QALY gain estimates relative to usual care ranging from 0.004 to 0.33. A second model by Verhaeghe et al. assessed osteopathic SMT relative to usual care for back or neck pain using a decision tree. The decision tree captured the probability of improvement with each treatment approach and assumed further care (i.e. medications, ambulatory care, or hospitalization) for those who did not improve. The authors noted that relative to usual care, osteopathic SMT resulted in lower costs and higher QALYs for LBP and higher costs and QALYs with incremental cost-effectiveness ratios well below accepted thresholds used in Europe. The third decision model was conducted as part of the Bone and Joint Decade Task Force on Neck Pain and Its Associated Disorders.[122] This model included health states reflecting potential harms from common neck pain treatments (e.g. gastrointestinal bleeding from medication) in addition to health states capturing the impact of neck pain on quality of life. While the model structure captured benefits and harms of common interventions, it did not assess costs. Further, treatment effectiveness estimates were based on a single high-quality trial with 183 participants.[123] Importantly, none of the existing models have modeled both benefits and harms of common neck and back pain treatments, including SMT, to assess their cost-effectiveness.

Table 13. Decision Models assessing SMT for spinal pain

Study	Condition/ Analysis type	Model Type	Treatments	Health States/Pathways
Herman	Chronic back pain / Cost-effectiveness	Markov	Active trunk exercise, cognitive behavioral therapy, **chiropractic care (primarily SMT)**, exercise, **exercise + manipulation**, **flexion distraction (a form of SMT)**, acupuncture, **manipulation**, multidisciplinary program, physical therapy, **spinal manipulation**, structural massage, TCM acupuncture, therapeutic massage, yoga, usual care	**Spinal pain states:** No pain, low-impact pain, moderate-impact pain, high-impact pain **Treatment related states:** None
Verhaeghe	Back pain and Neck pain (separate models) / Cost-effectiveness	Decision tree	**Osteopathic care (primarily SMT)** + usual care, usual care	**Spinal pain pathways:** Clinical improvement, no improvement. If no improvement then medication, physical therapy, or hospitalization
Van der Velde	Neck pain / Comparative effectiveness	Markov	Non-steroidal anti-inflammatory drugs (NSAIDs), Cox-2 NSAIDs, exercise, **SMT**	**Spinal pain states:** No troublesome neck pain, troublesome neck pain, death **Treatment related states:** upper GI bleeds, stroke, myocardial infarction

The project's purpose was to estimate the cost-effectiveness of SMT relative to other commonly used interventions for chronic spine pain using a decision analysis model. Our model captured the potential benefits, harms, and costs associated with common front-line treatments for spine pain and follows recommendations for conducting decision analysis models.[34,119] Home exercise instruction and basic self-management advice are commonly recommended as a frontline approach in guidelines for the management of back and neck pain, thus the decision model assessed the cost-effectiveness of this approach relative to other common management approaches for spinal pain.[81,124]

Methods

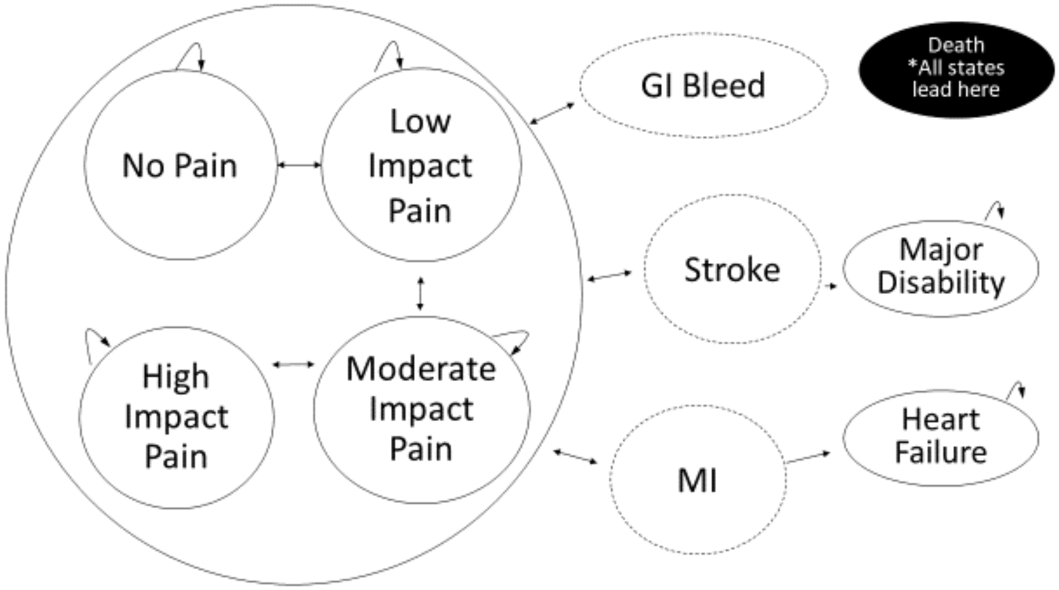
Model Structure

Health States & Treatment Strategies

We developed a state-transition (Markov) model with four-week cycles to evaluate the cost-effectiveness of common conservative treatment approaches for chronic spinal pain from the healthcare perspective. The model included health states representing the range of morbidity associated with spine pain in addition to potential harmful effects from common treatments. Figure 5 displays the Markov model used to evaluate the treatment strategies for different target populations of patients with chronic spine pain. The model consisted of four health states with varying impact due to spinal pain: no pain, low-impact pain, moderate-impact pain, and high-impact pain. Each 4-week cycle, patients could only transition to adjacent pain impact states (e.g., from moderate-impact pain to low- or high-impact pain, but not no pain). In addition, patients could experience: 1) the background risk of death; 2) intervention-specific risks for upper gastro-intestinal bleeds, strokes, and myocardial infarctions; and 3) adverse event related deaths or complicated health states (i.e., major disability from stroke or heart failure following myocardial infarction). The risks of adverse events related to treatments and background mortality unrelated to treatments (i.e. age-related death from any cause) were modeled using a Markov cycle tree presented in Appendix Figure 21.

In clinical trials of spinal pain interventions, a short course of treatment (6-12 weeks) is commonly applied and outcomes are rarely monitored for longer than one year. To better assess the long-term impact of treatment approaches, we used a time horizon of five years for the primary analysis. We applied transition probabilities between pain-impact states for three distinct time periods: 1) the initial 12 weeks when treatment was administered; 2) from the end of treatment to one year, when data from clinical trials were available; and 3) from years 2 to 5, when clinical trial data were not available. Analyses extending beyond one year applied a 3% annual discount rate to account for time preferences for health and costs. We compared the following treatment strategies, which include a mix of traditional and emerging treatments for the management of spinal pain in the U.S.: medical care, acupuncture, massage, supervised exercise therapy, home exercise, spinal manipulation with home exercise, cognitive behavioral therapy, yoga, and mindfulness-based stress reduction. All analyses were conducted from the healthcare perspective.

Figure 5. Model structure



Patient Population

Our target population was adults with chronic spine pain seeking conservative non-invasive care. For the base case model, we used 40 year old adults with chronic spinal pain with an initial distribution of pain impact (low, moderate, or high) based on U.S. national estimates.[125] We assumed half of the population had neck pain and half had low back pain, unless noted differently. We chose 40-year-old adults as the target population for two reasons. The mean age of participants within RCTs used for the model was often near 40 years old and the frequency of adverse events (heart attacks, strokes, gastrointestinal bleeds) starts to increase in a non-trivial manner at 40 years. Additional analyses were conducted using the following target populations:

- 40-year-old adults with high-impact spine pain to assess impact of treatments in those responsible for a disproportionate share of the costs and disease burden.
- 80-year-old adults with spine pain to assess impact of adverse events in an older population where the incidence is higher.
- To assess the impact of SMT-related harms on cost-effectiveness outcomes we assessed the following populations:
    - 40-year-old adults with neck pain (where everyone is at risk)
    - 40-year-old adults with low back pain (where no one is at risk)

Parameter Sources (Tables 14-16)

Transition probabilities

We estimated transition probabilities between pain impact health states using individual participant data from randomized trials in chronic spinal pain populations. We defined pain impact states with the commonly used revised graded chronic pain scale,[126] which includes the following states:

- Low-impact pain: Mild pain with little to no interference with enjoyment of life and general activities
- Moderate-impact pain: Bothersome pain with some interference with enjoyment of life and general activities
- High-impact pain: Pain that limits life activities or work on most days

We did not have access to clinical trials that included the graded chronic pain scale as a direct measure, so we mapped participants to pain-impact states using data from the SF-36 and pain severity. The SF-36 includes a question regarding frequency of pain interference with normal work including work outside the home and housework. We classified participants reporting pain that interfered with their normal work “not at all” or “a little bit” with Low-impact pain. We classified participants with spinal pain that “moderately” interfered with their normal work with Moderate-impact pain. Finally, those reporting “quite a bit” or “extreme” pain interference with normal work were classified as High-impact pain.

We estimated transition probabilities between pain states using individual-level participant data for two distinct time frames. The short-term time frame lasted from the start of treatment (week 0) to week 12, as most trials provided spinal pain treatments for 12 weeks. Next, we estimated long-term transition probabilities that applied from week 12 to week 52, as all studies included assessments at 26 and 52 weeks. We assumed that transition probabilities from year 1 to 5 (very long-term) were the same for all treatments to model diminished treatment effects over the very long term. Home exercise and advice was chosen as the standard comparison as it represents a minimal intervention commonly recommended in guidelines for the management of spine pain.[81,124] We modeled alternative treatment strategies using risk ratios relative to home exercise and advice for 1) a worsening in pain impact (e.g., decreased risk of transitioning from Low to Moderate-impact pain) and 2) an improvement in pain impact (e.g., increased risk of transition from High to Moderate-impact pain) in the both the short and long term. For example, a risk ratio of 2 for an improvement in pain impact would double the transition probabilities from the reference strategy (home exercise and advice) for moving from 1) high to moderate-impact pain; 2) moderate to low-impact pain; and 3) low-impact to no pain. In the very long term, all treatment strategies reverted to the same pain-impact transition probabilities as the home exercise and advice strategy.

We calibrated transition probabilities for the home exercise and advice strategy and risk ratios for adding spinal manipulation or supervised exercise relative to home exercise and advice using individual participant data from five randomized clinical trials.[43-45,47,48] The proportion of participants in each of the four pain impact states at weeks 12, 26, and 52 were used as calibration targets. For each treatment strategy, differences between the model output and individual trial results for the calibration targets were squared and summed, and model parameters that minimized this difference were chosen. We did not have access to individual-level data for other treatment strategies (e.g., medication, massage) and estimated risk ratios for these treatments using the following approach. To start, we identified clinical trials with similar populations (chronic spine pain) from high-quality systematic reviews using a Cochrane review when available. We used the mean disability outcomes at baseline, after treatment, and at long-term follow up (6-months or later) to calibrate the baseline distribution of pain-impact states and short and long-term risk ratios for the respective treatment. This required us to assign disability outcomes to each pain-impact state within our model. We used the Roland Morris disability scale for back pain and the Neck Disability Index for neck pain to convert from pain-impact to disability scores typically collected in pain trials. We used two parameters to assign disability outcomes to each pain-impact health state: 1) a maximum value for the high-impact pain state and 2) a distance parameter that either widened or narrowed the spread between the high-impact pain state and the other two states, assuming an equal distance between states. These parameters were calibrated separately for neck and back pain using individual participant data from trials with a home exercise and advice strategy. Finally, risk ratios for treatments with only summary level data available were then manually selected based on their ability to minimize the sum of squared differences in mean disability outcomes between the model and included trials for each treatment.

We used large cohort studies within the general population for parameter estimates of the baseline risk of adverse events and subsequent health consequences (e.g., death, heart failure).[127-130] We estimated the excess risk of upper gastrointestinal bleed, stroke, or myocardial infarction due to non-steroidal anti-inflammatory medications (NSAIDs) using a large individual participant data meta-analysis.[131] The excess risk of stroke due to neck manipulation was assumed to be the same as the excess risk due to NSAIDs based on findings from case-crossover and cohort studies showing similar risks for stroke between chiropractor and primary care providers following visits for neck pain.[132,133]

Quality of life

We calculated quality-adjusted life years (QALYs) by assigning health-related quality-of-life weights to health states within the model. The weights for each pain state were assigned using SF-12 data from individuals living with chronic spine pain included in the Medical Expenditures Panel Survey (MEPS), a representative survey of U.S. adults. Using 2002 to 2010 MEPS data, we identified individuals with chronic neck or back pain by selecting those with healthcare expenditures for spine problems in at least 2 of the 5 interviews over the 2.5 years the MEPS is administered. We used the Clinical Classification Code 205 within the Medical Conditions File to identify individuals with healthcare visits for spondylosis, intervertebral disc disorders, or other back problems. Quality-of-life weights were calculated using the SF-6D, which is derived from the SF-12 measure included in the MEPS. The SF-6D includes six dimensions (each with 4-6 levels) to describe health: physical functioning, role limitations, social functioning, pain, mental health, and vitality. Higher scores within each domain indicate higher morbidity. Preferences for SF-6D health states were taken from a study that used discrete choice experiments within a U.S. population.[53] U.S. preferences for SF-6D health states were similar to a previous study assessing preferences in a UK population using standard gamble methods (Lin's coefficient of agreement = 0.941).[52,53] Similar to trial participants, individuals with chronic spine pain in the MEPS survey were categorized as low, moderate, or high-impact pain based on their response to the SF-12 question regarding frequency of pain interference with their normal work including work in and out of the home. For each pain state, we assigned the mean SF-6D value from MEPS respondents in that pain state, which was calculated using sample weights and design variables (stratification factors and primary sampling unit) to account for the stratification and clustering used in the complex multi-stage survey design. We identified disutility values for acute events such as a stroke or myocardial infarction in addition to the potential chronic health states that may follow the acute event from a study in the UK general population using time trade off methods.[134] Disutility due to an upper gastrointestinal bleed was derived from a study in Dutch patients with new or past episodes of thromboembolism using time trade off methods.[135]

Costs

We evaluated costs from the healthcare perspective, including both third-party payer and patient out of pocket costs. All costs were adjusted for inflation to reflect 2020 U.S. dollars using the Personal Health Care Expenditure deflator developed by the Centers for Medicare and Medicaid Services.[34] We used estimates from MEPS for spine-related healthcare costs for low, moderate, and high-impact spine pain.[136] Spine-related healthcare costs were identified using International Classification of Disease, 9th Revision codes (ICD-9) or Clinical Classification Codes (CCC). Spine-related healthcare costs for the no pain state were assumed to be $0. Costs for upper gastrointestinal bleeds were taken from a study using the U.S. nationwide inpatient sample.[137] The cost for a stroke and subsequent major disability were identified from a study using a large U.S. commercial claims database.[138] Costs for myocardial infarction and heart failure were derived from systematic reviews of cost studies for the conditions.[139,140] Costs for the treatment strategies were taken from the randomized trials that informed the effectiveness parameters when available. When costs for the treatments were not reported, we used unit costs from Medicare's national allowable payment schedule to assign costs for the reported procedures in the trials.

Analyses

Cost-effectiveness analysis

We compared all treatment strategies using an incremental cost-effectiveness analysis.[66] Initially we ranked all treatments in ascending order by total QALYs over the 5-year time horizon. Next, we removed treatment strategies that were dominated (more costly and less effective) by other strategies. Following this, we calculated differences in costs and QALYs along with the incremental cost-effectiveness ratio (ICER) for each strategy relative to the adjacent strategy with lower costs and QALYs. The strategy with the lowest costs and effects was defined as the base strategy. The ICER was calculated by dividing the additional costs by the additional QALY gains for each adjacent strategy. Strategies with extended dominance that had a higher ICER relative to the next most costly strategy were noted if present. Extended dominance refers to the situation where funding a combination of two other treatment strategies is more efficient than funding the treatment with extended dominance. We also calculated ICERs for each treatment strategy relative to home exercise and advice, a common self-management approach, as individual preferences and availability of assessed treatment strategies varies substantially. Finally, ICERs were calculated for a limited set of treatment strategies that are commonly available across health systems and covered by insurance in the U.S.

Sensitivity Analyses

We performed one-way sensitivity analyses varying treatment effectiveness and costs as listed in Tables 14 and 16. When available, we used the 25th and 75th percentile costs for a provider-based visit (e.g. primary care, physical therapist, chiropractor) using data from MEPS to inform the lower and higher end treatment costs. Sensitivity analyses assessed the impact of model parameters on ICERs for treatment strategies relative to home exercise and advice. We also conducted a worst-case sensitivity analyses for treatment strategies that were not impacted by one-way sensitivity analyses, which assumed the lower treatment effectiveness and higher costs. Finally, we conducted an analysis to assess the impact of our assumption regarding diminished treatment effects over the very long term (years 2-5). In this analysis, we assumed treatment effects at the end of one year would be maintained over the very long term and assessed impact on cost-effectiveness.

Validation

Internal consistency was assessed by varying model parameters by extreme amounts to ensure the expected results occurred. External consistency was assessed by comparing model outputs to available cohort or trial data that were used to calibrate model parameters.

Table 14. Transition probabilities and effectiveness of alternative strategies [sensitivity analysis values]

	Short Term (0 to 12 weeks)		Long Term (12 to 52 weeks)	
Home Exercise & Advice (Reference Strategy)[43-45,47,48]	Transition Probability		Transition Probability	
No Pain to LIP	0.20		0.25	
LIP to MIP	0.10		0.10	
MIP to HIP	0.10		0.15	
LIP to No Pain	0.025		0.025	
MIP to LIP	0.40		0.30	
HIP to MIP	0.50		0.40	
Treatment	RR for Improving	RR for Worsening	RR for Improving	RR for Worsening
Spinal Manipulation Therapy plus Home Exercise & Advice [44,47,48,141]	1.2 [±50%]	0.75 [±50%]	1.1 [±50%]	0.9 [±50%]
Supervised Exercise Therapy [44,45,47,48]	1.05 [±50%]	0.95 [±50%]	1.05 [±50%]	1
Medications (NSAIDs) [142-144]	1.05 [±50%]	0.95 [±50%]	1	1
Massage [145,146]	1.50 [±50%]	0.70 [±50%]	1	1
Acupuncture [145,147]	1.2 [±50%]	0.70 [±50%]	0.95 [±50%]	1.15 [±50%]
MBSR [148]	1.05 [±50%]	0.95 [±50%]	1	1
CBT [148,149]	1.05 [±50%]	0.95 [±50%]	1	0.95 [±50%]
Yoga [150-152]	1.30 [±50%]	0.75 [±50%]	1.15 [±50%]	0.85 [±50%]

Table 15. Model parameters for adverse events

Death	Age-specific [153]		*Myocardial Infarction*	
Gastro-intestinal bleeding			Age-specific risk	Age-specific [127]
Age-specific risk	Age-specific [130]		28-day mortality (%)	14.8 [154]
28-day mortality (%)	7.0 [130]		Excess risk with NSAIDs	1.7 [131]
Excess risk with NSAIDs	2.2 [131]		Heart failure after MI (%)	0.28 [128]
Stroke			5-year mortality from heart failure (%)	0.518 [155]
Age-specific risk	Age-specific [129]			
28-day mortality (%)	10 [129]			
Excess risk with NSAIDs	1.2 [131]			
Excess risk with neck manipulation	Similar to PCP care which is primarily NSAIDs[132,133]			
Major disability after stroke (%)	0.24 [156]			
5-year mortality from major disability (%)	0.54 [157]			

Table 16. Model parameters for utilities, disutilities, and costs [sensitivity analysis values]

Utilities			**Disutilities**	
No pain	0.88†		GI Bleed	-0.35 [135]
Low-impact pain	0.86†		Stroke	-0.67 [134]
Moderate-impact pain	0.70†		Myocardial Infarction	-0.33 [134]
High-impact pain	0.50†			
Major disability after stroke	0.52 [134]			
Heart failure	0.57 [134]			
Costs				
Spine-related			*Treatment Strategies*	
No pain	$0		Home exercise	$526 [43-45,47,48] [$324 to $738]
Low-impact pain	$2480 [136]		SMT+Home exercise	$1047 [44,47,48] [$521 to $1463]
Moderate-impact pain	$4638 [136]		Supervised exercise	$2047 [44,45,47,48] [$1296 to $2950]
High-impact pain	$6447 [136]		Medications (NSAIDs)	$518 * [$259 to $777]
Adverse event-related			Massage	$661 [146] [$500 to $900]
Major disability after stroke	$50,517[138]		Acupuncture	$1203 [147] [$602 to $1805]
Heart failure	$29,758[140]		MBSR	$350 ‡ [$200 to $600]
GI Bleed	$7411[137]		CBT	$422 [149] [$211 to $633]
Stroke	$40,112[138]		Yoga	$331 [150] [$160 to $480]
Myocardial Infarction	$27,152[139]			

† Estimated using MEPS data for pain-impact states using US values for SF6D[53]
*Costs estimated using CMS data for 90 day supply of NSAIDS and MEPS data for 2 physician visits
‡ Costs from comparable programs at University of Minnesota and University of California-San Francisco

Results

Base Case

Figure 6 displays the cost and QALYs for all treatment strategies on the cost-effectiveness plane. Yoga resulted in the lowest costs and the highest QALYs and was dominant over all other treatment strategies (cost less, more effective). In addition, results for each treatment strategy compared to home exercise, a common self-management approach, are outlined in Table 17. All treatment strategies increased QALYs relative to home exercise. In addition, yoga, MBSR, massage, and CBT all resulted in lower costs and thus dominated home exercise. The other strategies produced higher costs relative to home exercise. Adding SMT (manual treatment) to home exercise resulted in an ICER of $9,169/QALY. Medications had an ICER of $103,625/QALY. ICERs for supervised exercise and acupuncture relative to home exercise were each above $200,000/QALY relative to home exercise.

Figure 6. Base case results

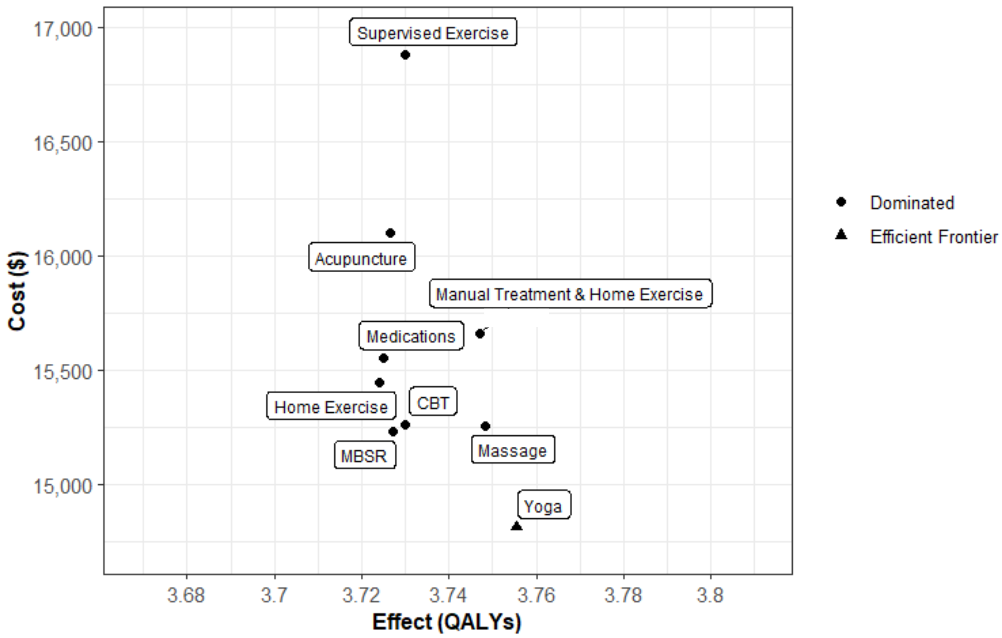


Table 17. Comparison to Home Exercise and Advice – Base Case

Strategy	Cost	Effect	Incr. Cost	Incr. Effect	ICER
Yoga	$14,812	3.755	-$636	0.031	NA
MBSR	$15,231	3.727	-$217	0.003	NA
Massage	$15,257	3.748	-$191	0.024	NA
CBT	$15,264	3.730	-$184	0.006	NA
Home Exercise	$15,448	3.724	REF	REF	REF
Medications	$15,552	3.725	$104	0.001	$103,625
SMT & Home Exercise	$15,659	3.747	$211	0.023	$9,169
Acupuncture	$16,099	3.727	$651	0.003	$252,396
Supervised Exercise	$16,881	3.730	$1,433	0.006	$239,811

Treatments available in health systems and covered by insurance

Figure 7 displays the cost and QALYs for only those treatment strategies available within health systems and covered by insurance. CBT and SMT plus home exercise were the only two strategies on the Cost-efficient frontier. CBT resulted in lower costs and higher QALYs and dominated home exercise, medications, acupuncture, and supervised exercise. SMT plus home exercise resulted in an additional 0.017 QALYs and cost $395 more than CBT, for an ICER of $23,266/QALY gained (Table 18).

Figure 7. Results for treatments available in health systems and covered by insurance

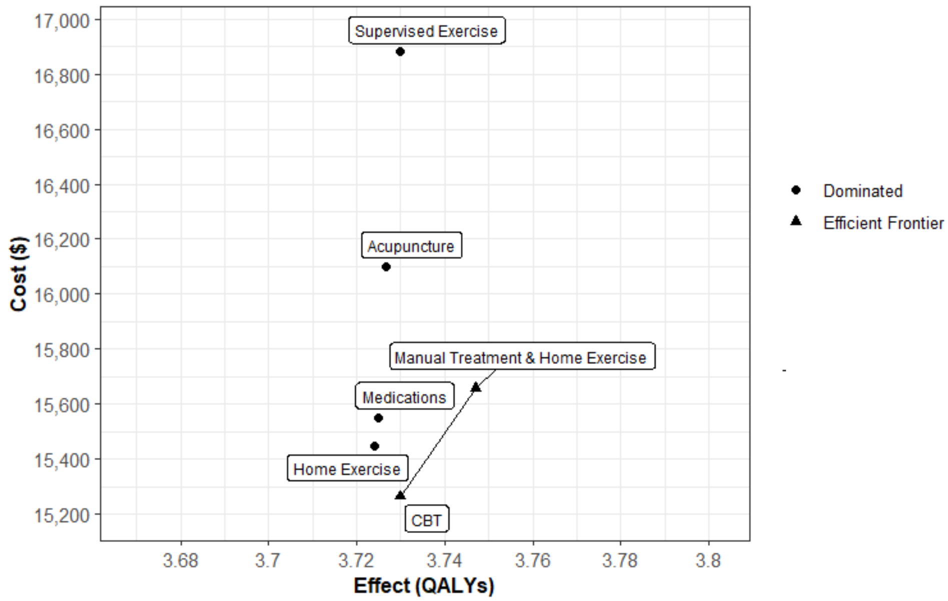


Table 18. Treatments available in health systems and covered by insurance

Strategy	Cost	Effect	Incr. Cost	Incr. Effect	ICER
CBT	$15,264	3.730	REF	REF	REF
SMT & Home Exercise	$15,659	3.747	$395	0.017	$23,226

<u>Analyses of Different Target Populations</u>

Results from the analyses specifying different populations are presented in Tables 19-21. Yoga remained the dominant treatment strategy (lowest cost, highest QALYs) across all analyses. Massage, MBSR and CBT also resulted in lower costs and higher QALYs compared to home exercise across all scenario analyses. For the population with high-impact pain, incremental costs were lower and incremental effects were larger for all strategies compared to home exercise. ICERs relative to home exercise lowered to $5,258/QALY for SMT, $37,250/QALY for medications, $81,777/QALY for acupuncture, and $180,684/QALY for supervised exercise. The scenario analysis with an older population (80 years old) increased the ICER for SMT compared to home exercise to $20,291/QALY. Medications resulted in higher costs and lower QALYs relative to home exercise this older population. Scenario analyses for populations with all LBP or neck pain were performed to assess the impact on SMT since adverse events with this treatment strategy are only present with treatment for neck pain. The ICER for SMT compared to home exercise varied from $8,612/QALY for LBP to $9,730 for neck pain.

Table 19. Comparison to Home Exercise and Advice – High Impact Pain population

Strategy	Cost	Effect	Incr. Cost	Incr. Effect	ICER
Yoga	$15,239	3.721	-$727	0.040	Dominant
Massage	$15,638	3.718	-$328	0.037	Dominant
MBSR	$15,735	3.685	-$231	0.005	Dominant
CBT	$15,769	3.688	-$197	0.007	Dominant
Home Exercise	$15,966	3.681	REF	REF	REF
Medications	$16,055	3.683	$90	0.002	$37,250
SMT & Home Exercise	$16,118	3.710	$152	0.029	$5,258
Acupuncture	$16,567	3.688	$601	0.007	$81,777
Supervised Exercise	$17,379	3.689	$1,413	0.008	$180,684

Table 20. Comparison to Home Exercise and Advice – 80 year old population

Strategy	Cost	Effect	Incr. Cost	Incr. Effect	ICER
Yoga	$13,092	3.309	-$622	0.030	Dominant
MBSR	$13,497	3.281	-$216	0.003	Dominant
Massage	$13,528	3.302	-$185	0.024	Dominant
CBT	$13,531	3.284	-$182	0.006	Dominant
Home Exercise	$13,713	3.278	REF	REF	REF
SMT & Home Exercise	$14,137	3.299	$424	0.021	$20,291
Acupuncture	$14,360	3.281	$647	0.003	$229,140
Supervised Exercise	$15,148	3.284	$1,435	0.006	$248,066
Medications	$16,761	3.245	$3,048	-0.033	NA

Table 21. Impact of pain location for SMT compared to Home Exercise and Advice

Strategy	Cost	Effect	Incr. Cost	Incr. Effect	ICER
Home Exercise	$15,448	3.724	REF	REF	REF
SMT & Home Exercise – Neck Pain	$15,671	3.747	$223	0.023	$9,730
SMT & Home Exercise - LBP	$15,647	3.747	$199	0.023	$8,612

<u>Sensitivity Analyses</u>

Table 22 presents results from the one-way sensitivity analyses on the ICER for each treatment strategy relative to home exercise when varying the effectiveness and treatment costs. Yoga, MBSR, Massage, CBT, and SMT were either dominant or had ICERs less than $50k/QALY across all analyses and were not sensitive to changes in model parameters for treatment effectiveness or cost. Results for supervised exercise also did not change the interpretation of findings with ICERs above $150k/QALY for all sensitivity analyses except when assuming treatment costs were on the low end ($114k/QALY). Medication and acupuncture were the two strategies most sensitive to changes in effectiveness and treatment cost. For medication, increasing the effectiveness estimate by 50% lowered the ICER relative to home exercise to $32,723/QALY and using the lower end treatment cost estimate resulted in lower costs and higher effects (dominant). The ICER relative to home exercise increased to $361,594 when using the high end for treatment costs and medication cost more and was less effective when lowering the effectiveness estimate by 50%. For acupuncture, increasing the effectiveness estimate by 50% and using the low end for treatment costs both resulted in ICERs <$50k/QALY relative to home exercise. The ICER relative to home exercise increased to $485,626 when using the high end for treatment costs and acupuncture cost more and was less effective when lowering the effectiveness estimate by 50%. Table 23 presents the results of two-way sensitivity analyses assuming a worst-case scenario of 50% lower effectiveness and high-end treatment costs for strategies that were not sensitive to changes in the one-way sensitivity analyses. Assuming a worst-case scenario had minimal impact on these strategies. Relative to home exercise, yoga still cost less and was more effective. ICERs for massage, MBSR, and CBT were all below $50k/QALY and the ICER for SMT increased to $65,262/QALY. Table 24 shows results from the analysis where we assumed treatment effects after 1 year would be maintained. Yoga remained the dominant therapy with costs that were over $1000 lower than any other treatment and the largest QALYs. Costs for all treatments relative to home exercise decreased under this assumption, except for medications (which remained the same) and acupuncture (which increased). SMT, CBT, MBSR, and massage all resulted in lower costs and greater QALYs relative to home exercise. The ICER for supervised exercise relative to home exercise was reduced to $71,363/QALY down from over $200k/QALY in the base case which did not assume treatment effects were maintained past one year. The cost-effectiveness of medications relative to home exercise was similar to findings in the base case analysis.

Table 22. ICERs relative to Home Exercise with one-way sensitivity analyses on treatment effectiveness and costs.

		Effectiveness		Treatment Costs	
Strategy	Base Case	+50% HR	-50% HR	Low End	High End
Yoga	Dominant	Dominant	Dominant	Dominant	Dominant
MBSR	Dominant	Dominant	Dominant	Dominant	$10,324
Massage	Dominant	Dominant	Dominant	Dominant	$1,961
CBT	Dominant	Dominant	Dominant	Dominant	$4,454
Medications	$103,625	$32,723	Dominated	Dominant	$361,594
SMT & Home Exercise	$9,169	$1,967	$30,556	Dominant	$27,254
Acupuncture	$252,396	$33,838	Dominated	$19,166	$485,626
Supervised Exercise	$239,811	$158,409	$484,221	$114,122	$391,036

Table 23. ICERs relative to Home Exercise with worst case scenario analysis. Limited to strategies with ICERs <$150k/QALY across all one-way sensitivity analyses and assumed worst case where treatment is 50% less effective and high end treatment costs.

Strategy	Cost	Effect	Incr. Cost	Incr. Effect	ICER
Home Exercise	$15,448	3.724	REF	REF	REF
Massage	$15,645	3.737	$197	0.013	$14,660
MBSR	$15,502	3.726	$54	0.002	$33,206
CBT	$15,515	3.727	$67	0.003	$22,231
Yoga	$15,172	3.741	-$276	0.017	Dominant
SMT & Home Exercise	$16,230	3.736	$782	0.012	$65,262

Table 24. ICERs relative to Home Exercise assuming treatment effects are maintained after one year

Strategy	Cost	Effect	Incr. Cost	Incr. Effect	ICER
Yoga	$13,826	3.820	-1,622.15	0.096	Dominant
SMT & Home Exercise	$14,988	3.792	-$460.05	0.068	Dominant
CBT	$15,086	3.742	-$362.34	0.018	Dominant
MBSR	$15,231	3.727	-$216.86	0.003	Dominant
Massage	$15,257	3.748	-$191.34	0.024	Dominant
Home Exercise	$15,448	3.724	REF	REF	REF
Medications	$15,552	3.725	$104.04	0.001	$103,625
Supervised Exercise	$16,711	3.742	$1,262.99	0.018	$71,363
Acupuncture	$16,805	3.676	$1,356.62	-0.048	Dominated

Validation and Calibration Results

All internal consistency checks that varied model parameters by extreme amounts resulted in expected outcomes. This included changes to the population age, risk of adverse events, transition probabilities between pain-impact states, and effectiveness parameters for treatment strategies. Comparisons between trial data used for calibration and model output for mean disability over time is shown in Appendix Table 2. A small number of trials were excluded from the model due to large differences between model output and trial data. This was likely due to differences between trial populations (e.g. patients from tertiary pain clinics or underserved communities). Appendix figures 22 and 23 show disability outcomes over the five-year time horizon for the assessed treatments within our base case analysis and analysis assuming maintained treatment effects beyond one year.

Discussion

Summary of Findings

We estimated the cost-effectiveness of common interventions for chronic spinal pain by creating a decision-analytic model that included the potential benefits, harms, and costs associated with treatments using a combination of individual and summary level data from clinical trials, cohort studies, and nationally representative surveys. Among the interventions assessed, yoga resulted in the lowest costs and highest QALYs. This finding was consistent across analyses varying the population as well as sensitivity analyses for treatment effectiveness and costs. Availability, access, insurance coverage, and individual preferences for spinal pain treatments are highly variable across the U.S., so we also presented results for each treatment relative to a self-management approach consisting of home exercise and advice. ICERs for massage, MBSR, CBT, and SMT compared to home exercise and advice were consistently below $100k/QALY across all analyses and these treatments often resulted in lower costs and higher QALYs.

Potential adverse events associated with SMT had minimal impact on the cost-effectiveness of this approach relative to home exercise and advice. Observational studies have consistently reported an increased risk of stroke after SMT (spinal manipulation) of the neck, but the latest evidence suggests this relationship is not causal.[132,133,158-163] Neck pain and headache are common early symptoms of vertebral artery dissection, which will lead to a subsequent stroke, and are also two common reasons for visiting SMT providers. Patients experiencing these symptoms due to an impending stroke commonly visit health care providers, including manual therapists. Thus, the association between treatment applied and subsequent stroke would be confounded by indication. Large case-crossover studies have shown that the increased risk of stroke associated with visits to manual therapists is similar to the increased risk associated with visits for medical providers.[132,158] For our analyses, we assumed the risk of stroke with SMT was similar to NSAIDs, one of the more common medications prescribed for spine pain. Given NSAIDs are prescribed for less than half of all spine pain patients,[13,164] our analysis was conservative and likely overestimated the risk of stroke associated with SMT. Serious adverse events such as cauda equina syndrome, disc herniations, fractures, and hematoma or hemorrhagic cysts have been documented following Lumbar SMT.[165] However, these events are extremely rare, their incidence is unclear, and whether the risk of such events are increased due to lumbar SMT is unknown, thus they were not included in our model.[165]

Supervised exercise resulted in ICERs above recommended willingness to pay thresholds for QALYs in the U.S. ($150 to $200k/QALY) in most analyses.[80] The only exception was when considering only individuals with high-impact pain, where the ICER was $188k/QALY. The supervised exercise interventions implemented in the trials were resource intensive and included 16 to 20 hour-long visits with an individual therapist. The cost for this intervention was difficult to overcome, even when assuming higher treatment effectiveness or lower costs. Medications and acupuncture were the treatment strategies most sensitive to varying populations and model parameters for treatment effectiveness and cost. The cost-effectiveness of medications relative to home exercise and advice improved when treating only those with high-impact pain or when assuming increased treatment effectiveness or lower treatment costs. Medications were not cost-effective when treating an 80-year-old population due to the increased risk of adverse events, or when assuming a lower treatment effectiveness or higher treatment costs. Base-case estimates for both medication effectiveness and costs were similar to home exercise and advice, which is likely why findings were most sensitive to changes in these model parameters. ICERs for acupuncture relative to home exercise and advice reduced from $250k/QALY in the base case to below $50k/QALY when assuming higher treatment effectiveness or lower costs. Acupuncture was less effective in the long term relative to home exercise and long-term effects have a larger impact on costs and QALYs. This is likely the explanation for why acupuncture was more sensitive to changes in the effectiveness parameters.

An important finding was the decrease in ICERs relative to home exercise and advice for all assessed treatments when limiting the population to those with high-impact pain. Studies consistently show individuals with high-impact pain have higher costs and worse outcomes, including lower quality of life, higher disability, and more missed work. [125,136,166] As expected, we found higher overall costs and lower QALY outcomes under all treatment within the high-impact pain population. However, the incremental costs and effects for all treatments relative to home exercise and advice improved, which suggests more intensive treatments are warranted and provide good value in this population.

Strengths & Limitations

This study has many important strengths. We were able to use both individual participant and summary level data from published RCTs to calibrate model parameters for treatment effectiveness. This flexibility allowed us to expand the model to include treatments from trials where we did not have access to individual-level data. We also used a variety of study designs to inform model parameters: RCTs for effectiveness, nationally representative survey data for costs and QALYs associated with health states, large cohort studies for risk of harms. We included both benefits and harms in addition to reporting costs and effects over a five-year time frame, which is not common among decision analyses for spine pain management.[115] Finally, the consistency of our main findings across multiple populations and when varying important model parameters and assumptions with the largest potential impact on overall costs and effects is a strength.

This study also has a number of important limitations. First, we excluded a number of trials from the analysis when model results were not consistent with trial findings. These differences were often due to a difference in the population or setting (See appendix table 1; e.g. underserved population, specialty pain clinic). Thus, our results may not readily translate to populations not well represented in the included RCTs. Second, the proportion of participants in different pain-impact states are rarely reported in spine pain RCTs and calibration was needed to include studies with only summary level data on disability, a more commonly reported outcome. Model parameters based on calibration from summary level data are more uncertain than those using individual level data, but we found minimal changes in our overall findings when varying these parameters. Third, we made a number of assumptions that could impact study findings. Long-term effectiveness estimates for NSAID medications were not available from trial data and were assumed to be the same as home exercise and advice. This assumption likely favored medications as their effects are more likely to be short lasting than exercise, one of the few interventions with supporting evidence for the back pain prevention. Fourth, we only modeled healthcare costs associated with spine pain and assumed $0 costs for individuals with no spine pain. We considered this a reasonable assumption as it is extremely rare for individuals with no pain to use spine-related healthcare resources for prevention. Including only spine-related healthcare costs, instead of all healthcare costs, can underestimate the impact of treatments that have an impact on mortality. Given the limited impact of treatments on mortality and our relatively short time horizon (5 years), we were more interested in spine-related healthcare costs and did not model total healthcare costs. Fifth, we presented results for 40-year-old and 80-year-old populations, but did not present results for additional age groups. The cost-effectiveness of medication was the only treatment strategy meaningfully impacted by age. Finally, we did not have access to individual level data from the graded chronic pain scale to categorize trial participants as high, moderate, or low pain-impact health states. We used individual level data from trial participants for a question from the SF-36 regarding frequency of pain interference with normal work including work outside the home and housework to assign pain impact. This question asks about impact on work due to pain in general, not just spine pain. However, all information was collected from participants in clinical trials of treatments for back or neck pain, so it’s likely that responses to this question were primarily driven by impact from back or neck pain. In addition, the graded chronic pain scale is also a general pain impact scale and is not spine specific.

Comparisons to other studies

Our study design is most similar to a recent study by Herman et al. that assessed the cost-effectiveness of nonpharmacologic therapies for chronic LBP using a Markov model.[120] We used the same four health states as their model (high-, moderate-, and low-impact pain and no pain). Herman et al. estimated transition probabilities using individual level data from 10 randomized trials, including some of the trials included in our model.[141,145-147,152] Direct measurement of chronic pain impact level using the Graded Chronic Pain Scale (GCPS) were available in four trials and impact levels from other trials were estimated using logistic models that considered pain intensity, disability, and general health measures from the SF-12 or SF-36.[167] Both societal and payer perspectives were considered. The authors did not model potential adverse events associated with treatments and the common comparison for all treatments was usual care, which can vary considerably between trials. Usual care in the included studies ranged from no study-based care to receiving self-management advice to 3 visits with a medical provider and was assigned minimal costs within the model ($0 to $22). Despite these differences, our overall findings were remarkably similar. Yoga resulted in the lowest costs and greatest effects across analyses, and most of the assessed interventions were cost saving or had ICERs below $50k/QALY from the payer perspective. In general, ICERs for supervised exercise and acupuncture were lower compared to our findings. This is likely due to the differences in comparison group (home exercise and advice vs usual care) and assigned treatment costs, which in Herman et al.'s study were similar to values we used for the low end of costs in our sensitivity analyses. We plan on further developing our model by adding a usual care comparison and including societal costs for a future publication.

Systematic reviews assessing the cost-effectiveness of non-invasive and non-pharmacologic interventions for back or neck pain using trial-based analyses without decision models have also noted similar findings. Psychological interventions, SMT, and yoga appear to be cost-effective options, while findings for structured exercise programs have been mixed and depend largely on the structure and format of the program and the comparison.[18,168,169] Findings for the cost-effectiveness of acupuncture have been more favorable, but studies have been conducted in settings outside the US, typically with a usual care comparison. Our own trial-based analyses from the first paper for SMT were largely similar with ICERs below $100k/QALY when adding SMT to home exercise and advice. Trial-based analyses rarely have time horizons beyond one year. Our primary analyses were conservative in regard to our assessment of potential treatment differences over the 5-year time horizon. We assumed similar transition probabilities between pain-impact health states for all treatment strategies after one year which diminished treatment effects over the five-year time horizon. Our sensitivity analysis that assumed maintained treatment effects beyond a year showed increased value for most treatments, but this is a questionable assumption given the short duration of treatments (6-12 weeks) and recurrent nature of chronic spine pain.

Implications for clinical practice and research

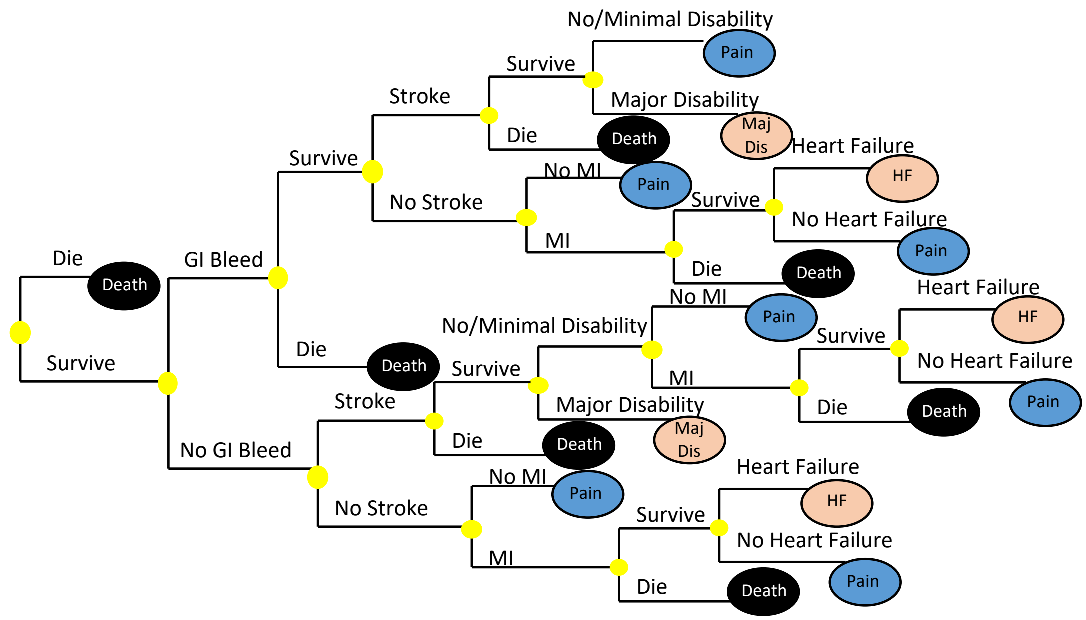
This study adds to the emerging literature using decision analysis models to better understand the risks, benefits, and costs of common non-invasive treatments for chronic spine pain. The management of chronic spine pain is an ideal subject matter for decision analysis models as there are a large number of treatment options with similar effects. Clinical trials, the gold standard for comparing treatments, have limitations in the number of treatments that can be compared and the ability to assess effects over a longer time horizon. Decision analysis models provide a method to compare benefits, risks, and costs for a large number of treatments for multiple populations within a single framework. We found a number of non-invasive treatments are cost-effective for chronic spinal pain. Importantly, our analysis which limited treatments to those widely available in health systems and commonly covered by health insurance plans excluded treatments that provided good value for the management of chronic spine pain (i.e. yoga, MBSR, massage). Health systems and insurance plans should consider innovative approaches for improving access to these approaches. Although our findings are largely consistent with other decision models on this topic, the total number of models developed in this field remains small. Further models with varying assumptions and structures are needed to confirm our findings. In addition, while we found the cost-effectiveness of all assessed treatments improved in high-impact pain populations, primary studies measuring the effect of these treatments in this severely impacted population are needed to confirm findings from this and other models.

Conclusions

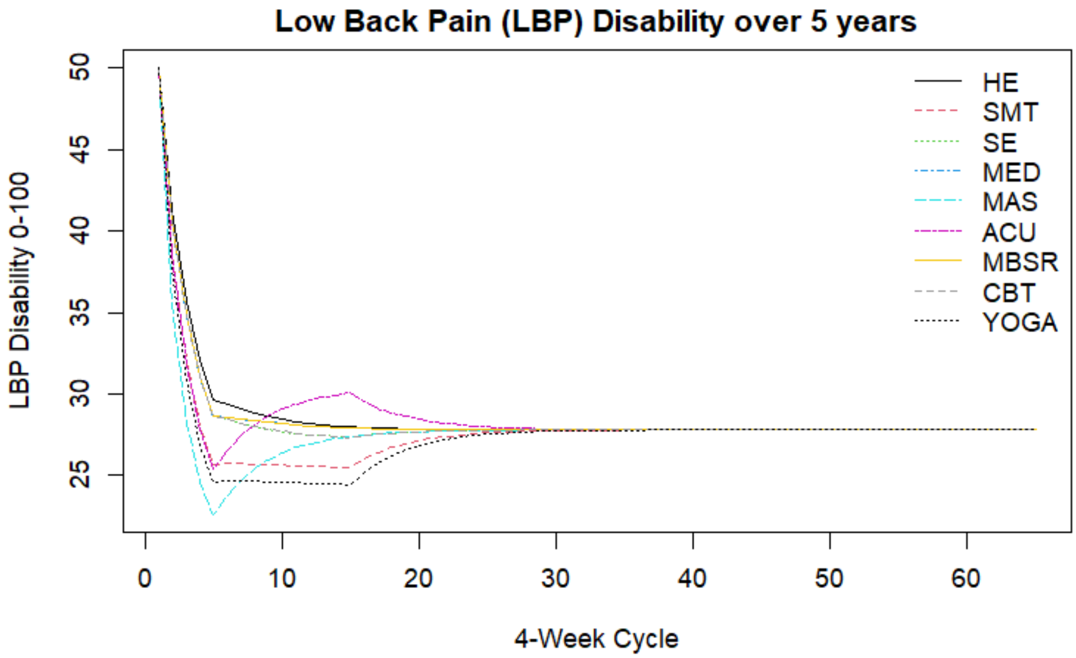
We developed a state-transition model to compare non-invasive treatments for chronic spine pain and found that yoga resulted in the lowest costs and largest health benefits across multiple populations (e.g. high-impact pain, older adults). Massage, mindfulness based stress reduction, cognitive behavioral therapy, and SMT were also shown to be cost-effective options compared to home exercise and advice for chronic spine pain across different populations. Findings for these treatments were not sensitive to changes in key parameters impacting costs or effectiveness. Supervised exercise was not cost-effective unless assuming treatment effects would be maintained beyond one year. The cost-effectiveness of medications decreased in older populations where the risk of adverse events was higher. Acupuncture was only cost-effective when limiting the population to those with high-impact pain. Findings for medications and acupuncture were the most sensitive to changes in model parameters. The value for all treatments was increased for high-impact pain.

Appendix materials

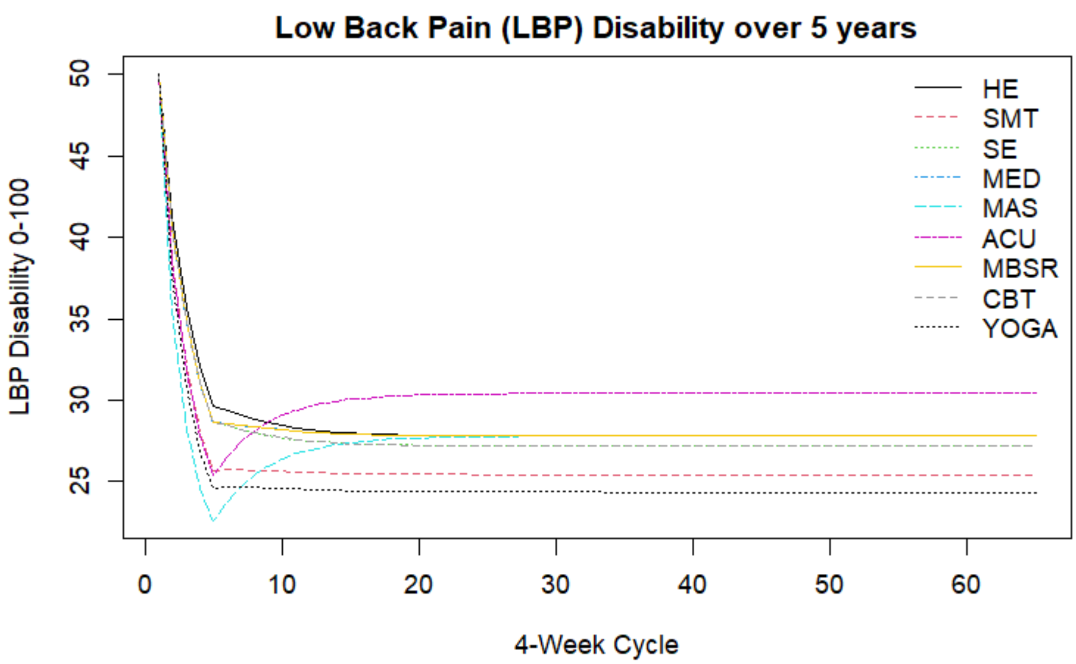
Appendix Figure 21. Markov cycle tree describes the possible event paths each cycle



Appendix Figure 22. Mean disability by treatment assuming treatment effects are not maintained beyond one year



Appendix Figure 23. Mean disability by treatment assuming treatment effects are maintained beyond one year



Appendix Table 2. Comparison of trial results and model output for mean disability over time

	Mean Disability (0 to 100)					Mean Disability (0 to 100)		
NSAIDs	Trial	Model	Difference		**Massage**	Trial	Model	Difference
Katz 11 [143]					*Cherkin 01* [145]			
Baseline	51.7	51.6	0.1		Baseline	51.3	51.2	0.1
Week 12	32.9	31.6	1.3		Week 10	27.4	26.7	0.7
Pallay 04 [144]					Week 52	29.6	27.6	2.0
Baseline	61.3	61.2	0.1		*Cherkin 11* [146]			
Week 12	32.5	34.2	-1.7		Baseline	50.4	50.4	0.0
Birbara 03 [142]					Week 10	26.1	26.5	-0.4
Baseline	61.3	61.2	0.1		Week 52	26.1	27.6	-1.5
Week 12	34.2	34.2	0.0		**CBT**			
Yoga					*Cherkin 16* [148]			
Sherman 11 [152]					Baseline	50.0	50.0	0.0
Baseline	42.6	42.6	0.0		Week 8	35.2	34.9	0.3
Week 12	20.0	25.5	-5.5		Week 52	29.1	27.5	1.6
Week 26	19.6	25.0	-5.4		*BeST Trial* [149]			
Tillbrook 11 [151]					Baseline	36.7	36.6	0.1
Baseline	32.5	32.8	0.3		Week 12	27.1	27.4	-0.3
Week 12	23.8	23.6	0.2		Week 52	25.4	27.2	-1.8
Week 52	24.2	24.4	-0.2		Smeets 06** [170]			
Saper 17** [101]					Baseline	57.1	57.2	-0.1
Baseline	64.3	64.4	-0.1		Week 12	44.6	33.2	11.4
Week 12	47.8	29.6	18.3		Week 52	41.7	27.7	14.0
Week 52	38.7	24.8	13.9		**MBSR**			
Groessl 17 [150]					*Cherkin 16* [148]			
Baseline	39.2	39.2	0.0		Baseline	51.3	51.4	-0.1
Week 12	30.4	24.9	5.6		Week 8	36.5	35.6	0.9
Week 26	25.0	24.7	0.3		Week 52	28.3	28.2	0.1
SMT					Morone 16** [171]			
*Bronfort 11^* [44]					Baseline	65.0	65.0	0.0
Baseline	37.8	31.4	6.4		Week 10	50.4	38.1	12.3
Week 12	21.3	24.1	-2.8		Week 26	50.8	31.1	19.7
Week 52	22.2	25.4	-3.2		**Acupuncture**			
*Maiers 14^* [47]					*Cherkin 01* [145]			
Baseline	22.8	22.4	0.4		Baseline	55.7	55.6	0.1
Week 12	14.4	18.2	-3.8		Week 10	34.3	31.6	2.7

Week 52	15.8	19.1	-3.3		Week 52	34.8	30.4	4.4
Haas 14 [141]					*Cherkin 09* [147]			
Baseline	46.1	46.2	-0.1		Baseline	47.0	47.0	0.0
Week 12	25.8	27.3	-1.5		Week 12	27.8	30.9	-3.1
Week 52	22.4	25.6	-3.2		Week 52	26.1	30.2	-4.1
*Schulz 19^* [48]					**Home Exercise**			
Baseline	45.7	41.4	4.3		*Evans 12^* [45]			
Week 12	30.0	26.3	3.7		Baseline	28.6	22.8	5.8
Week 52	34.3	25.6	8.7		Week 12	19.6	20.0	-0.4
Supervised Exercise					Week 52	19.3	20.7	-1.4
*Bronfort 11^* [44]					*Bronfort 11^* [44]			
Baseline	36.5	32.8	3.7		Baseline	37.8	34.4	3.4
Week 12	17.0	24.6	-7.6		Week 12	18.7	27.7	-9.0
Week 52	16.5	25.8	-9.3		Week 52	17.8	27.8	-10.0
*Evans 12^* [45]					*Maiers 14^* [47]			
Baseline	26.1	20.5	5.6		Baseline	24.2	24.3	0.1
Week 12	16.0	16.5	-0.5		Week 12	16.9	20.5	3.6
Week 52	17.5	19.3	-1.8		Week 52	18.3	20.7	2.4
*Maiers 14^* [47]					*Bronfort 14^* [43]			
Baseline	22.9	21.3	1.6		Baseline	44.3	38.8	5.5
Week 12	14.7	16.7	-2.0		Week 12	27.8	28.8	-1.0
Week 52	16.6	19.3	-2.7		Week 52	25.2	27.9	-2.7
*Schulz 19^* [48]					*Schulz 19^* [48]			
Baseline	42.9	35.2	7.7		Baseline	45.2	35.8	9.4
Week 12	25.3	23.9	1.4		Week 12	30.0	28.0	2.0
Week 52	33.4	25.9	7.5		Week 52	33.0	27.9	5.1

**Trial excluded from model: Smeets 06: Population from a tertiary pain clinic; Saper 17: Underserved population; Morone 16: Older adult population
^Model calibrated using proportion in pain-impact states at relevant time points with individual level data from trial

Overall Dissertation Discussion

We used multiple approaches to assess the cost-effectiveness of spinal manipulation for neck or back pain. For aim 1, we used individual patient data to conduct standardized RCT-based cost-effectiveness analyses of spinal manipulation therapy using data from eight RCTs with comparable treatments, methods, and clinical and cost outcomes. There are a number of potential generalizability concerns when using RCTs for cost-effectiveness analyses. Important limitations inherent to RCT-based CEAs include the small number of available treatments assessed (typically two or three strategies), the limited time horizon (often one year or less), and the narrow patient populations included in RCTs (less inclusive population relative to how intervention is applied in general practice. For aim 2, we evaluated the generalizability of the RCT populations from aim 1 by comparing socio-demographic and clinical characteristics to a nationally representative sample of U.S. adults with chronic spine pain. For aim 3, we created a decision model using data from the trials in aim 1, along with important evidence from the existing literature to assess the cost-effectiveness of spinal manipulation relative to other recommended conservative interventions for spine pain. Key findings from each aim are presented below:

Aim 1 - When compared with or added to home exercise and advice interventions, cost-effectiveness findings were favorable for using SMT for acute neck pain (may be cost-effective), chronic neck pain in older adults (likely cost-effective), and chronic back-related leg pain (very likely cost-effective). However, SMT was not likely cost-effective relative to home exercise approaches for chronic back pain in adults or older adults. When compared with exercise therapy approaches, SMT may be cost-effective for adults and older adults with chronic back pain and was very likely cost-effective for older adults with chronic neck pain. For adults with chronic neck pain, SMT is not likely cost-effective relative to ET, but may be cost-effective when added to ET depending on outcome. Adding SMT to ET is likely cost-effective for adolescents with chronic back pain.

Aim 2 - This project assessed the generalizability of randomized trial populations participating in research assessing spinal manipulation for chronic spinal pain. The clinical trials had an under-representation of individuals from underserved communities with lower percentages of racial and ethnic minorities, less educated, and unemployed relative to the U.S. population with spine pain. While the odds of chiropractic use in the U.S. are lower for individuals from underserved communities, the trial populations also under-represented these populations relative to U.S. adults with chronic spine pain who visit a chiropractor.

Aim 3 - We conducted a health state transition model to compare non-invasive treatments for chronic spine pain and found that yoga resulted in the lowest costs and largest health benefits across multiple populations. Massage, mindfulness-based stress reduction, cognitive behavioral therapy, and SMT were also shown to be cost-effective options for chronic spine pain across different populations. Findings for these treatments were not sensitive to changes in key parameters impacting costs or effectiveness. Supervised exercise was not cost-effective unless assuming treatment effects would be maintained beyond one year. The cost-effectiveness of medications decreased in older populations where the risk of adverse events was higher. Acupuncture was only cost-effective when limiting the population to those with high-impact pain. Findings for medications and acupuncture were the most sensitive to changes in model parameters. The value for all treatments was increased for high-impact pain.

This work has a number of important strengths and limitations. Each project used individual patient data from multiple RCTs with strong methods ensuring random treatment assignment, high participant adherence to treatment protocols, and low amounts of missing data. In addition, the trials used similar methods and collected similar demographic, health characteristics, cost, and clinical outcomes data, which is not common for spine pain trials. We assessed the cost-effectiveness of SMT using recommended approaches including the "piggyback" or "Count Dracula" approach where economic outcomes are collected prospectively alongside a RCT as secondary or exploratory outcomes and the "Frankenstein" approach where a decision-analysis model is constructed using pieces of information from different sources, including RCTs, large cohort studies, nationally representative surveys, etc.[172] The general consistency of our findings across these two approaches is an important finding.

While our work contributes to the understanding of the cost-effectiveness of spinal manipulation in U.S. healthcare settings, there are limitations to consider and many important questions remain. Individual patient data from clinical trials used for this project were conducted by one research group with most participants recruited from a single geographic location. In addition, as highlighted by findings from Aim 2, trial participants were not representative of the U.S. population with spine pain in terms of many important demographic and health characteristics. Importantly, the distribution of demographic and health characteristics of trial participants were similar to other international spinal pain trials, suggesting the entire spine pain trial community needs to better engage underrepresented populations. This is equally important for future cost-effectiveness studies as there is a need to better understand the impact of treatment approaches for spinal pain in populations most severely impacted including those experiencing health disparities, those with radiating arm or leg pain, and those with high-impact chronic pain (high impact on daily work activities).

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