FINAL PROTOCOL AND STATISTICAL ANALYSIS PLAN

Spine Pain INtervention to Enhance Care quality And Reduce Expenditure (SPINE CARE) – Randomized Clinical Trial

NCT03083886

10-01-2021

FINAL PROTOCOL

1. Synopsis

Low back and neck pain are among the leading causes of medical visits, lost productivity and disability. There is an urgent need to identify effective and efficient ways of helping subjects with acute spine pain while guiding practitioners towards high-value care. This trial will be a block and cluster-randomized open-label multi-centered pragmatic randomized clinical trial comparing healthcare spending and clinical outcomes for subjects with spine pain of less than three months' duration, in whom there are no red flag signs or symptoms. Subjects will be randomized to one of three treatment strategies: (1) usual primary care provider-led care; (2) usual PCP-led care with spine pain treatment directed by the Identify, Coordinate, and Enhance decision making (ICE) care model, and (3) usual PCP-led care with spine pain treatment directed by the Individualized Postural Therapy (IPT) care model. Our outcomes of interest will be spine-related healthcare utilization at one year as well as pain and functionality of the study participants.

2. Background

Direct healthcare spending on neck and back pain (spine pain) exceeds $86 billion annually in the United States. While up to 80% of adults will experience clinically significant spine pain during their lifetimes, only a minority will progress to chronic pain with resultant high health care utilization (1–9). For the vast majority of subjects, spine pain complaints are self-limited (10–12). As a result, there is little evidence that the large amounts currently spent on spine pain has significantly improved population outcomes.

Many clinical guidelines exist for the treatment of spine pain, but much of the evidence supporting specific treatment modalities addresses subjects with chronic back pain rather than individuals presenting with more acute or subacute complaints (13). Despite many clinical guidelines for the management of low back pain, research in this area has shown mixed results and has led to a non-uniform clinical approach to treating spine pain with predictably variable outcomes of pain progression (14–16). Many patients with low back pain begin to incur substantial resource use and associated expenses soon after their first episode of pain (14). For example, there is mounting clinical evidence that imaging offers little help for the initial care of a subject with nonspecific spine pain (17,18), but despite the lack of utility therein, nearly 15% of clinicians admit it would be difficult to not order advanced imaging when subjects present for care (15).

Currently there is also widespread use of non-traditional modalities of care, such as comprehensive and alternative medicine (CAM). A recent study suggested that 30% of subjects are using CAM, and 42% of those subjects did not disclose this to their primary care physician (19). A particularly promising strategy appears to be exercise or postural therapy, which is defined as "a series of specific movements with the aim of training or developing the body by a routine practice to promote good physical health (20–23)." Despite this, there are substantial inconsistencies in the literature and many of the existing studies have been of low-quality (20). Given the discordance between number of subjects using these techniques and the amount of reliable data by which to judge their effectiveness, it is necessary to perform a rigorous evaluation.

One strategy for enhancing the efficiency of spine pain interventions is to target them at individuals with a high probability of progressing from acute to chronic pain. For example, the STarT Back tool uses a biopsychosocial framework to identify features of a subject that helps to predict the likelihood of developing chronic pain, which can then direct treatments to improve pain and functioning (24). Applying this risk stratification method to subjects with low back pain (24,25) and guiding treatment based upon it has been shown to improve clinical outcomes and reduce health spending (26). However, the majority of subjects included in the studies evaluating the STarT Back tool had been experiencing back pain for more than three months and thus, further research is needed to risk stratify subjects earlier in the course of their illness to prevent the transition of acute pain into chronic pain. These strategies must also be well-received by providers, as acceptance of these new treatment pathways has been limited (27).

The SPINE CARE trial seeks to fill the gaps in our knowledge about how to manage subjects presenting with acute and subacute spine pain by rigorously evaluating two methods of care: Individualized Postural Therapy (IPT) and the Identify, Coordinate, and Enhance decision making (ICE) Care Model developed by the Clinical Excellence Research Center (CERC) at Stanford University. These two models of care represent novel approaches to the comprehensive treatment of subjects with spine pain with the potential to significantly reduce spine related cost of care and improve clinical outcomes.

3. Objectives and Overall Design

This block and cluster-randomized, open-label, multi-centered three-arm pragmatic randomized clinical trial seeks to compare healthcare spending, pain, physical functioning, and

quality of life for subjects with acute and subacute spine pain receiving care in one of three ways: (1) usual primary care provider (PCP)-led care; (2) usual PCP-led care with spine pain treatment directed by the ICE care model, and (3) usual PCP-led care with spine pain treatment directed by the IPT care model. ICE and IPT will both be integrated with typical clinical practice to test strategies that, if effective, could easily be incorporated into existing models of care. We hypothesize that the ICE and IPT models of care will decrease spine related healthcare spending while improving physical functional and quality of life.

4. Study Setting

This trial will be conducted in primary care clinics in geographically distinct areas in the U.S. with the following characteristics:

1. Provide primary care to adult subjects with acute back and neck pain.
2. Offer same day or next day appointments.
3. Do not have an existing specialized program for back or neck pain subjects.
4. Are located within 30 minutes driving distance of an Individualized Postural Therapy clinic.
5. Agree to equipoise for all study arms and study protocol, and defer spine related pain treatment direction to ICE staff for subjects randomized to the ICE treatment arm.

The sites will be selected so as to not have overlapping clinical staffs in order to minimize the risk of contamination (given that sites are cluster randomized) and to thereby minimize the possibility that subjects at control sites will be exposed to potentially beneficial aspects of either of the interventions.

5. Subjects

5.1. Inclusion Criteria

- Patients with back or neck pain of ≤ 3 months' duration. All patients must have spine pain with or without radiation to the extremities or the head
- Age ≥ 18 years
- Willing and able to provide informed consent

5.2. Exclusion Criteria

- Patients with symptoms attributed to the spine but without actual pain in the spine (e.g. those with cervicogenic headache without neck pain)
- Currently pregnant
- Currently receiving disability benefits, worker's compensation, or involved in litigation for a workplace injury
- Currently enrolled in another intervention trial for the management of acute back or neck pain
- Cancer that is metastatic or being actively treated. (i.e., chemotherapy, radiation, surgery)
- History of receiving active therapy for back or neck pain in the past 3 months (7+ consecutive days of narcotic use, 6+ sessions of PT, chiropractic care, acupuncture, postural therapy, or other spine therapy delivered by a trained provider)
- History of spine surgery or spine injections/ablation in the past 6 months
- Severe, active psychosis or major depression inhibiting ability to physically participate in intervention
- Red Flag Symptoms (fever, night sweats, unintentional weight loss, bowel or bladder dysfunction, neurologic weakness, current intravenous drug use)

6. Interventions

Clinics will be randomized to one of the following three arms as described below.

6.1 ARM 1: Usual care

Subjects seeking care at a clinic assigned to this arm will receive usual care as directed by their primary care provider. Treatment modalities may include medications, specialty referrals, imaging, procedures such as injections, physical and psychological therapy, as appropriate.

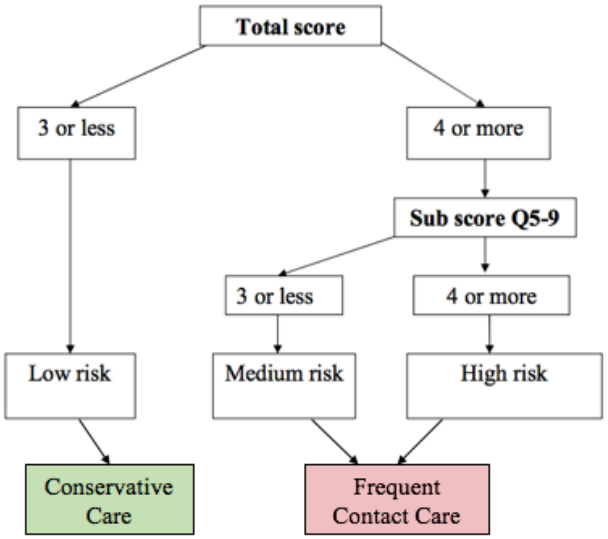
6.2 ARM 2: PCP-led care + ICE

Subjects seeking care at a clinic assigned to this arm will receive the ICE care model through referral by their primary care provider. The ICE care model was developed by the Clinical Excellence Research Center at Stanford University based on a review of the peer-reviewed literature for adult subjects with incident neck or back pain who are not using high-dose opioid medications or receiving spine-related long-term disability payments. The care pathway is designed to take place over the course of six weeks and is intended to avoid low-value healthcare expenditures for subjects presenting with spine pain by:

1. Stratifying subjects with back or neck pain into “low” and “high” risk groups, based on the STarT Back risk assessment tool (Appendix A) (25), and directing care accordingly (Figure 1). The STarT Back tool is a validated instrument that was created to assist with the prediction of the transition of acute to chronic pain. This tool measures a subject’s physical functionality as well as their experience with pain by determining how much

their pain causes psychological distress that may magnify the disability caused by the pain itself. Baseline STarT Back tool responses have been shown to be predictive of pain intensity at six months (28).

Figure 1. Care Stratification Based on STarT Back Scoring Tool (©Keele University 01/08/07 Funded by Arthritis Research UK)



2. Directing low-risk subjects with uncomplicated back or neck pain and few psychosocial risk factors to a limited physical therapy course without additional diagnostic evaluation or specialty referral (Table 1). If subjects do not improve, they will be referred back to their primary care providers for further evaluation and treatment.
3. Referring high- and medium-risk subjects with significant biopsychosocial risk factors (i.e., a high degree of pain catastrophizing) predictive of chronicity to a novel spine team which focuses treatment on physical rehabilitation, normalization of experience, and self-management skills. The team will consist of a physical therapist serving as the

rehabilitation lead, a “Spine Coach” focusing on enabling subject self-motivation and an “ICE MD” who fulfills an advanced medical consultation role for those who do not improve after initial course of therapy. The Spine Coach is a psychology counselor trained in motivational interviewing and supportive care delivered by telephone.

The specific components of the ICE model are summarized below:

Table 1. Levels of care: Proposed frequency of contact

Subject Risk	**Physical Therapy**	**Spine Coach**	**ICE MD**
Low risk	1 session*	1 session	None. Patients who do not improve in six weeks will return to usual care.
High and medium risk	Up to 3 sessions	Up to 3 sessions†	Consult to provide an individual treatment plan for all subjects.

*If subject has improved prior to visit they will be able to cancel PT session in the conservative care pathway.
†Frequency will be determined by subject and spine coach

Responsibilities of the ICE care providers will be as follows:

1. **Physical Therapy** (PT) – The ICE PT will perform their typical practice of taking a detailed history pertinent about the subject’s spine pain, perform a thorough physical exam, and then tailor the frequency and goals of therapy based on the subject’s STarT Back risk level. Each practitioner will be trained to communicate with subjects using enabling language that reinforces self-efficacy skills and provides tools for self-management. These encounters will take place in a local physical therapy practice commonly used by participating referring clinics that are willing to undergo training about the ICE pathway.
2. **Spine Coach** – The Spine Coach will use motivational interviewing to teach coping skills, improve subject self-efficacy, and provide ongoing reinforcement. These encounters will

occur by telephone with frequency directed by the STarT Back tool. Subjects who are at low risk for chronicity will receive one call whereas individuals who are medium or high risk will receive up to three calls over the first six weeks of the intervention. The coach will provide recommendations on self-management, guided by principles in the Back Book (29) and normalize the subject's experience. The Back Book was developed to explain the most common causes of musculoskeletal spine pain, and ways to stay active while recovering. The first outreach will take place within 3 business days of the initial visit to the PCP for spine pain to the primary care provider and be provided at regular intervals based on the needs of the subject, as agreed upon by the spine coach and subject. The Spine Coach and the Physical Therapist will coordinate care using a Communication Checklist (Appendix K) after each visit.

3. **ICE MD** – All subjects who are stratified to high or medium risk by the STarT Back Tool as well as low-risk subjects who have no improvement in their pain despite treatment with the ICE pathway for 6 weeks will receive an ICE MD consultation. The ICE MD will be an MD or DO with pain medicine or physical medicine and rehabilitation specialty experience. They will be experienced in conservative musculoskeletal care and have an active medical license in the state in which they are providing consultations. All assessments by the ICE MD will occur remotely via chart review of the subject's electronic health record available through their primary care provider's office in conjunction with any study communication between the physical therapy team and spine coach. Based on review of this information, individualized treatment

recommendations will be provided to the primary care provider in a written summary that can then be carried out at the discretion of the primary care provider (Appendix B).

6.3. ARM 3: PCP-led care + IPT

The Individualized Postural Therapy (IPT) is an alternative method of care for subjects with neck and back pain. This intervention was chosen to be representative of an alternative care model that is commonly used by individuals with back pain, either in conjunction with, or as an alternative to, usual care.

IPT involves the evaluation of a subject's posture to identify postural and alignment deviations and, based on this, a personalized corrective exercise program is prescribed. This method does involve the use of prescription medications, surgery, or manipulation. The initial consultation typically takes between 60-90 minutes, at which time a regimen of exercises is provided. The exercise menu consists of exercises, specific to the individual, which take between 15-75 minutes daily and can be performed at home once the subject has been evaluated by an IPT clinician. The amount of exercise required depends on the individual's postural and mechanical dysfunctions, and time allowance. A treatment course typically lasts eight sessions over eight weeks. In order to allow for the consistent delivery of this arm of the study at multiple study-sites across the country, IPT will be delivered by The Egoscue Method (30). Egoscue was founded in 1971 and has 25 clinics worldwide.

7. Study Procedures

7.1 Randomization

Randomization will occur at the clinic level (i.e. subjects will be cluster randomized) in a 1:1:1 ratio to usual care, usual primary care + ICE, and usual primary care + IPT. To ensure adequate balance between the treatment arms with respect to sample size practices will be categorized into blocks of 3 based on the average number of patients with spine pain that they see in a typical week, their location, and/or their provision of other services such as urgent/walk-in care. Because of differences between the delivery networks participating in the trial, the stratification factors may differ by location. Randomization will occur within these blocks.

7.2 Subject Identification

The study will include individuals presenting for care with a chief complaint of back pain or neck pain. Potentially eligible subjects will be identified by reviewing clinic schedules for upcoming visits and/or through screening when they present to the clinic for "same-day" or "walk-in" care.

7.3 Eligibility Screening

Patients presenting for care with spine pain will be informed of the study when they arrive for care and will be given a screening form to assess them for eligibility. Subjects who meet the initial eligibility criteria will be given either a written informed consent form (Vanderbilt and UBC, Appendix D) or a verbal informed consent form (HonorHealth, Appendix

D) detailing the potential benefits and risks of participating in the study, and what would be required of them. Consenting subjects will then be asked to complete the baseline surveys while waiting to be seen by their primary care provider. Their primary care provider will confirm that their symptom criteria are completed correctly and evaluate them for additional exclusion criteria that require clinical expertise (Appendix E). Subjects who meet all the inclusion and exclusion criteria will be enrolled in the study.

7.4 Baseline Surveys

After providing consent, subjects will be asked to complete the baseline demographic data (Appendix F) and other baseline surveys (Table-3) using the study's electronic data capture system (see Section 9.3).

7.5 Subject cost-sharing

Subjects randomized to the usual care arm will pay standard copayments as determined by their insurance carrier for all services recommended by their PCPs. Subjects randomized to the ICE or IPT will face no out-of-pocket costs for study recommended visits but will, as in the usual care arm, pay standard copayments as determined by their insurance carrier for other services recommended by their PCPs.

8. Informed Consent

Vanderbilt and UBC sites will be required to obtain subject authorization to participate in the study using written informed consent at the time of their enrollment clinic visit.

HonorHealth sites will be required to obtain verbal consent for the subject to participate in the study. Information about the trial and the requirements of trial participation will be summarized in an informed consent document, whether verbal or written consent is obtained (Appendix D).

9. Outcomes

9.1 Primary Outcomes

The two primary outcomes for the trial will be: (a) spine-related cost of care at one year and (b) change in pain at three months as assessed by the Oswestry Disability Index (ODI, Appendix G). Secondary outcomes will include pain at 12 months, quality of life at 12 months assessed using the EQ-5D, and self-efficacy at 12 months assessed using a scale developed by Lorig et al. (31).

Table 2: Outcomes

Primary	Spine related cost of care at one year Change in pain (measured by ODI) at three months
Secondary	Change in pain (measured by ODI) at one year Quality of life (measured by EQ-5D) at one year Self-efficacy (measured by scale developed by Lorig et. al) at one year

9.1.1 Spine-Related Cost of Care

Spine-related cost of care will be estimated by applying unit costs incurred by subjects or third-party payers to estimates of resource utilization obtained from subject-reported utilization data (Appendix H). Subject-reported utilization will be collected using monthly checklists for the first three months, then bimonthly for the following nine months, that are

based upon the approach recently employed by Fritz et al. (15) and originally developed by Goosens et al. (33). Subjects will be asked about all healthcare services used, including primary care visits, emergency room encounters, hospital admissions, imaging studies (including MR and CT), prescriptions, and physical therapy services that pertain to spine-related healthcare (14,34).

Data from the utilization checklists will be categorized using Current Procedural Terminology (CPT) and International Classification of Disease (ICD) codes. Medications will be characterized using the Unified Medical Language System® Master Drug Database, Medi-Span®.

Unit cost of these different services will be estimated using publicly available data sources. In specific, for outpatient visits to PCPs, specialists, physical therapists and other providers and for tests and procedures, we will use the Centers for Medicare & Medicaid Services Physician Fee Schedule Look-Up Tool.[1] For hospitalizations, we will use the hospital adjusted expenses per inpatient day value calculated by the Kaiser Family Foundation.[2] For emergency department visits, we will use estimates from the Medical Expenditure Panel Survey.[3] To calculate the average retail price of medications, we will use average retail prices from GoodRx.com.[4],

9.1.2 Pain

The ODI is the most commonly used scale for low back pain (35). It is a self-administered questionnaire that has ten topics: intensity of pain, lifting, sexual function, social life, sleep, and ability to walk, sit, stand, care for oneself, and travel. It has been recommended as one of the standardized metrics for research of low back pain based on its ability to quantify functional

status in this population (36). The ODI typically takes three to five minutes to complete, and one minute to score (37). Previous studies have evaluated the ODI in pain-free subjects and found that mean score to be 10.19 (35, 38, 39) and those with disability from low back pain is 22.07 (40). Previous studies have indicated that a change in ODI by 6 points is clinically meaningful (41).

9.2 Other outcomes

9.2.1 Quality of Life

Quality of life will be assessed by the EQ-5D (Appendix I), which has been shown to be beneficial in describing and valuing health related quality of life (42, 43). It was developed for self-completion, and has been validated against other measures of quality of life, including SF-12 (44). The EQ-5D has been shown to correlate well with low back pain specific measurements, and also be responsive to change (45,46). The instrument consists of a descriptive section and a visual analogue scale. The descriptive section measures 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with each dimension having 5 levels ranging from “no problem” to “extreme problem”. The visual analogue scale is a self-rated horizontal health scale with end points labelled as “the best health you can imagine” and “the worst health you can imagine”. The raw scores are converted into index scores based on US norms[5]. Previous studies identify a change in EQ-5D index of 0.08 as a minimal important clinical distance (47), and in a study evaluating the sensitivity to change of EQ-5D index with back pain it was seen that after two weeks there was a decrease of 0.21 after treatment; albeit this was in an interventional study that included steroid injections (46). The

EQ-5D is also helpful in converting to quality adjusted life years (QALY) to perform a cost utility analysis, and is the most common measure for conversion (37).

9.2.2 Self-Efficacy

We will evaluate self-efficacy at baseline, six months, and one year. As the focus of this trial is to support those with acute spine pain to prevent the development of chronic pain, measuring self-efficacy both as a predictor and outcome of the treatment arms will be necessary as a metric of self-management for future episodes. We will use Lorig et al.'s self-efficacy scale for individuals with musculoskeletal complaints, which has three subscales that focus on pain, functioning, and other symptoms (31). Because spine-specific pain is already captured with ODI, we will use the "functioning" and "other symptoms" subscales in this trial to measure self-efficacy (Appendix J). The "function" subscale produces an average of 73.27 (s.d. 20.22), and the "other symptoms" subscale produces an average of 55.62 (s.d. 21.64).

9.2.3 Productivity

We will also evaluate the impact of spine pain on work-related activities by evaluating absenteeism and presenteeism. Absenteeism will be assessed by subject self-report. Time lost from work, or other usual activities, associated with spine pain and all other health problems will be collected and measured. The total number of unplanned work absences will be multiplied by an average employee's daily wage to obtain the cost per participant of work absenteeism. Presenteeism will be assessed using the methods of van den Heuvel, et al (49). Three assertions will be ranked on a scale of 1-5: 1) I achieve all objectives of the job, 2) Job-

related tasks come easily to me, and 3) I perform well in my job. The scores will be dichotomized using the median value from all respondents. A study participant will be described as suffering from presenteeism if they are above the median value.

9.2.4 Other outcomes

We will measure implementation-related outcomes to assess intervention fidelity. These will include the number of protocol-specified appointments (i.e., Spine Coach, physical therapist, or the Egoscue practitioner) scheduled and attended, the timing of visits and the length of the treatment course, which we originally expected to last 6 to 8 weeks.

9.3 Data Collection

Study data will be collected and managed using REDCap electronic data capture tools (50) hosted at Brigham and Women's Hospital. Data will be collected based on the schedule in Table 3. Study subjects will be contacted by email five business days prior to a survey being due for completion to be notified that the survey is available. If the survey is not completed they will be notified again three and five business days after the due date. Should the study subject still not complete the survey, they will have three phone attempts to be reached and guided through completion.

Table 3: Subject Reported Outcome Administration Schedule

	Months After Enrollment													
Metric	**0**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
STarT Back Tool	x													
Healthcare Utilization Checklist		x		x	x		x		x		x		x	x
Oswestry Disability Index	x		x		x			x						x

EQ-5D	x		x					x					x
Self-Efficacy Questionnaire	x							x					x

10. Statistical considerations

10.1 Analysis plan

All analyses will be performed using intention to treat principles based on study arm with which a subject is assigned at study enrollment and regardless of whether or not all protocol steps have been completed. We will report means and frequencies of pre-randomization variables separately by study arm. Comparison of these values will be made with generalized estimating equations to adjust for the block and cluster randomized design.

Because cost data in healthcare is not normally distributed (32) due to significant zero data representing subjects for whom there is little to no cost, we will have to model the data accordingly. We will evaluate the two primary outcomes, total cost of care, using generalized estimating equations with gamma distributed errors and an identity link function which can account for a positively skewed distribution. Changes in ODI from baseline to three months will be compared for the treatment arms using generalized estimating with normally distributed errors and an identity link function. All models will adjust for age and sex, account for the cluster and block randomized study design and include fixed effects for the 3 different delivery networks that were used for recruitment. In secondary analyses, we will repeat our models adjusting for unmatched confounders that remained despite randomization. Our primary analyses will compare each of the two treatment arms separately with usual care (i.e., ICE compared with usual care and IPT with usual care). Because we are evaluating two primary

outcomes, we will use a Bonferroni-corrected two-tailed type 1 error of 0.025. Analysis of secondary outcomes will also be performed using generalized estimating equations with error distributions and link functions appropriate to the outcomes being evaluated.

Missing data will be accounted for using multiple imputation (51), which has been determined an adequate strategy to minimize both false positive and false negatives in clinical trials. We will perform 20 imputations using Proc MI in SAS with a fully conditional specification. The following variables will be used to perform the imputation: age, study arm, study site, clinic, sex, race/ethnicity, BMI, exercise frequency at baseline, education level, employment status, smoking status, other medical conditions at baseline, number of medications used for spine pain at baseline, length of pain at baseline, number of previous pain episodes, STarT back score, baseline ODI, baseline self-efficacy, baseline EQ-5D, and scores for patient-reported outcomes at every follow-up timepoints (ODI, cost, Lorig self-efficacy scale, and EQ-5D).

As resource utilization and ODI were collected at multiple time points, we will also evaluate non-missing cost and ODI data from each time point using a repeated measures design. In specific, we will use generalized estimating equations, with link functions and error distributions appropriate to the study outcomes, to assess changes in outcomes over the 12 months of follow-up, while accounting for correlations in the repeated measurements. For spine-related health spending, these analyses will be conducted using the time intervals at which raw data were collected as well as after converting estimates to evenly-spaced months. Because cost data in healthcare is not normally distributed with zero values for participants with no resource utilization during follow-up, we will winsorize estimated costs at the 95th

percentile in secondary analyses. We will report relative spending differences with confidence intervals and a two-tailed p value. As a sensitivity analysis, we will conduct a complete-case analysis on all non-missing values.

Exploratory analyses will be performed evaluating the effect of the interventions on cost in various strata of clinical interest, including age, sex, STarT Back risk group, location of pain, and whether or not this was the subject's first pain episode. We will also evaluate the percentage of subjects in each arm with a decrease in ODI of six points at three, six, and twelve months of follow-up.

10.2 Sample size

The ICE model was anticipated to reduce total cost of care by 25% compared to usual care (52–54). Because of the lack of peer-reviewed literature evaluating the economic impact of IPT, an effect similar to ICE was assumed for the purpose of performing power calculations. We will need to enroll a total of 3,096 patients (1,032 per arm) to conservatively detect a change in spending of 20% between either treatment arm and usual care with 80% power and an alpha of 0.05, with 33 clusters, and 10% loss to follow-up over the 12-month study period. Our results are robust to a standard deviation of 1.25 times the mean and an ICC value of 0.01. Given the substantially larger sample size required for our economic analyses, we powered our trial on the basis of this outcome, which would also give us more than 98% power to detect a 6-point change in ODI between each intervention arm and the usual care arm.

11. Risk Protection

11.1 Risks Associated with the Inventions Under Investigation

Since the interventions under investigation are accepted forms of treatment for neck and lower back and leg symptoms, it is anticipated that the potential risks to the subjects are the same as for any standard treatment in these areas. If adverse effects occur, we anticipate that appropriate medical care will be provided by the subject's primary care physicians, who will continue to be involved in the care of subjects in all three of the study arms. Systemic red flag symptoms, including leg weakness and urinary incontinence are not expected to occur because enrolled subjects will be screened by their primary care doctors and are required to be low risk at study entrance. However, in the event a red flag symptom occurs, subjects in all 3 arms will be instructed to urgently report this to their primary care physician, who will arrange for triage per standard of care. Adverse events will not be actively solicited but they will be tracked should an event come to the awareness of the investigators.

11.2 Subject Confidentiality

Identifiable research material shall consist of medical records, questionnaires, and data that will be obtained specifically for the study. Identifiable data will be retained and secured in a locked cabinet at each site. In specific, electronic study data will be stored in a 21 CRF part 11 compliant system and all paper documentation with personal health information would be stored in a secured location at each site. Each study site will be individually responsible for complying with all local and state laws, regulations and Human Subjects Committee policies

regarding collection and distribution of subject information. The questionnaire information is not unusually sensitive and will be subject to strict confidentiality safeguards.

Subjects will be informed of the confidentiality of the data and assured that it will be used only in aggregate for statistical purposes, with no identification of individuals. No data beyond what is included in the informed consent will be sought without authorization from hospitals and doctors and without signed medical release from the subjects. All study personnel will be instructed not to discuss any cases with persons other than other study personnel. All hard copies of study records will be kept in locked files to which only study personnel have access.

11.3 Reporting requirements

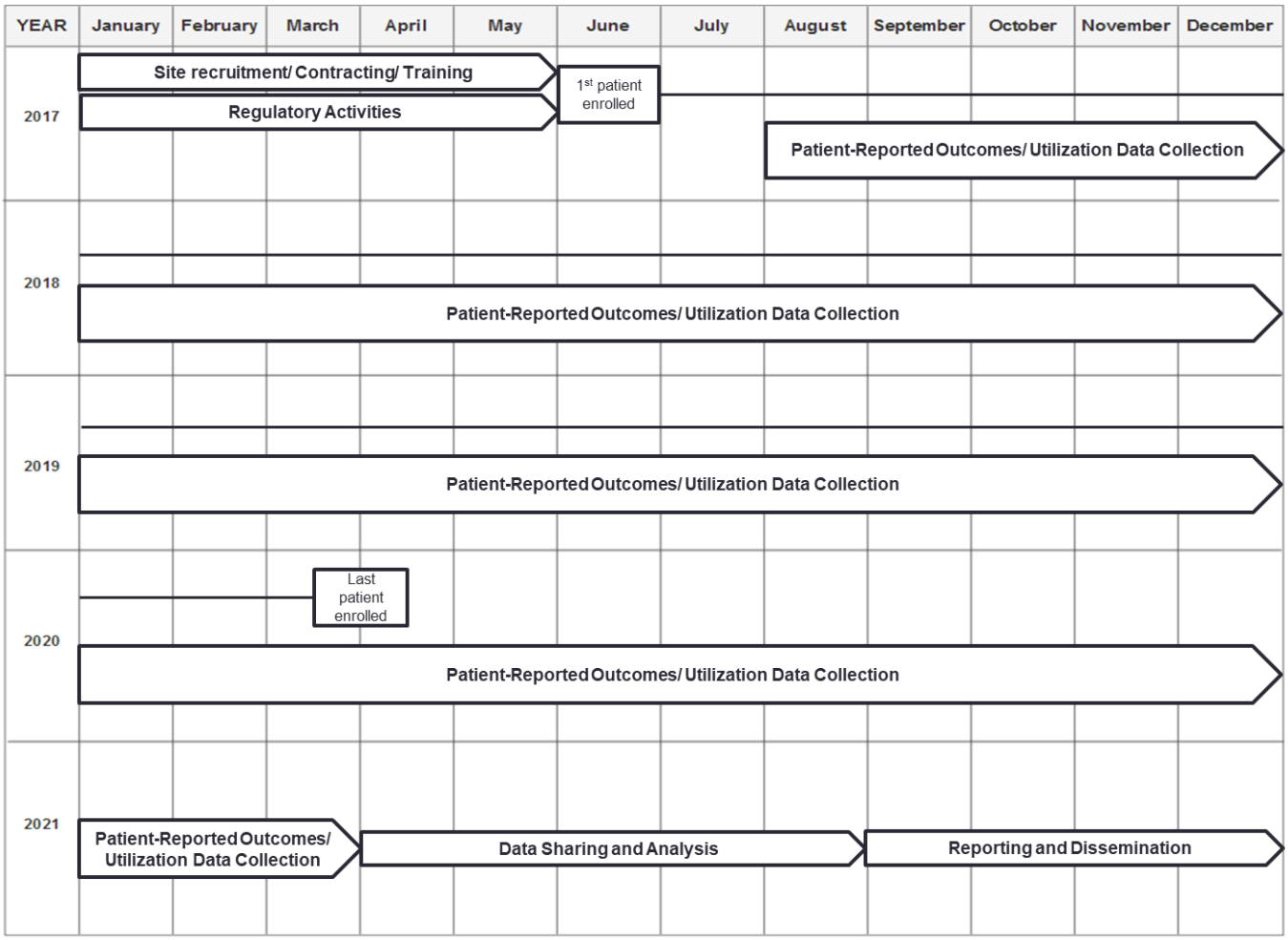
The Site Principal Investigator or Designee will report to the IRB any of the following *adverse events* that occur: 1) during the conduct of the study, 2) after study completion (if study staff become aware), or 3) after participant withdrawal or completion (if study staff become aware).

1. *Unanticipated adverse effects* that are serious and caused by, or associated with, the study treatments (ICE care or IPT care).

2. Breach of confidentiality or violation of HIPAA (e.g., lost or stolen laptop).

Reports will be submitted within 5 working days or 7 calendar days of the date the investigator first becomes aware of the problem. In cases involving serious adverse events, reports will be submitted to IRB within 48 hours of the investigator becoming aware of the event.

12. Study Timeline



STATISTICAL ANALYSIS PLAN

Outcomes

1 Primary Outcomes

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Table 1: Outcomes

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1.1 Spine-Related Cost of Care

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Unit cost of these different services will be estimated using publicly available data sources. In specific, for outpatient visits to PCPs, specialists, physical therapists and other providers and for tests and procedures, we will use the Centers for Medicare & Medicaid Services Physician Fee Schedule Look-Up Tool.[1] For hospitalizations, we will use the hospital adjusted expenses per inpatient day value calculated by the Kaiser Family Foundation.[2] For emergency department visits, we will use estimates from the Medical Expenditure Panel Survey.[3] To calculate the average retail price of medications, we will use average retail prices from GoodRx.com.[4],

1.2 Pain

The ODI is the most commonly used scale for low back pain (35). It is a self-administered questionnaire that has ten topics: intensity of pain, lifting, sexual function, social life, sleep, and ability to walk, sit, stand, care for oneself, and travel. It has been recommended as one of the standardized metrics for research of low back pain based on its ability to quantify functional status in this population (36). The ODI typically takes three to five minutes to complete, and one minute to score (37). Previous studies have evaluated the ODI in pain-free subjects and found that mean score to be 10.19 (35, 38, 39) and those with disability from low back pain is

22.07 (40). Previous studies have indicated that a change in ODI by 6 points is clinically meaningful (41).

2 Other outcomes

2.1 Quality of Life

Quality of life will be assessed by the EQ-5D (Appendix I), which has been shown to be beneficial in describing and valuing health related quality of life (42, 43). It was developed for self-completion, and has been validated against other measures of quality of life, including SF-12 (44). The EQ-5D has been shown to correlate well with low back pain specific measurements, and also be responsive to change (45,46). The instrument consists of a descriptive section and a visual analogue scale. The descriptive section measures 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with each dimension having 5 levels ranging from "no problem" to "extreme problem". The visual analogue scale is a self-rated horizontal health scale with end points labelled as "the best health you can imagine" and "the worst health you can imagine". The raw scores are converted into index scores based on US norms[5]. Previous studies identify a change in EQ-5D index of 0.08 as a minimal important clinical distance (47), and in a study evaluating the sensitivity to change of EQ-5D index with back pain it was seen that after two weeks there was a decrease of 0.21 after treatment; albeit this was in an interventional study that included steroid injections (46). The EQ-5D is also helpful in converting to quality adjusted life years (QALY) to perform a cost utility analysis, and is the most common measure for conversion (37).

2.2 Self-Efficacy

We will evaluate self-efficacy at baseline, six months, and one year. As the focus of this trial is to support those with acute spine pain to prevent the development of chronic pain, measuring self-efficacy both as a predictor and outcome of the treatment arms will be necessary as a metric of self-management for future episodes. We will use Lorig et al.'s self-efficacy scale for individuals with musculoskeletal complaints, which has three subscales that focus on pain, functioning, and other symptoms (31). Because spine-specific pain is already captured with ODI, we will use the "functioning" and "other symptoms" subscales in this trial to measure self-efficacy (Appendix J). The "function" subscale produces an average of 73.27 (s.d. 20.22), and the "other symptoms" subscale produces an average of 55.62 (s.d. 21.64).

2.3 Productivity

We will also evaluate the impact of spine pain on work-related activities by evaluating absenteeism and presenteeism. Absenteeism will be assessed by subject self-report. Time lost from work, or other usual activities, associated with spine pain and all other health problems will be collected and measured. The total number of unplanned work absences will be multiplied by an average employee's daily wage to obtain the cost per participant of work absenteeism. Presenteeism will be assessed using the methods of van den Heuvel, et al (49). Three assertions will be ranked on a scale of 1-5: 1) I achieve all objectives of the job, 2) Job-related tasks come easily to me, and 3) I perform well in my job. The scores will be dichotomized using the median value from all respondents. A study participant will be described as suffering from presenteeism if they are above the median value.

2.4 Other outcomes

We will measure implementation-related outcomes to assess intervention fidelity. These will include the number of protocol-specified appointments (i.e., Spine Coach, physical therapist, or the Egoscue practitioner) scheduled and attended, the timing of visits and the length of the treatment course, which we originally expected to last 6 to 8 weeks.

Data Collection

Study data will be collected and managed using REDCap electronic data capture tools (50) hosted at Brigham and Women's Hospital. Data will be collected based on the schedule in Table 3. Study subjects will be contacted by email five business days prior to a survey being due for completion to be notified that the survey is available. If the survey is not completed they will be notified again three and five business days after the due date. Should the study subject still not complete the survey, they will have three phone attempts to be reached and guided through completion.

Table 2: Subject Reported Outcome Administration Schedule

	Months After Enrollment													
Metric	**0**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
STarT Back Tool	x													
Healthcare Utilization Checklist		x		x	x		x		x		x		x	x
Oswestry Disability Index	x		x		x			x						x
EQ-5D	x		x					x						x
Self-Efficacy Questionnaire	x							x						x

Statistical considerations

1 Analysis plan

All analyses will be performed using intention to treat principles based on study arm with which a subject is assigned at study enrollment and regardless of whether or not all protocol steps have been completed. We will report means and frequencies of pre-randomization variables separately by study arm. Comparison of these values will be made with generalized estimating equations to adjust for the block and cluster randomized design.

Because cost data in healthcare is not normally distributed (32) due to significant zero data representing subjects for whom there is little to no cost, we will have to model the data accordingly. We will evaluate the two primary outcomes, total cost of care, using generalized estimating equations with Poisson distributed errors and a log link function which can account for a positively skewed distribution. Changes in ODI from baseline to three months will be compared for the treatment arms using generalized estimating with normally distributed errors and an identity link function. All models will adjust for age and sex, account for the cluster and block randomized study design and include fixed effects for the 3 different delivery networks that were used for recruitment. In secondary analyses, we will repeat our models adjusting for unmatched confounders that remained despite randomization. Our primary analyses will compare each of the two treatment arms separately with usual care (i.e., ICE compared with usual care and IPT with usual care). Because we are evaluating two primary outcomes, we will use a Bonferroni-corrected two-tailed type 1 error of 0.025. Analysis of secondary outcomes will also be performed using generalized estimating equations with error distributions and link functions appropriate to the outcomes being evaluated.

Missing data will be accounted for using multiple imputation (51), which has been determined an adequate strategy to minimize both false positive and false negatives in clinical trials. We will perform 20 imputations using Proc MI in SAS with a fully conditional specification. The following variables will be used to perform the imputation: age, study arm, study site, clinic, sex, race/ethnicity, BMI, exercise frequency at baseline, education level, employment status, smoking status, other medical conditions at baseline, number of medications used for spine pain at baseline, length of pain at baseline, number of previous pain episodes, STarT back score, baseline ODI, baseline self-efficacy, baseline EQ-5D, and scores for patient-reported outcomes at every follow-up timepoints (ODI, cost, Lorig self-efficacy scale, and EQ-5D).

As resource utilization and ODI were collected at multiple time points, we will also evaluate non-missing cost and ODI data from each time point using a repeated measures design. In specific, we will use generalized estimating equations, with link functions and error distributions appropriate to the study outcomes, to assess changes in outcomes over the 12 months of follow-up, while accounting for correlations in the repeated measurements. For spine-related health spending, these analyses will be conducted using the time intervals at which raw data were collected as well as after converting estimates to evenly-spaced months. Because cost data in healthcare is not normally distributed with zero values for participants with no resource utilization during follow-up, we will winsorize estimated costs at the 95th percentile in secondary analyses. We will report relative spending differences with confidence intervals and a two-tailed p value. As a sensitivity analysis, we will conduct a complete-case analysis on all non-missing values.

Exploratory analyses will be performed evaluating the effect of the interventions on cost in various strata of clinical interest, including age, sex, STarT Back risk group, location of pain, and whether or not this was the subject's first pain episode. We will also evaluate the percentage of subjects in each arm with a decrease in ODI of six points at three, six, and twelve months of follow-up.

2 Sample size

The ICE model was anticipated to reduce total cost of care by 25% compared to usual care (52–54). Because of the lack of peer-reviewed literature evaluating the economic impact of IPT, an effect similar to ICE was assumed for the purpose of performing power calculations. We will need to enroll a total of 3,096 patients (1,032 per arm) to conservatively detect a change in spending of 20% between either treatment arm and usual care with 80% power and an alpha of 0.05, with 33 clusters, and 10% loss to follow-up over the 12-month study period. Our results are robust to a standard deviation of 1.25 times the mean and an ICC value of 0.01. Given the substantially larger sample size required for our economic analyses, we powered our trial on the basis of this outcome, which would also give us more than 98% power to detect a 6-point change in ODI between each intervention arm and the usual care arm.

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