Protocol Summary
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Comparative Effectiveness of Management Strategies for Acute Low Back Pain

Principal Investigator
Julie M. Fritz
Associate Professor, Physical Therapy Department
520 Wakara Way
Salt Lake City, UT  84108
(801) 581-6287
julie.fritz@hsc.utah.edu

Co-Investigator(s)
Carl V. Asche
Research Associate Professor, Department of Pharmaco therapy
30 South, 2000 East, Room 258
Salt Lake City, UT  84112
(801) 581-5941
Carl.Asche@pharm.utah.edu

Tom Greene
Professor, Division of Clinical Epidemiology
295 Chipeta Way
Salt Lake City, UT  84132
(801) 585-6667
Tom.Greene@hsc.utah.edu

Elizabeth Joy
Associate Professor, Clinical, Department of Family and Preventive Medicine
375 Chipeta Way
Salt Lake City, UT  84108
(801) 581-7234
eajslc@aol.com

Sponsor Contact Information
Agency for Health Research Quality
Karen Siegel
540 Gaither Road
Rockville, MD  20850
(301) 427-1321
karen.siegel@ahrq.hhs.gov
BACKGROUND AND INTRODUCTION:
Current practice guidelines for patients with acute low back pain (LBP) recommend a stepped care approach with initial treatment of education and advice to remain active. Referral to physical therapy is considered only when patients fail to recover after a few weeks. Recent research has led to the identification a subgroup of patients likely to experience rapid, pronounced, and sustained decreases in disability and pain with a brief manipulation and exercise intervention, suggesting it may be more cost-effective to manage this sub-group with early referral to physical therapy instead of the usual care approach. The integration of this evidence into routine practice has not been evaluated. We will assess the outcomes of integrating this evidence into the management of patients with low back pain. The study is a randomized trial, comparing management with early manipulation with the current care process model. Patients fitting the inclusion criteria will be randomized into one of two groups. One group will be managed with the current care process model. The other group will be managed consistent with the decision rule recommending early referral for a brief manipulation and exercise intervention during the first 4 weeks. Patients will be followed over 1 year. Outcomes will include measures of disability, pain, satisfaction, and direct medical costs. The study will examine the costs and effectiveness of integrating the alternative care model into practice.

OBJECTIVES:
The specific aims of this study are the following:
1. Compare the effectiveness of two primary care management strategies for a subgroup of patients with LBP. We hypothesize the early intervention strategy will result in greater improvements in function and quality of life, and increased patient satisfaction over 1 year as compared to a stepped care strategy.
2. Compare the costs (direct and indirect) associated with two management strategies for a subgroup of patients with LBP. We hypothesize the early intervention strategy will result in decreased costs over 1 year as compared to a stepped care strategy.
3. Examine the cost-effectiveness of the two management strategies. We hypothesize the early intervention strategy will be more cost effective over one year than a stepped care strategy.

PARTICIPANT SELECTION CRITERIA:
This study will recruit patients with a new episode of LBP visiting a primary care provider at a participating clinic. A new episode will be defined as not seeking any treatment from a healthcare provider in the past 6 months. Patients with a recurrence of a LBP problem will be eligible if they have not sought treatment in the past 6 months. Potential candidates must satisfy all inclusion criteria listed below:

I. Symptoms of pain and/or numbness between the 12th rib and buttocks with or without symptoms into one or both legs, which, in the opinion of the primary care provider, are originating from tissues of the lumbar region.
II. Age 18 - 60 years
III. Oswestry disability score > 20%
IV. Both of the following clinical decision rule criteria
   a. Duration of current symptoms < 16 days
   b. Patient report of no symptoms (pain, numbness, etc.) distal to the knee in past 72 hours.
These criteria are designed to select patients who fit the sub-group for whom the rule was created (i.e., those fitting the 2 criteria that are less than age 60 with at least moderate disability). Patients will be excluded if they meet any one of the following exclusion criteria:
I. Prior surgery to the lumbosacral spine

II. Currently know to be pregnant

III. Currently receiving treatment for LBP from another healthcare provider (e.g., chiropractic, massage therapy, injections, etc.)

IV. Presence of neurogenic LBP defined as the presence of either of the following:
   a. Positive ipsilateral or contralateral straight leg raise (reproduction of symptoms at <45°)
   b. Reflex, sensory, or strength deficits in a pattern consistent with lumbar nerve root compression

V. Judgment of the primary care provider of “red flags” of a potentially serious condition including cauda equina syndrome, major or rapidly progressing neurological deficit, fracture, cancer, infection or systemic disease

These criteria are designed to exclude patients who do not fit the sub-group identified by the decision rule. Patients with medical red flags typically require early specialist referral. Patients with signs of nerve root compression likely comprise separate sub-groups requiring different management strategies. Patients who know they are pregnant may be more appropriate for different management, and may find some procedures in the study uncomfortable. Spinal manipulation may be contraindicated for some post-operative patients (e.g., spinal fusion), thus these patients will be excluded.

DESIGN:
This study is a randomized clinical trial. This is the appropriate trial design to compare the costs and effectiveness of two different management strategies. No interim analyses or stopping criteria are defined for this study due to the low risk associated with the procedures.

STUDY PROCEDURES:
Recruitment will occur in Community Clinics in the University of Utah Healthcare System. All patients visiting a primary care clinic within a clinic with a chief complaint of LBP will be potentially eligible. Recruitment will be coordinated by the University of Utah Health Research Network (UHRN), a practice-based research network registered with AHRQ. The UHRN will identify patients with an initial appointment (defined as no appointments in the past 6 months for LBP) with a primary care provider in one of four Community Clinics with an ICD-9 code related to LBP, and between the ages of 18-60 with a current symptom duration of 2 weeks or less. These patients will be informed of their potential eligibility by mail. Interested individuals will be contacted within 24 hours by the Study Coordinator. The Study Coordinator will screen the patient’s eligibility based on age and duration and location of symptoms. Potentially eligible and interested patients will be scheduled for an initial assessment with the Study Coordinator.

Patients who meet all eligibility criteria and provide informed consent will undergo a baseline assessment performed by a Research
Assessment followed by randomization into one of two groups (CP or DR). Baseline assessment will include completion of self-report measures and a physical examination. Follow-up assessments will be conducted 4 and 12 weeks, and 1 year after baseline. Outcomes will include the self-report measures, indirect and direct costs, and patient satisfaction. The specific measures to be collected are detailed below:

**Physical Examination**
The physical examination includes neurologic testing (strength, sensation, straight leg raise, reflexes) to confirm eligibility, and the physical impairment index\(^{107}\) composed of 7 measures of range of motion and strength. Each measure has excellent reliability and validity.\(^ {107,108}\)

**Self-Report Measures**

- **The Oswestry Disability Questionnaire (OSW),**\(^ {110}\) a condition-specific disability measure for patients with LBP with high levels of test-retest reliability (ICC = 0.90), good construct validity, and responsiveness to change for patients with acute LBP, with a minimum clinically important difference of 6 points for patients with acute LBP receiving physical therapy.\(^ {111}\)
- A 0-10 Numeric Pain Rating Scale (NPRS) will be used to assess LBP intensity. The NPRS has excellent test-retest reliability,\(^ {112}\) and is responsive to change, with a minimum clinically important difference of 2 points among patients with acute LBP receiving physical therapy.\(^ {114}\)
- The EuroQol (EQ-5D), generic, quality of life instrument\(^ {115}\) will be used to assess health outcomes on a scale that may be referenced to other disease conditions.\(^ {116}\) The EQ-5D is reliable and responsive to change in patients with LBP\(^ {118,119}\) and is commonly used in economic evaluation of interventions for LBP.
- A body diagram will be used to identify the location of symptoms.\(^ {120}\) Body diagrams can be used to reliably categorize the distal-most extent of a patient’s symptoms.\(^ {120,121}\)
- The Fear Avoidance Beliefs Questionnaire (FABQ)\(^ {122}\) will be used to measure patients’ beliefs about how physical activity and work may affect their LBP and perceived risk for re-injury. The FABQ has excellent test-retest reliability,\(^ {122,124}\) and validity is supported by associations with disability and work loss in patients with acute and chronic LBP.\(^ {125,126}\)
- The Pain Catastrophizing Scale (PCS) will be used to measure the extent to which people catastrophize in response to pain.\(^ {129}\) The PCS has high levels of internal consistency and construct validity,\(^ {130,131}\) and is predictive of the transition from acute to chronic LBP.\(^ {127}\)

**Direct and Indirect Costs**
Direct and indirect costs due to lost work productivity related to LBP will be collected using a cost diary method collected via the internet. Cost diaries have been reported to offer advantages in terms of feasibility and validity as compared with patient-reported questionnaires for collecting cost data.\(^ {132,133}\) Each cost diary will ask patients if they have utilized healthcare resources in the past month specifically related to LBP in 4 categories: provider visits, medications (prescription or over-the-counter), interventions (injections, surgery, etc.), or testing (x-rays, MRI, etc.). Patients who are seeking care are given follow-up questions to ascertain the number and nature of utilization in each of these categories in the past month.

**Patient Satisfaction**
Patient satisfaction with the care received will be measured using a 10-item instrument that has been validated and found capable of distinguishing different dimensions of satisfaction (caring, information and treatment effectiveness) among patients with LBP attending primary care.\(^ {138}\)

**Procedures for Treatment**

**Aspects Common to Both Groups**
Patients in both groups will continue to be managed by their primary care provider on an as-needed basis. All patients will be recommended to follow-up with their primary care provider on
an as-needed basis if they are not satisfied with their progress after 4 weeks. This recommendation will be reinforced by the Study Coordinator after completion of the baseline assessment. All patients will receive the following treatments recommended by evidence-based practice guidelines for the initial management of patients with acute LBP:

- Education on the favorable natural history of LBP; reassurance that no serious condition exists
- Advice for early return to normal activity without bed rest

The advice and education interventions will be provided by the Study Coordinator after completion of the baseline assessment but prior to randomization. The Study Coordinator will be a licensed physical therapist and will receive additional training by the Principal Investigator in provision of the advice and education intervention. All patients will be given copies of the Back Book, a booklet developed to help change the beliefs and behavior of patients with LBP. Research has found the Back Book to be well-accepted by patients, and capable of shifting beliefs about recovery and activity, particularly when used in collaboration with an interactive educational session. The Study Coordinator will review the contents of the Back Book with the patient, and answer any questions the patient may have.

Care Process (CP) Treatment Group

The CP group will be managed with a stepped care approach supported by current practice guidelines. Initial management will be the education and assurance intervention as outlined above for the first 4 weeks following the initial primary care visit. Patients in the CP group will be recommended to follow-up with their primary care provider if unsatisfied with their progress after 4 weeks. At that time, consistent with guidelines, decisions on further treatments and/or referrals will be made by the primary care provider in consultation with the patient. Further follow-up in primary care will also be at the discretion of the patient and primary care provider consistent with the current care process. If a decision is made to refer the patient to physical therapy at this time, the referral will be made to a clinic that is not providing the DR intervention to reduce the potential for bias or contamination.

Decision Rule (DR) Treatment Group:

The DR group will receive the same initial education and reassurance intervention described above. Patients in the DR group will also be referred immediately to physical therapy. The first physical therapy session will be scheduled within 3 days after baseline assessment. Four treatment sessions will be administered within the first 4 weeks after baseline. Each session will begin with a brief assessment performed by the physical therapist, followed by administration of the spinal manipulation intervention. All patients will then be instructed in a range-of-motion exercise to be performed in the clinic and 3-4 times daily at other times throughout the day. The second treatment session will be scheduled 2-3 days after the first. The second session will begin with the spinal manipulation intervention, followed by a review of the exercise. Next, the patient will be instructed in a series of strengthening exercises designed to strengthen trunk muscles identified as primary stabilizers of the spine, and with some evidence to support their effectiveness in reducing the risk of recurrence in individuals with LBP. Patients will demonstrate performance of these exercises during the treatment session, and will be instructed to perform the exercises daily until the next session. The third and fourth sessions will be scheduled at approximately 1 week intervals after the second session. During these sessions, the physical therapist will review and progress the patient’s strengthening exercise program and answer any questions the patient may have.

Standard of Care vs. Research-Related Procedures: Procedures considered standard of care in this study are all visits with the primary care provider, and any referrals, tests, procedures, etc. recommended by the primary care provider outside of the study-related procedures outlined...
above. Research-related procedures include the education and advice intervention provided by
the study coordinator, and the 4 physical therapy sessions provided to the DR group.

Data Safety and Monitoring: Please see attached data and safety monitoring plan.

STATISTICAL METHODS, DATA ANALYSIS AND INTERPRETATION:
Because the study has a relatively small sample size and involves procedures associated with
minimal risk to subjects; we will not perform any planned interim analyzes for between-group
differences due to the risk of inflated Type I error rates imposed by performing multiple
analyzes.\textsuperscript{167} Major outcomes will be analyzed for each of the follow-up points separately to
determine if different relationships exist between the outcomes and the interventions at the
various time points.

Principal analysis to compare outcomes between groups will use analyses of covariance. For
each quantitative functional outcome (including the OSW, NPRS, FABQ, and PCS), separate
analyses of covariance will be used to compare mean change in outcome from baseline to each
follow-up assessment between the CP and DR groups controlling for baseline level of the
outcome being analyzed. The primary analysis will compare the mean changes in the OSW
score to week 12; while other comparisons will be interpreted as secondary analyses.

Multinomial logistic regression analyses will be used to compare the proportions of patients
reporting the respective categories of each of the 5 EQ-5D subscales at weeks 4 and 12 and at
year 1 between groups after controlling for the baseline EQ-5D scores. If proportional odds
assumptions are satisfied,\textsuperscript{147} treatment comparisons will be performed using a proportional odds
model to increase power and to provide a more parsimonious presentation of the results.

Direct and indirect costs will be computed and examined separately, then combined to examine
overall costs associated with each treatment. As recommended, we will value the cost data
collected using standard unit prices.\textsuperscript{150} Standard unit costs of direct healthcare costs, including
medications, provider office visits, diagnostic imaging, surgical procedures, etc., will be
determined using costs obtained from the Clinical Research Billing rates used at the University
of Utah for healthcare services provided. The monthly cost diaries specifically ask patients to
indicate if they experienced work absence or reduced work performance (as a percentage of
normal work performance) due to losing concentration, repeating a task, feeling fatigued at
work, or doing nothing at work due to LBP. Lost productive time will be calculated as the
number of days absent from work ("absenteeism") and the number of hours of reduced
productivity at work ("presenteeism") multiplied by the patient's self-reported salary.\textsuperscript{23} Patients
not employed outside the home (e.g., homemaker, full-time student) will also be asked to report
absenteeism and presenteeism. Lost productive time will be based on the average salary for
individuals matched for age and sex in the United States according to the Bureau of Labor
Statistics (www.bls.gov). Sensitivity analyses will be used to examine the impact of differing
methods of valuing direct and indirect costs. We will use both parametric and non-parametric
methods to compare costs. We will calculate means and standard deviations for direct, indirect
and overall costs for each group. We will further explore the distribution of direct, indirect, and
total cost data for each treatment group by graphically displaying the data, and calculating
median, quartile, and skewness values. Using univariate and multivariate techniques, we will
determine the relationship between use of the two treatment strategies and the costs of care.
Recognizing that cost data are typically positively skewed by a few patients with very high costs,
we will use nonparametric bootstrapping methods with associated 95% confidence intervals to
compare mean costs between groups. The bootstrap method avoids distributional assumptions
and is therefore a preferred method for the analysis of cost data.\textsuperscript{153} The bootstrap method
randomly selects patients from the study population and calculates the statistics of interest
(mean and standard deviation). The distribution of these values is used to provide an approximation of its population sampling. We will bootstrap 2000 replications of pair-wise cost comparisons. Confidence intervals around the mean difference in costs between groups will be calculated using bias corrected and accelerated (BCa) methods to permit comparison between groups. Regression analyses will also be used to allow the costs to be adjusted for patient characteristics, including socioeconomic status and co-morbidities. We will analyze sources of variation in costs, which will allow us to perform various sensitivity analyses.

Analysis of cost-effectiveness will be based on total costs and clinical effectiveness (i.e., OSW scores) at the 1-year follow-up. We will examine mean costs and the mean OSW change for each group. If one group is associated with significantly less cost and superior clinical effect, the treatment may be recommended, and no additional cost-effectiveness analysis is indicated. If either group is associated with higher cost and inferior effects, the treatment cannot be recommended and no further analysis is indicated. If either group is associated with higher costs and superior effects, a cost-effectiveness analysis will be performed by examining the incremental cost-effectiveness ratio (ICER). The ICER is computed as the difference in costs between treatments divided by the difference in effectiveness: \[(\text{cost}_{\text{group1}} - \text{cost}_{\text{group2}}) / (\text{clinical effect}_{\text{group1}} - \text{clinical effect}_{\text{group2}})\]. The ICER represents the cost per unit health benefit obtained by switching from one treatment approach to another. Uncertainty in the ICER estimate will be examined using bootstrapping techniques to examine cost-effectiveness planes and acceptability curves. Sensitivity analyses will be used to explore the robustness of the results.

Sample size assumes at least 90% of patients will complete the 12-week OSW. Enrolling 110 subjects per group (total sample = 220) will provide at least 86% power to detect a difference of 7 points of OSW change to 12 weeks, assuming a standard deviation of 16 points (treatment effect = 43.8% of 1 standard deviation). The MCID for the OSW is estimated at 6 points. Our previous work indicates these estimates of effect size and standard deviation are realistic, and would be consistent with detecting an effect at least slightly in excess of the threshold for minimum clinical importance. This sample size provides at least 82% power to detect a treatment effect for 1-year OSW change assuming the same standard deviation and 80% 1-year follow-up, and provides at least 99% power to detect a clinically important difference of 2.0 on the NPRS assuming a standard deviation of 2.4 and at least 80% follow-up. These estimates of effect for the NPRS are also consistent with our prior research on patients with acute LBP.

**ADMINISTRATIVE RESPONSIBILITIES:**

**Study Resources:** Dr. Fritz is a licensed Physical Therapist and will conduct training for all study personnel. Dr. Joy is a primary care physician who will assist with training. The UHRN has participated in several funded studies at the University of Utah and will be used for recruitment. The University of Utah Community Clinics manage numerous potentially-eligible patients and will provide excellent resources for recruitment. Many Community Clinics also have physical therapy clinics with licensed providers that will provide excellent resource for treatment procedures.

Data management will be maintained throughout the study by Caracal, Inc, using the BrightOutcome™ web-based data management system, and overseen by the Investigators at the University of Utah. This web-based system will facilitate data collection via the internet for long-term follow-ups and collection of costs diaries. Prior to beginning data collection, the data collection interface will be developed by the BrightOutcome™ group with direction from the study Investigators. During the data collection period, all study-related data will be entered into the central study database maintained by the BrightOutcome™ group, with weekly reports sent to the Investigators at the University of Utah. Periodically during the study, and at completion of the data collection, the database will transferred by via a secure file transmission protocol to the
The BrightOutcome™ System was developed to support patient-reported outcomes data collection. Key features relevant to this study are: 1) support for questionnaires with a variety of response types; 2) support for conditional branching logic in questionnaires; 3) collection of data and outcomes on the Internet, over the phone (via Interactive Voice Response), and/or on PDAs; 4) weekly system usage reports distributed automatically by e-mail; 5) monthly data exports; 6) longitudinal reports per respondent; and 7) HIPAA compliance. This system is currently used by the Centers of Disease Control and Prevention in a 5-year surveillance study to collect behavioral outcomes data from patients with HIV nationwide.

Each patient entered in the study will receive a unique Patient Identifier that will be generated prior to beginning the study. Once a patient provides informed consent, the Study Coordinator will create a new Patient Profile in the web-based data collection platform. The Patient Profile will be identified by the unique Patient Identifier, and will not contain the patient’s name, Social Security number, or any other type of Personal Health Information data that could be used to identify the individual patient. The link between the Patient Identifier and the patient’s Personal Health Information will be maintained by the Principal Investigator, and will be available only to the Study Coordinator and Principal Investigator. After the Patient Profile is created, the patient will be able to input all self-report data directly via a desktop computer that will be available in the examination room using a web-based interface. All data entered by the patient into the database is identified only by the unique Patient Identifier.

All self-report patient data will be collected using the BrightOutcome™ data collection platform. Additional patient information (e.g., informed consent documents, patient demographic and physical examination forms completed by the Research Assistant) will be entered into the data collection platform by the Study Coordinator or Research Assistant as appropriate. Monthly data reports will be exported to the CCTS on a monthly basis using secure procedures. At the completion of data collection, the project database will be transferred to the researchers at the CCTS, and will be maintained on a server supplied by the University of Utah Health Sciences Center (UUHSC). The UUHSC utilizes technology from Hitachi Data Systems called the Universal Storage Platform for providing a virtualized storage area network. This network is maintained and supported by the University of Utah Health Sciences Information Technology Support. All programming for the analyses will also be stored on the same server. All data will be backed up onto removable media and stored in a secure location on a daily, weekly, and monthly schedule. The accuracy, quality, and completeness of all data collected is monitored at the data collection interface by the BrightOutcome™ system. Each self-report data point entered into the system must pass identification checks using login names and passwords, range and type verification, required field verification, and duplicate record detection. These restrictions will minimize data input errors. In addition to passing point of entry edits, all data appended to the central database will be subjected to extensive monitoring procedures on a routine basis by the BrightOutcome™ system, and by the CCTS following completion of data collection. The Principal Investigator will be in regular contact with the Investigators to discuss progress or trouble-shoot any problems with data entry or integrity.

**Recruitment:** The UHRN has established a process for recruiting research subjects from the Community Clinics that has received expedited approval from the University of Utah Institutional Review Board. The process uses the electronic medical record that is used in each Community Clinics to identify patients with specific characteristics based on demographic information and
ICD-9 codes. These patients are informed of their potential eligibility, either in the clinic by a staff member, or by mail. Interested individuals will be contacted within 24 hours by the Study Coordinator. For this project we will identify all patients with an initial appointment (defined as no appointments in the past 6 months for LBP) with a primary care provider in one of four Community Clinics who have an ICD-9 code related to LBP, and are between the age of 18-60, with a current symptom duration ≤ 2 weeks. We performed a query of the EMR database for a 30-day period (4/1/09 – 4/30/09) to gauge the number of potentially-eligible patients with LBP seen in the four Clinics from which patients for this study will be primarily recruited. During this time a total of 640 visits to primary care providers were recorded for patients with an ICD-9 code related to LBP who were within the required age range. Further examination found 113 unique patients whose symptom duration matched the study requirements.

When a potentially eligible patient speaks with the Study Coordinator, the Coordinator will further explain the project and confirm preliminary eligibility by insuring appropriate age, symptom duration, and post-surgical status. If the preliminary criteria are met, the Study Coordinator will proceed to the baseline assessment within 48 hours. At the baseline assessment the Coordinator will confirm eligibility and have the patient sign an informed consent document. Patients who are not interested, or are not eligible, will be instructed to follow-up with their primary care provider as needed. Once consent is obtained, the baseline examination procedures will be performed by a Research Assistant, blinded to the patient’s treatment group assignment throughout the study. After completing the baseline examination the patient will again meet with the Coordinator for the advice and education intervention, after which the Coordinator will reveal the patient’s treatment group and schedule the appropriate treatment procedures. All patients will be reminded to return to their primary care provider as needed.

REFERENCES:


I. SPECIFIC AIMS
The research dissemination and demonstration project described in this proposal examines the translation of a new strategy for managing individuals with LBP from a primary care setting, and compares the effectiveness and costs of this new strategy to current care practices. If the new strategy proves more cost-effective than current care practices, broader dissemination into healthcare delivery systems could be advocated. This project fits the current AHRQ Research Portfolio; specifically the Comparative Effectiveness Portfolio. The project examines the impact of translation of new scientific information into clinical care, and develop evidence to inform clinical decision-making for an important priority condition.

Most patients with a new episode of LBP enter the healthcare system through primary care. Primary care management of patients with LBP is characterized by a high degree of variability in decision-making regarding prescription medication, diagnostic imaging, and referral to specialties such as physical therapy. In the face of this variability it is not surprising that the outcomes of primary care management of patients with an acute episode of LBP are inconsistent, with a considerable proportion of patients going on to persistent or recurrent symptoms. Costs associated with patients who fail to recover quickly or completely can be substantial, including both direct costs for health care services and indirect costs related to lost productivity and other expenses. More effective management of patients with acute LBP may impact progression of the condition before the additional concerns associated with chronic pain become evident, and is therefore central to reducing costs and improving outcomes.

Current evidence-based clinical practice guidelines have been developed in an attempt to reduce variability and improve outcomes for patients with acute LBP managed in primary care. Current practice guidelines recommend a “stepped care” approach to management involving an initial period of advice, assurance, and non-steroidal medication, with referral to physical therapy considered for patients who fail to improve after several weeks. Recent studies, including our own prior work, suggest that early implementation of physical therapy may provide more effective initial management for some patients.

The most recent guidelines published by the American College of Physicians/American Pain Society recommend consideration of earlier implementation of additional treatment for individuals with acute LBP, however no studies have examined the comparative effectiveness or economic consequences of a stepped care approach to an approach using earlier treatment implementation. Our previous research has developed a clinical decision rule to identify a specific subgroup of patients with acute LBP highly likely to experience rapid and sustained improvement with early implementation of a standardized physical therapy intervention, however the impact of translating of this rule into clinical practice has not been examined. This project will examine the translation of this new clinical decision-making strategy into clinical care, and compare the effectiveness of the new strategy to a stepped care approach.

We will conduct a randomized trial comparing the effectiveness and costs associated with translating the decision rule into the primary care management of patients with LBP. The study will compare management based on the decision rule with a usual stepped care approach within primary care clinics. Patients with LBP who fit the criteria of the decision rule will be randomized into one of two groups. One group will be managed with stepped care; the other with early implementation of physical therapy. Patients will be followed for 1 year. Outcomes will include measures of disability, pain, patient satisfaction, and direct medical costs. This study will permit an examination of impact of translating preliminary evidence supporting the decision rule into clinical practice by comparing the effectiveness of the approach to a usual stepped care approach. The overall hypothesis guiding the study is that the additional initial treatment expense incurred by early implementation will result in superior short-term clinical effectiveness, and will be more cost-effective in the long-term due to reduced healthcare utilization.

The specific aims of this study are the following:

1. Compare the effectiveness of two primary care management strategies for a subgroup of patients with LBP. We hypothesize the early intervention strategy will result in greater improvements in function and quality of life, and increased patient satisfaction over 1 year as compared to a stepped care strategy.

2. Compare the costs (direct and indirect) associated with two management strategies for a subgroup of patients with LBP. We hypothesize the early intervention strategy will result in decreased costs over 1 year as compared to a stepped care strategy.

3. Examine the cost-effectiveness of the two management strategies. We hypothesize the early intervention strategy will be more cost effective over one year than a stepped care strategy.
C. Approach
This study will be a randomized trial comparing the effectiveness of two strategies for managing a sub-group of patients with LBP in primary care. One strategy will be usual care (UC) based on a stepped care approach advocated by most clinical practice guidelines. The other strategy is based on the previously-developed decision rule, and will consist of early intervention (EI) with a standardized manipulation + exercise protocol in physical therapy. The study will examine functional outcomes, patient satisfaction, and costs (direct and indirect) resulting from the two strategies. The primary difference between the strategies is the management occurring during the first 4 weeks after the initial primary care visit. The UC group will be managed with stepped care during this period. During the first 4 weeks these patients will receive advice and education, but no referral to physical therapy. The EI group will receive 4 sessions of physical therapy during the first 4 weeks in addition to the advice and education intervention. This study will use a pragmatic approach in order to compare the effects of the two management strategies under realistic clinical circumstances. Therefore, we will not attempt to balance provider contact time between groups over the first 4 weeks.

Recruitment will occur in four Community Clinics in the University of Utah Healthcare System. All patients visiting a primary care clinic within one of these Clinics with a chief complaint of LBP will be potentially eligible. Patients meeting the criteria of the decision rule and all other eligibility criteria who provide informed consent will undergo a baseline assessment followed by randomization into one of two groups (UC or EI). The UC group will be managed consistent with evidence-based guidelines advocating a stepped care approach. Initial management will include advice and education without early referral to physical therapy. Referral for additional care will be considered after 4 weeks if symptoms do not improve. The EI group will also receive advice and education, and will be referred to physical therapy for 4 sessions of the standardized intervention protocol.

A total of 220 patients will be recruited. Baseline information will be collected including severity and duration of symptoms, current employment status, prior history of LBP and treatment expectations. Self-report measures of disability related to LBP, quality-of-life, psychosocial factors, pain location and intensity will be collected. A physical examination will be conducted and measures of physical impairment taken. Follow-up assessments will be conducted 4 and 12 weeks, and 1 year after baseline. Outcomes will include the self-report measures, indirect and direct costs, and patient satisfaction.

C.1 Subjects
This study will recruit patients with a new episode of LBP visiting a primary care provider at a participating clinic. A new episode will be defined as not seeking any treatment from a healthcare provider in the past 6 months. Patients with a recurrence of a LBP problem will be eligible if they have not sought treatment in the past 6 months. Potential candidates must satisfy all inclusion criteria listed below:

I. Symptoms of pain and/or numbness between the 12th rib and buttocks with or without symptoms into one or both legs, which, in the opinion of the primary care provider, are originating from tissues of the lumbar region.

II. Age 18 - 60 years

III. Oswestry disability score > 20%

IV. Both of the following clinical decision rule criteria
   a. Duration of current symptoms < 16 days
   b. Patient report of no symptoms (pain, numbness, etc.) distal to the knee in past 72 hours.

These criteria are designed to select patients who fit the sub-group for whom the rule was created (i.e., those fitting the 2 criteria that are less than age 60 with at least moderate disability). Patients will be excluded if they meet any one of the following exclusion criteria:

I. Prior surgery to the lumbosacral spine

II. Current pregnancy

III. Currently receiving treatment for LBP from another healthcare provider (e.g., chiropractic, massage therapy, injections, etc.)

IV. Presence of neurogenic LBP defined as the presence of either of the following:
   a. Positive ipsilateral or contralateral straight leg raise (reproduction of symptoms at <45°)
   b. Reflex, sensory, or strength deficits in a pattern consistent with lumbar nerve root compression
v. Judgment of the primary care provider of “red flags” of a potentially serious condition including cauda equina syndrome, major or rapidly progressing neurological deficit, fracture, cancer, infection or systemic disease

These criteria are designed to exclude patients who do not fit the sub-group identified by the decision rule. Patients with medical red flags typically require early specialist referral. Patients with LBP who are pregnant or have signs of nerve root compression likely comprise separate sub-groups requiring different management strategies.\textsuperscript{104,105} Spinal manipulation may be contraindicated for some post-operative patients (e.g., spinal fusion), thus these patients will be excluded. The reason(s) for a patient’s ineligibility will be monitored and recorded using an ineligibility tracking form so that eligibility and consent rates can be determined.

C.2 Subject Recruitment

Subjects will be recruited from primary care providers working within the University of Utah Community Care Clinics in the Salt Lake City region. Recruitment will be coordinated by the University of Utah Health Research Network (UHRN). The UHRN is a practice-based research network, registered with AHRQ, that was formed in 2001 to promote collaboration between the University of Utah Health Sciences Center and the Community Physician Group for the facilitation of clinical research within the Community Clinics in the University Healthcare System. Dr. Elizabeth Joy, Director of the UHRN, is a co-investigator on this project and will oversee study recruitment from the UHRN. Currently the UHRN includes 12 clinics, with approximately 130 clinicians, of which 80 are primary care providers. The clinics in the UHRN provide healthcare services for more than 100,000 unique patients, and over 300,000 patient visits per year. The UHRN has assisted with subject recruitment for 37 funded research studies (5 NIH-funded).

The UHRN has established a process for recruiting research subjects from the Community Clinics that has received expedited approval from the University of Utah Institutional Review Board. The process uses the electronic medical record that is used in each of the Community Clinics to identify patients with specific characteristics based on demographic information and ICD-9 codes. These patients are informed of their potential eligibility, either in the clinic by a staff member, or via the mail. Interested individuals will be contacted within 24 hours by the Study Coordinator. For this project we will identify all patients with an initial appointment (defined as no appointments in the past 6 months for LBP) with a primary care provider in one of four Community Clinics who have an ICD-9 code related to LBP, and are between the ages of 18-60, with a current symptom duration of 2 weeks or less. We performed a query of the electronic medical record database for a 30-day period (4/1/09 - 4/30/09) to gauge the number of potentially-eligible patients with LBP seen in the four Clinics from which patients for this study will be recruited. During this time period a total of 640 visits to primary care providers were recorded for patients with an ICD-9 code related to LBP who were within the age range required for this study. Further examination of these visits revealed a total of 113 unique patients whose symptom duration matched the requirements for this study. Based on this query we are confident of our ability to recruit an adequate number of patients from these four clinics.

When a potentially eligible patient initially speaks with the Study Coordinator, the Coordinator will further explain the project, including the treatment options in the study and confirm preliminary eligibility by insuring the patient is of appropriate age and symptom duration, and is not post-surgical. If the patient meets the preliminary eligibility criteria and is interested, the Study Coordinator will proceed to the baseline assessment at that time, or within 48 hours depending on patient availability. At the baseline assessment the Coordinator will first insure all eligibility criteria are met, and have the patient sign an informed consent document approved by the Institutional Review Board of the University of Utah. The informed consent document will describe the two treatment options in this study. Because this study uses a pragmatic approach, and does not use a placebo treatment, we will not conceal the intent of the study in the informed consent document. The Institutional Review Board a the University of Utah permits the use of incomplete disclosure in the informed consent document only under very specific circumstances, and considers the practice generally undesirable. The treatment options in this study will be presented in the informed consent document as the current standard of care, or an alternative approach involving 4 sessions in physical therapy. Patients who are not interested, or are not eligible, will be instructed to follow-up with their primary care provider as needed. Once consent is obtained, the baseline examination
procedures will be performed by a Research Assistant who will remain blinded to the patient’s treatment group assignment throughout the study. After completing the baseline examination the patient will again meet with the Study Coordinator to receive the advice and education intervention consistent with current evidence (see details on Education Intervention in the Management section). Following the advice and education intervention, the Study Coordinator will reveal the patient’s treatment group assignment, and schedule the appropriate treatment procedures based on the patient’s treatment group. All patients will be reminded to return to their primary care provider as needed.

C.3 Randomization
Because this study is being conducted in one geographic region with a limited number of clinic sites, we will randomize individual patients instead of using a cluster-randomized design to avoid the loss of statistical power that would occur with randomization by clinics.\textsuperscript{106} In addition, because the treatment provided in primary care will be the same for patients in the study, there is little risk for contamination between treatment groups. Randomization will be conducted using a blocked randomization procedure. A random list of differing block sizes (2 or 4) will be generated prior to the start of the study. Sequentially numbered and sealed envelopes will be prepared containing the treatment group assignment for each patient. The randomization envelope will not be opened until completion of the baseline examination and the advice and education intervention to avoid any bias in the delivery of this aspect of the intervention. The envelope will be opened by the Study Coordinator. Patients in both groups will be instructed to follow-up with their primary care provider on an as-needed basis. Patients in the EI group will also be scheduled for physical therapy to begin within 3 days following randomization. Three different physical therapy clinics in the University Healthcare system will be available to provide treatment for patients randomized to the EI group. These physical therapy clinics are located either in the same building with, or in close proximity to, the primary care clinics, which will facilitate communication and timely scheduling (see letters of support from Director of the Physical Therapy Clinics).

C.4 Blinding
Patients cannot be blinded to the treatment they receive in this project. Consistent with a pragmatic study examining effectiveness and costs under routine circumstances, we will not use placebo or sham procedures to attempt to blind patients or balance provider contact time. At baseline, the randomization assignment will not be revealed until the patient has completed all assessment procedures with both the primary care provider and Study Coordinator, and has received the advice and education intervention by the Study Coordinator. This will reduce the potential for bias during contact with the primary care provider or staff in offering advice and making medication decisions. Follow-up assessments will be performed by a Research Assistant, who will remain blinded to the patients’ treatment group assignment for the duration of the study. Patients will be reminded at each follow-up that the Research Assistant must remain blinded, and not to disclose their treatment group. If the patient has questions about their treatment group, he or she will be instructed to contact the Study Coordinator. The occurrence of unblinding of the Research Assistant will be recorded at the follow-up assessments. The primary care provider cannot be masked to the treatment group should a study patient chose to return for a follow-up visit due to lack of progress. Regardless of the initial treatment group, if a patient decides to return for follow-up to his or her primary care provider, we will instruct the provider to base follow-up care decisions on the needs of the patient and usual care procedures at the site. This pragmatic approach is necessary to preserve appropriate communication between patient and provider, and will permit an examination of effectiveness and costs under realistic clinical circumstances, consistent with a comparative effectiveness study.

C.5 Procedures for the Baseline Examination
All patients meeting the eligibility criteria and providing informed consent will undergo a baseline examination performed by a Research Assistant, who will remain blinded to the patient’s treatment group throughout the study. The baseline examination will consist of self-report questionnaires and a physical examination. The physical examination includes neurologic testing (strength, sensation, straight leg raise, reflexes) to confirm eligibility. The physical impairment index (PII)\textsuperscript{107} composed of 7 measures of range of motion and strength, will be assessed. Each measure is graded positive (1) or negative (0) for a total score of 0-7 with higher numbers indicating more impairment. Each measure has excellent reliability and validity.\textsuperscript{107,108}
Self-Report Data Collection

All study data including self-report questionnaires will be collected using a web-based data collection platform developed by Caracal, Inc., a premier research and development firm specializing in technology solutions to integrating patient-reported outcomes research into clinical practice. Caracal, Inc, has worked closely with researchers in the NIH-PROMIS Network to develop innovative methods for collecting patient-reported information using the BrightOutcome™ system. We will use the BrightOutcome™ system as the data collection platform for this project. At the baseline examination, and at each subsequent examination, patients will input self-report data directly via the internet using a desktop computer. Most examination rooms in the participating clinics are equipped with desktop computers. The Study Coordinator and Research Assistant will also be equipped with a laptop computer to permit direct input of study data by the patient or the researcher. If a patient is unable to directly input self-report data, paper forms will be available, or the patient may input the self-report data over the phone (via interactive voice response). Options for data input at follow-up examination will include the internet, phone, or personal digital assistants including Blackberry, Treo, or iPhone devices.

Demographic Information

Patients will provide demographic information including age, sex, ethnicity, race, employment status, and general medical and back pain history. Patients will be asked about expectations for various treatments including spinal manipulation, exercise, and education prior to being informed of their group assignment according to procedures described by Torgerson et al.109 This information will be considered as a potential covariate in the analysis to mitigate the potentially confounding effect of treatment preference. (See Appendix A for paper copies of all self-report forms)

Primary Outcome

- The Oswestry Disability Questionnaire (OSW), originally described by Fairbank et al110 as a condition-specific measure of functional status for patients with LBP. The OSW is a 10-item scale with higher numbers indicating greater disability. We will use the modified version that replaces the sex life item with an employment/homemaking item due to poor compliance with the former.111,112 The OSW is widely used in research on non-operative management of patients with LBP.113 Our previous research has found the modified OSW to be used in this study to have high levels of test-retest reliability among stable patients (ICC = 0.90), good construct validity, and responsiveness to change for patients with acute LBP, with a minimum clinically important difference of 6 points for patients with acute LBP receiving physical therapy.111

Secondary Outcomes

- Numeric Pain Rating: A 0-10 numeric pain rating scale (NPRS) (‘0’ indicating no pain, and ‘10’ worst imaginable pain) will be used to assess LBP intensity. Numeric pain scales are known to have excellent test-retest reliability.112 Our previous research has found the NPRS to be responsive to change, with a minimum clinically important difference of two points among patients with acute LBP receiving physical therapy.114

- EuroQol (EQ-5D): A generic, quality of life instrument115 will be used to assess health outcomes on a scale that may be referenced to other disease conditions.116 The EQ-5D covers 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain has 3 response categories: level 1, “no problems”; level 2, “some problems”; and level 3, “inability or extreme problems.” Responses are combined to give a 5-digit descriptive health state classification (e.g., 11222). The EQ-5D yields a total of 243 possible health states. Valuations for each health state is available.117 The EQ-5D has been shown to be reliable and responsive to change in patients with LBP118,119 and is commonly used in economic evaluation of interventions for LBP.

- Pain Body Diagram: A body diagram will be completed to identify the location and nature of symptoms.120 Body diagrams can be used to reliably categorize the distal-most extent of a patient’s symptoms.120,121

- Fear Avoidance Beliefs: The Fear Avoidance Beliefs Questionnaire (FABQ)122 will be used to measure patients’ beliefs about how physical activity and work may affect their LBP and perceived risk for re-injury. The FABQ contains two subscales; a 7-item work subscale (FABQW), and 4-item physical activity subscale (FABQPA). Test-retest reliability of the FABQ subscales is high,122,124 and validity is supported by associations with disability and work loss in patients with acute and chronic LBP.125,126
Heightened fear-avoidance beliefs have been shown to be a risk factor for the development of chronic LBP following an acute episode.¹²⁷,¹²⁸

- **Catastrophizing:** The Pain Catastrophizing Scale (PCS) is a 13-item patient-report scale developed to measure the extent to which people catastrophize in response to pain.¹²⁹ Each item is scored from 0 (‘not at all’) to 4 (‘all the time’). The PCS is reported as a total score, with higher scores indicating greater catastrophizing, and is composed of three sub-scales: Rumination (four items; e.g. ‘When I am in pain, I keep thinking about how badly I want the pain to stop’), Magnification (three items; e.g. ‘When I am in pain, I become afraid that the pain will get worse’), and Helplessness (six items; e.g. ‘When I am in pain, I feel I can’t go on’). The PCS has been shown to have high levels of internal consistency and construct validity.¹³⁰,¹³¹ Pain catastrophizing has also been found to play a role in the transition from acute to chronic LBP.¹²⁷

- **Healthcare Utilization and Direct and Indirect Costs:** We will examine costs from a societal perspective, collecting both direct and indirect costs due to lost work productivity related to LBP over the 1-year follow-up period. We will use a cost diary method, integrated into the web-based data collection system, to collect utilization and cost data. Cost diaries have been reported to offer advantages in terms of feasibility and validity as compared with patient-reported questionnaires for collecting cost data.¹³²,¹³³ Cost diaries provide information at regular intervals over a period of time instead of relying on patient recall over a longer time period, minimizing recall error, and resulting in better and more complete reporting of the data.¹³⁴ Indirect costs related to lost work time and productivity, are important considerations in examining the effectiveness of care process models for managing LBP, and are captured by the cost diary. We will collect cost and utilization data monthly via the online system using the input options outlined above. The cost diary will be modeled on paper-based cost diaries developed by Goossens and colleagues¹³⁵,¹³⁶ for economic analysis in studies involving patients with LBP. Studies using these procedures have reported compliance rates of around 85% with the paper cost diaries, with no relationship observed between response rate and patient characteristics (e.g, age, sex, education, quality of life, etc).¹³⁵-¹³⁷ We expect the use of multiple input options will result in even higher compliance. Prior research has reported no differences between cost diaries completed for an entire year and the extrapolation of data for limited time periods, indicating a robustness to impute scores for random missing data. Patient-reported cost diary data has also been found to be generally in agreement with data obtained from insurance providers, supporting the validity of the self-report cost and utilization data.¹³⁶

Each monthly cost diary will ask patients if they have utilized healthcare resources in the past month specifically related to LBP in 4 categories: provider visits (traditional or complementary/alternative), medications (prescription or over-the-counter), interventions (injections, surgery, etc.), or testing (x-rays, MRI, etc.). Conditional logic will be used to reduce the response burden for patients not seeking any care for their LBP. Patients who are seeking care will be given follow-up questions to ascertain the number and nature of utilization in each of these categories in the past month.

### C.6 Procedures for Follow-Up Examinations

Cost and utilization data will be collected monthly as described above. Complete follow-up examinations will be conducted 4- and 12 weeks, and 1 year after baseline. The 4-week examination will permit an evaluation of the immediate effects following the treatment period. The 12-week and 1-year examinations will evaluate the short- and long-term persistence of the difference in treatment received during the first 4 weeks. The 4-week follow-up will be conducted face-to-face by a Research Assistant, blinded to the patient’s treatment group. The physical examination will be repeated at the 4-week examination and the patient will complete all self-report measures previously described with the exception of the demographic information. The 12-week and 1-year follow-up examinations will be conducted online (or via alternative input options). In addition, to the self-report forms described previously, the following additional self-report measures will be used at each follow-up examination. (See Appendix A for copies of all forms)

- **Satisfaction:** Patient Satisfaction with the care received for their LBP will be measured using a 10-item instrument that has been validated and found capable of distinguishing among three different dimensions of satisfaction (caring, information and treatment effectiveness) among patients with LBP attending primary care.¹³⁸
Global Rating of Change: The patient will complete a global rating of change scale at each follow-up. A 15-point scale is used as described by Jaeschke and colleagues.\textsuperscript{139} that asks the patient to rate the degree of change in his or her condition from the beginning of treatment to the present. The mid-point of the scale is no change (0). Ratings from -1 to -7 represent varying degrees of a worsening of the patient's condition, while rating from +1 to +7 represent varying degrees of improvement.

C.7 Procedures for Treatment

Aspects Common to Both Groups

All eligible, consenting patients will undergo a baseline assessment and will be randomized to either the usual care (UC) or early intervention (EI) treatment groups. All participants in both groups will continue to be managed by their primary care provider on an as-needed basis. Consistent with common clinical practice and routine procedures in the participating primary care clinics, all patients will be recommended to follow-up with their primary care provider on an as-needed basis if they are not satisfied with their progress after 4 weeks. This recommendation will be reinforced by the Study Coordinator after completion of the baseline assessment. All patients will receive the following treatments recommended by evidence-based clinical practice guidelines for the initial management of patients with acute LBP:

- Education on the favorable natural history of LBP and reassurance that no serious condition exists
- Advice for early return to normal activity without bed rest

The advice and education interventions will be provided by the Study Coordinator after completion of the baseline assessment, but prior to randomization. The Study Coordinator will be a licensed physical therapist and will receive additional training by the Principal Investigator in provision of the advice and education intervention (see training procedures section below). The Study Coordinator will provide the advice and education intervention to all patients to insure consistency, but prior to the patient’s randomization to avoid the potential for bias. All patients will be given copies of the Back Book (Appendix B). The Back Book is a booklet that was developed to help change the beliefs and behavior of patients with LBP.\textsuperscript{140} The message of the booklet is based on research demonstrating the beneficial effects of advice and education to remain active for patients with LBP. Research has found the Back Book to be well-accepted by patients, and capable of shifting beliefs about recovery and activity, particularly when used in collaboration with an interactive educational session.\textsuperscript{140,141} The Study Coordinator will review the contents of the Back Book with the patient, and answer any questions the patient may have.

The initial primary care visit will occur prior to the patient’s consent to participate in this study, and will therefore be based on usual care procedures for all patients. The Principal Investigator will meet with primary care providers and staff at each participating clinic to describe the study and review evidence-based guidelines for patients with acute LBP. Guideline recommendations regarding imaging procedures, medications and specialist referrals will be highlighted. Evidence-based guidelines permit the use of certain medications for patients with acute LBP. Current guidelines recommend non-steroidal anti-inflammatories or acetaminophen as appropriate first-line medications for most patients with acute, non-radicular LBP. Diagnostic imaging and specialist referral are not recommended for patients with acute LBP who do not have signs of radiculopathy, spinal stenosis, or a serious underlying condition.\textsuperscript{4,142} Although we will provide this evidence-based information in an attempt to standardize decision-making in each of these areas, decisions will ultimately be at the discretion of the primary care provider. This is consistent with a pragmatic research design, and these decisions will not be subjected to any bias from the patient or primary care provider because study enrolment and randomization will occur after these decisions are made. We will record medication, imaging, and specialist visits at baseline and at subsequent examinations to permit comparison of between-group differences on these factors.

Management common to all study patients therefore includes; 1) The Study Coordinator will educate and reassure the patient about the favorable prognosis of LBP and advantages of staying active, 2) all patients will be given a copy of The Back Book, and its contents will be reviewed, to reinforce these messages, 3) all patients will be managed by their primary care provider with respect to medication, diagnostic imaging, and specialist referrals decisions, guided by current evidence-based recommendations, 4) all patients will be recommended to return to their primary care provider if unsatisfied with their progress after 4 weeks. If the patient returns to their primary care provider, and referral to physical therapy is recommended at this stage, the patient will be referred to a physical
therapy clinic other than the clinic used to deliver the study-related intervention to avoid contamination, and treatment decisions will be left to the discretion of the new physical therapist.

**Usual Care (UC) Treatment Group**

Patients in the UC group will be managed with the usual stepped care approach supported by current practice guidelines. Consistent with this approach, initial management for patients in the UC group will involve the education and assurance intervention, with or without medication, as outlined above for the first 4 weeks following the initial primary care visit. Patients in the UC group will be recommended to follow-up with their primary care provider if unsatisfied with their progress after 4 weeks. At that time, consistent with practice guidelines, decisions on further treatments and/or referrals will be made by the primary care provider in consultation with the patient. Further follow-up in primary care will also be at the discretion of the patient and primary care provider consistent with a usual care management strategy. If a decision is made to refer the patient to physical therapy at this time, the referral will be made to a clinic that is not providing the EI intervention to reduce the potential for bias or contamination.

Compliance with the treatment procedures for patients in the UC group will be monitored by recording any off-protocol events at the 4-week follow-up. Patients will be asked about visits to any providers (chiropractic, physical therapy, etc., use of additional medications, or any other interventions).

**Early Intervention (EI) Treatment Group:**

Patients in the EI group will receive the same initial education and reassurance intervention, with or without medication, described above. Patients in the EI group will also be referred immediately to physical therapy. The physical therapy treatment received will be standardized based on the intervention protocol on which the decision rule was based. The first physical therapy session will be scheduled within 3 days after baseline assessment. Four treatment sessions will be administered within the first 4 weeks after the baseline assessment.

Each physical therapy session will begin with a brief assessment performed by the physical therapist, followed by administration of the spinal manipulation intervention with the same technique used in the development of the decision rule. The technique is performed with the patient supine. The physical therapist stands opposite the side to be manipulated and side-bends the patient away from the therapist. The patient interlocks his or her fingers behind the head. The physical therapist rotates the patient, and delivers a high-velocity, low-amplitude thrust to the anterior superior iliac spine in a posterior/inferior direction (fig. 1). After the manipulation, the therapist will note whether a cavitation (i.e., a “pop”) was heard or felt by either the therapist or patient. If a cavitation is noted, the physical therapist will proceed to exercise instruction. If no cavitation is noted, the patient will be repositioned, and the manipulation will be attempted again. If no cavitation occurs on the second attempt, the physical therapist will manipulate the opposite side. A maximum of 2 attempts per side is permitted. If no cavitation is produced after the fourth attempt, the therapist will proceed to instruction in the ROM exercise.

At the first treatment session, all patients will be instructed in a supine pelvic tilt range-of-motion exercise following the spinal manipulation intervention. Patients will be instructed to perform 10 repetitions in the clinic and 10 repetitions of the exercise 3-4 times daily at other times throughout the day. The second treatment session will be scheduled 2-3 days after the first. The second session will begin with administration of the spinal manipulation intervention as previously described. Following the manipulation, the range-of-motion exercise will be reviewed. At the second session the patient will also be instructed in the same series of strengthening exercises used in the validation study of the decision rule. The strengthening exercise series is designed to strengthen muscles of the trunk identified as primary stabilizers of the lumbar spine, and with some evidence to support their effectiveness in reducing the risk of recurrence in individuals with LBP. Patients will demonstrate the performance of these exercises during the treatment session, and will be instructed to perform the exercises daily until the next treatment session. The third and fourth treatment sessions will be scheduled at approximately 1 week intervals following the second session. During the third and fourth sessions, the physical therapist will review and progress the patient’s strengthening exercise program and answer any additional questions the patient may have. (see Appendix C for copies of treatment forms to be used by therapists and exercise handouts for patients).

Compliance with the treatment procedures for patients in the EI group will be monitored on two levels. The physical therapist will record on the daily treatment form the patient’s self-reported compliance with
the exercises assigned for daily performance on days between treatment sessions. The Investigators will review the physical therapist’s compliance with the treatment protocol by examining the daily treatment forms following completion of the intervention. All off-protocol events will be recorded, such as the use of use of modalities (heat, cold, ultrasound, etc.), or the use of manual therapy or exercise procedures not outlined in the treatment protocol.

The Principal Investigator (Dr. Fritz) will conduct training sessions for all physical therapists who will perform the manipulation and exercise intervention. Training will consist of written instructions for the performance of all study-related procedures, and hands-on practice of the techniques. Dr. Fritz is experienced in training physical therapists to successfully perform these treatment procedures, irrespective of the therapist’s experience with the techniques.145

C.8 Training of Study Personnel and Health Care Providers
All study personnel will be trained for their role in the project before data collection begins. During the first 3 months of the study, prior to the initiation of data collection, a Manual of Operations and Procedures (MOP) will be developed and compiled under the supervision of the Principal Investigator with input from the Co-Investigators. The MOP will be approved by the DSMB prior to initiation of subject recruitment. The MOP will contain paper copies of all questionnaires and forms to be used in this study and will provide detailed operational definitions for all study procedures. A detailed description of quality control procedures to be implemented will provided. The MOP will consist of the following chapters:

1) Research Protocol (overview of objectives, rationale for the study, study design, methodology, data analysis, and references),
2) Consent and Randomization Procedures
3) Surveys and Questionnaires (paper copies of all surveys/questionnaires and rationale for their use)
4) History and Physical Examination (copy of the clinical examination form and detailed operation definitions of how to perform all clinical examination procedures)
5) Spinal Manipulation and Exercise Training Programs
6) Training and Quality Control/Assurance (description of training and quality control procedures to insure consistency in procedures)
7) Data Management

The MOP will also contain all material necessary to conduct the training sessions outlined below (ie, outline, study protocol, treatment guidelines, case examples, competency examination, etc.) All study personnel will review and familiarize themselves with the MOP in detail prior to participation.

After familiarizing themselves with the MOP, the Principal Investigator (Dr. Fritz) and a Co-Investigator (Dr. Elizabeth Joy) will conduct training sessions based on the MOP for all clinical staff and study personnel during the second month of the study, prior to enrolling any subjects. Dr. Fritz, who is a licensed physical therapist, will oversee all training and will focus on training for physical therapy personnel. Dr. Joy is a primary care physician and is the Director of the Primary Care Sports Medicine Fellowship program, and the University of Utah's practice-based research network (UHRN). Dr. Joy will focus on training of primary care personnel. All clinical staff at the participating clinics (primary care and physical therapy staff) as well as study personnel will receive instruction in the administrative aspects of the study (informed consent, subject recruitment, data and safety monitoring and subject confidentiality issues, etc.). Clinical personnel in primary care and physical therapy will receive training in current evidence-based practice guidelines for managing patients with acute LBP, the rationale for the present study, and will be familiarized with all study-related treatment procedures as previously described. Training goals will be accomplished by providing theoretical and practical information related to this project and the procedures employed. Management strategies based on group assignment will be highlighted with case examples. All clinical staff and study personnel must complete this training before becoming eligible to participate in study-related procedures.

C.9 Data Management Procedures
Data management for this project will be maintained throughout the study by Caracal, Inc, using the BrightOutcome™ web-based data management system, and overseen by the Principal Investigator and the co-Investigators at the University of Utah. Prior to beginning data collection, the data collection interface will be developed by the BrightOutcome™ group with direction from the study Investigators.
During the data collection period, all study-related data will be entered into the central study database maintained by the BrightOutcome™ group, with weekly reports sent to the Investigators at the University of Utah. Periodically during the study, and at completion of the data collection, the database will transferred by via a secure file transmission protocol to the University of Utah Study Design and Biostatistics Center (SDBC) at the University of Utah Center for Clinical and Translational Science (CCTS). The Center is directed by Dr. Tom Greene, a co-investigator on this project. During the study the SDBC will provide additional statistical analyses using the SAS statistical software to supplement the BrightOutcome™ reports for data quality control and to monitor study progress.

The BrightOutcome™ System was developed to offer sophisticated support for patient-reported outcomes data collection and reporting, and has the necessary flexibility to permit integration of additional data reporting elements required for this project. Key outcomes management features of the BrightOutcome™ System relevant to this project include: 1) support for questionnaires with a variety of response types; 2) support for conditional branching logic in questionnaires; 3) collection of data and outcomes on the Internet, over the phone (via Interactive Voice Response), and/or on PDAs; 4) weekly system usage reports distributed automatically by e-mail; 5) monthly data exports; 6) longitudinal reports per respondent; and 7) HIPAA compliance. This system is currently used by the Centers of Disease Control and Prevention in a 5-year surveillance study to collect behavioral outcomes data from patients with HIV nationwide.

BrightOutcome™ is implemented with a tiered service-oriented architecture (SOA) leveraging open-source solutions and web services technologies. The tiered architecture contains the Presentation Tier, the Business Tier, and the Persistent Tier to improve system scalability and maintainability. The hosting environment at BrightOutcome™ uses Tomcat 5.0 as the Servlet 2.4/JSP 2.0 application server and MySql 4.1 as the backend relational database. Because our implementation conforms to industry standards, our system can also be hosted by other J2EE-compliant application servers such as WebSphere, WebLogic and Jboss, as well as any relational databases such as Oracle, DB2, and SQL Server.

Each patient entered into the study will receive a unique Patient Identifier that will be generated prior to beginning the study. Once a patient provides informed consent to participate in the study, the Study Coordinator will create a new Patient Profile in the web-based data collection platform. The Patient Profile will be identified by the unique Patient Identifier, and will not contain the patient’s name, Social Security number, or any other type of Personal Health Information data that could be used to identify the individual patient. The link between the Patient Identifier and the patient’s Personal Health Information will be maintained by the Principal Investigator, and will be available only to the Study Coordinator and Principal Investigator. After the Patient Profile is created, the patient will be able to input all self-report data directly via a desktop computer that will be available in the examination room using a web-based interface. All data entered by the patient into the database is identified only by the unique Patient Identifier.

All self-report patient data will be collected using the BrightOutcome™ data collection platform. Additional patient information (e.g., informed consent documents, patient demographic and physical examination forms completed by the Research Assistant) will be entered into the data collection platform by the Study Coordinator or Research Assistant as appropriate. Monthly data reports will be exported to the CCTS on a monthly basis using secure procedures. At the completion of data collection, the project database will be transferred to the researchers at the CCTS, and will be maintained on a server supplied by the University of Utah Health Sciences Center (UUHSC). The UUHSC utilizes technology from Hitachi Data Systems called the Universal Storage Platform for providing a virtualized storage area network. This network is maintained and supported by the University of Utah Health Sciences Information Technology Support. All programming for the analyses will also be stored on the same server. All data will be backed up onto removable media and stored in a secure location on a daily, weekly, and monthly schedule.

C.10 Internal Quality Control Procedures
Once data collection begins, the Principal Investigator (Dr. Fritz), will be in at least weekly communication with the Study Coordinator to monitor overall study progress, subject recruitment, quality control issues, and any external factors or relevant information that might have an impact on the safety or
ethics of the study (ie, subject recruitment, retention, patient scheduling for treatment and testing, practitioner compliance in administering the study interventions, etc.). The Principal Investigator, Co-Investigators, and Study Coordinator will meet to discuss these issues on a quarterly basis. Minutes will be recorded for each quarterly meeting by the PI, and a copy of the minutes will included as part of the interim reports. Additional meetings may be scheduled on an as needed basis to address specific issues that arise during the study.

The accuracy, quality, and completeness of all data collected will be monitored at the data collection interface by the BrightOutcome™ system. For example, there will be restrictions on the data entry process. Each self-report data point entered into the BrightOutcome™ system must pass identification checks using login names and passwords, range and type verification, required field verification, and duplicate record detection. These restrictions will minimize data input errors. In addition to passing point of entry edits, all data appended to the central database will be subjected to extensive monitoring procedures on a routine basis by the BrightOutcome™ system, and by the CCTS following completion of data collection. The Principal Investigator will be in regular contact with the Co-Investigators to discuss progress or trouble-shoot any problems with data entry or integrity.

C.11 Attention Effect
The design of this study creates the potential for an attention (ie, ‘placebo’) effect to exist – essentially that patients in the EI group might be inclined to experience better clinical outcomes based on receiving increased contact time with health care providers. However, this is a pragmatic study attempting to characterize the effectiveness and costs associated with each management strategy. Introducing a sham or placebo intervention into the UC group to make the groups equivalent with respect to contact time resembles an efficacy-based approach (one that might be more appropriate for the early stages in determining an intervention’s treatment effectiveness) rather than a pragmatic one. Incorporating an efficacy-based approach in this study would make the results less generalizable to the realities of routine clinical practice based on the introduction of artificial aspects to the patient’s treatment plan. This has the potential for mitigating outcome and artificially increasing costs, obscuring the ability to obtain an accurate estimation of the effectiveness and costs that would emerge in a real world clinical setting.

C.12 Data Analysis
Data analyses will be carried out by members of the Study Design and Biostatistics Center (SDBC) for the University of Utah Center for Clinical and Translational Research. The SDBC director, Dr. Tom Greene, will assume primary responsibility for the statistical analyses. Dr. Greene has extensive experience as a data coordinating center statistician in the design, conduct, and analysis of randomized trials, and also has recognized expertise in longitudinal data analysis. The SDBC includes nine MS and PhD biostatisticians with broad collective expertise, including Molly McFadden, who will carry out the statistical analyses for this project under the direction of Dr. Greene. Data analyses will be carried out using the statistical software SAS (SAS Institute Inc. Cary, NC 27513, USA).

During the conduct of the trial, the SDBC will supplement monthly reports provided by the BrightOutcome™ system with additional statistical summaries to monitor the progress of the trial, including the rates of recruitment and retention of subjects and adherence to the study interventions. These summaries will be used by the Principal Investigator and other study investigators to identify and correct any difficulties with the conduct of the trial on a timely basis. The SDBC will also internally review distributions of baseline and follow-up levels of outcome variables to detect extreme outliers or inconsistent results, and will notify the PI in the event that problematic data are detected.

Because data quality and data completeness will be monitored on an ongoing basis throughout the study, we expect that outstanding data discrepancies can be resolved and that the final study database can be closed within several weeks of the completion of data collection. The SDBC will write the statistical software for conduct of the primary and main secondary analyses during the final months of the patient follow-up period prior to database closure (see timeline in section 4.13). These steps will facilitate the timely completion of data analyses and dissemination of the study results after the completion of data collection. Following closure of the study database, the SDBC will provide summaries of socio-demographic (age, sex, race, etc.) and health characteristics of the sample (disability, pain intensity, etc). Descriptive statistics, including measures of central tendency (means, medians, etc) and dispersion (standard deviations, ranges) will be computed for continuous data as appropriate. Frequency
distributions will be estimated for categorical data. Transformations will be sought for variables that fail to meet distribution assumptions for further analyses. While we are cognizant that unadjusted comparisons between treatment groups are valid as long as randomization has been achieved, regardless of imbalances, pre-treatment characteristics of the two groups will be compared in order to assess chance imbalances associated with the randomization procedures. If differences are found, these variables may be used as covariates in post-hoc sensitivity analyses.

The proposed trial is designed to be pragmatic. Results will be analyzed according to intention-to-treat principles, meaning all patients randomly assigned to a treatment group will be included in the analyses, regardless of compliance with the treatment program. Estimates of the effect of the interventions will therefore include data from participants who discontinue treatments early, or are non-compliant with treatment recommendations. Therefore, adherence to the treatment regimen is one of the outcomes of interest, as well as a potential confounding factor. We will therefore compare rates of treatment compliance between groups. A “per-protocol” secondary analysis will be considered if rates of non-compliance are high, or disproportionate between groups. We propose to use approaches that enable use of available information obtained at baseline and follow-up visits from subjects with missing data by using multiple imputation to substitute for any missing follow-up scores. The validity of inference from these approaches is dependent on data being missing at random; this is difficult to test formally, though comparisons of baseline characteristics and available follow-up data from completers versus dropouts or non-compliant patients may provide empirical evidence for or against this assumption. Sensitivity analyses will also be performed (see below).

Because this study has a relatively small sample size and involves procedures associated with minimal risk to subjects; we will not perform any planned interim analyzes for between-group differences due to the risk of inflated Type I error rates imposed by performing multiple analyzes. Major outcomes will be analyzed for each of the follow-up points separately. The rationale for analyzing the data separately at each of the time points is to determine if different relationships exist between the outcomes and the interventions at the various time points. In particular, the 4-week assessment will evaluate response at the completion of the intervention period, the 12-week assessment will evaluate short-term response 8 weeks after completion of the intervention period, and the 1-year assessment will evaluate long-term persistence of response to the interventions.

We now lay out the analysis plan for each Specific Aim.

**Specific Aim #1:** “Compare the effectiveness of two different management strategies (UC vs. IE) for a subgroup of patients with LBP seen in primary care.”

**Primary and Secondary Analyses of Covariance.** For each quantitative functional outcome (including the Oswestry disability score, the numeric pain score, the FABQ work and physical activity scales, and the PCS total score), separate analyses of covariance will be used to compare the mean change in the outcome from baseline to each follow-up assessment (at weeks 4 and 12 and at year 1) between the IE and UC groups after controlling for the baseline level of the outcome being analyzed. Adjustment for the baseline level of the outcome being analyzed accounts for regression to the mean, thus increasing statistical power for estimation of the treatment effects. The primary analysis will compare the mean changes in the Oswestry score to week 12; comparisons between the IE and UC groups in the mean changes in the Oswestry at other time points and in the mean changes for other functional outcomes at all three follow-up time points will be interpreted as secondary analyses. Additional analyses of covariance will also be performed to compare changes in the functional outcome scores from week 4 to week 12 and from week 4 and year 1 between the treatment groups after controlling for the baseline level to evaluate whether treatment effects strengthen or attenuate over time.

Multinomial logistic regression analyses will be used to compare the proportions of patients reporting the respective categories of each of the 5 EQ-5D subscales at weeks 4 and 12 and at year 1 between the IE and UC groups after controlling for the baseline EQ-5D scores. If proportional odds assumptions are satisfied, the treatment comparisons will be performed using a proportional odds model to increase statistical power and to provide a more parsimonious presentation of the results.

**Multiple Comparisons.** The primary assessment of comparative effectiveness of the two interventions will be based on the primary analysis of the change in the Oswestry index from baseline to 12 weeks...
using a 2-sided alpha level (Type I error) of 0.05. Two-sided p-values will also be computed for secondary analyses and interpreted on a comparison-wise basis without formal adjustment for multiple comparisons. However, to assist in interpretation of the results, a bootstrap procedure will be employed to obtain the probability of obtaining at least one p-value smaller than the minimum observed p-value from among the secondary functional outcome measures considered, based on the observed correlations among the estimated treatment effects for each outcome.¹⁴⁸ This analysis will provide an assessment of the probability that a given nominally significant result would have occurred by chance given the number of tests conducted and the observed association among the different outcome variables.

**Multiple imputation for missing observations.** As described above, multiple imputation (MI) will be used to address missing outcome measurements. Under the MI approach, baseline and follow-up factors beyond the variable being analyzed can be incorporated into the imputation model to account for dependence of the missing data mechanism on other measured factors, such as predictors of patient adherence. We will apply the method of data augmentation using Markov Chain Monte Carlo (MCMC) to generate imputed values.¹⁴⁹ Four steps are involved: a) preparing the dataset for MI, which includes identifying all outcome variables likely to be involved in later planned or unplanned analyses, as well as likely predictors of missingness itself, evaluating distributions for normality and outliers and taking appropriate transformations to normality as needed; b) carrying out the MI, where variance and covariance estimates based on observed data are used to iteratively estimate maximum likelihood values for all participants and then multiple replacement values for each missing data point are drawn randomly from the posterior distribution and perturbed with error; c) analyses are carried out identically on all versions of the imputed data; and d) parameter estimates and tests are combined and adjusted for between-imputation variance to yield final statistical results.

As noted previously, the MI approach provides valid inferences for the treatment effect so long as data are “missing at random”, which means that the probability of missingness should not depend on the values of missing outcome measurements after accounting for the predictor variables in the imputation model. Moderate violations of the missing at random assumption would not be expected to substantially bias the results of the MI procedure since the proportion of patients with missing data is expected to be low. We will evaluate this assumption by applying the approach suggested by Carpenter et al¹⁶⁸ in which importance sampling is used to evaluate the implications of violations of the missing at random assumption following completion of the basic MI procedure. In the unlikely event that this approach suggests a strong dependence of the results on the missing at random assumption, further sensitivity analyses will be performed using formal pattern mixture models.¹⁶⁹ Should the sensitivity analyses indicate a strong dependence of our results on untestable assumptions regarding missing data, this limitation to the interpretation of our results will be noted and conclusions will be appropriately qualified.

**Specific Aim #2:** "Compare the costs (both direct and indirect) of the two different management strategies (UC vs. IE) for a subgroup of patients with LBP seen in primary care.”

In this project, we will examine costs from a societal perspective. We will collect both direct and indirect costs due to lost work productivity using the monthly web-based cost diary method previously explained. Direct and indirect costs will be computed and examined separately, then combined to examine the overall costs associated with each treatment approach. As recommended, we will value the cost data collected using standard unit prices.¹⁵⁰ Standard unit costs of direct healthcare costs, including medications, provider office visits, diagnostic imaging, surgical procedures, etc., will be determined using costs obtained from the Clinical Research Billing rates used at the University of Utah for healthcare services provided. We have previously used standardized cost data in a similar manner to examine direct healthcare costs associated with LBP management (see prior work, table 5). We will use the billing rate cost for the year in which the healthcare cost was accrued to account for changes in medical billing rates and inflation of healthcare costs. Lost productive time at work will be computed using methods described by Stewart and colleagues.²³,¹⁵¹ The monthly cost diaries specifically ask patients to indicate if they experienced work absence or reduced work performance (as a percentage of normal work performance) due to losing concentration, repeating a task, feeling fatigued at work, or doing nothing at work due to LBP. Lost productive time will be calculated as the number of days absent from work ("absenteeism") and the number of hours of reduced productivity at work ("presenteeism")
multiplied by the patient’s self-reported salary. Patients not employed outside the home (e.g., homemaker, full-time student) will also be asked to report absenteeism and presenteeism. Lost productive time for these patients will be based on the average salary for individuals matched for age and sex in the United States according to the Bureau of Labor Statistics (www.bls.gov). Sensitivity analyses will be used to examine the impact of differing methods of valuing direct and indirect costs.

To compare costs between the treatment groups, we will use both parametric and non-parametric methods. Because the mean is the most useful statistic for evaluating costs associated with the implementation of a treatment, we will calculate means and standard deviations for direct, indirect and overall costs for each group. We will further explore the distribution of direct, indirect, and total cost data for each treatment group by graphically displaying the data, and calculating median, quartile, and skewness values. Using univariate and multivariate techniques, we will determine the relationship between use of the two management strategies and the costs of care. Recognizing that cost data are typically positively skewed by a few patients with very high costs, violating the assumption of normality, we will use nonparametric bootstrapping methods with associated 95% confidence intervals for the comparison of mean costs between the groups. The bootstrap method avoids distributional assumptions and is therefore a preferred method for the analysis of cost data. The bootstrap method randomly selects patients from the study population and calculates the statistics of interest (mean and standard deviation). The distribution of these values is used to provide an approximation of its population sampling. We will bootstrap 2000 replications of pair-wise cost comparisons from the sample. Confidence intervals around the mean difference in costs between groups will then be calculated using bias corrected and accelerated (BCa) methods to permit comparison between treatment groups. Regression analyses will also be used to allow the costs to be adjusted for patient characteristics, including socioeconomic status, and co-morbidities. We will analyze sources of variation in costs, which will allow us to perform various sensitivity analyses. We will perform separate analyses for patients with complete follow-up cost diary data only, and from the intention-to-treat analysis with imputed costs as described below.

Missing cost data due to missing or incomplete cost diaries will be handled using multiple imputation (MI). As described above, MI handles missing data by replacing each missing observation with a set of multiple plausible values reflecting uncertainty about the true missing value. The results of analyses performed with the plausible values produce a single result that includes the uncertainty due to missing data. The MI method for handling missing cost data is preferred over alternatives such as last score forward or mean or median imputation.

Specific Aim #3: “Compare the cost-effectiveness of the two different management strategies (UC vs. IE) for a subgroup of patients with LBP seen in primary care.”

The analysis of cost-effectiveness will be based on the total costs and the clinical effectiveness (i.e., OSW scores) at the one-year follow-up. We will examine the mean costs and the mean change in OSW for each group. If either treatment group is associated with significantly less cost and superior clinical outcomes, the treatment may be recommended, and no additional cost-effectiveness analysis would be indicated. If either treatment group is associated with greater costs and inferior outcomes, the treatment cannot be recommended and no further analysis is indicated. Because the treatment costs incurred during the first four weeks will be greater in the EI group, it is plausible that the EI group could be associated with higher costs and better clinical outcomes. If this is the case, a cost-effectiveness analysis will be performed by examining the incremental cost-effectiveness ratio (ICER). The ICER is computed as the difference in costs between the two treatments divided by the difference in effectiveness. The formula for the ICER would be: (cost_{EI} - cost_{UC}) / (health outcome_{EI} - health outcome_{UC}). The ICER represents the cost per unit health benefit obtained by switching from one treatment approach to another, and provides insight into the economic feasibility of more wide-spread integration of the decision rule into clinical practice. Consistent with the recommendations of the Panel on Cost-Effectiveness in Health and Medicine, we will use quality-adjusted life years (QALYs), as the measure of health outcome. A QALY assigns a weight from 0 (death) to 1 (perfect health) to each of the health state based on the EQ-5D questionnaire. Valuations for United States have been developed. Uncertainty in the ICER estimate will be examined using bootstrapping techniques to examine cost-
effectiveness planes and acceptability curves. Sensitivity analyses will be used to explore the robustness of the cost-effectiveness results.

**C.13 Sample Size Estimation**

Assuming that at least 90% of patients complete the OSW at 12 weeks, enrollment of 110 subjects per group (total sample size 220 subjects) will provide at least 86% power to detect a difference of 7 points on the change in OSW to 12 weeks, assuming a standard deviation in the change in OSW of 16 points (treatment effect = 43.8% of one standard deviation). The MCID for the OSW has been estimated at 6 points. Our previous work with patients with acute LBP indicate that these estimates of anticipated effect size and standard deviation are realistic, and would be consistent with detecting an effect that is at least slightly in excess of the threshold for minimum clinical importance. This sample size will also provide at least 82% power to detect a treatment effect on the 1-year change in the OSW assuming the same standard deviation and 80% follow-up at 1 year. In addition, this sample size will provide at least 99% power to detect a clinically important difference of 2.0 on the NPRS assuming a standard deviation in the change in NPRS of 2.4 and at least 80% follow-up. These power calculations are slightly conservative because they assume no information will be obtained from patients with missing outcome data; we can expect slightly smaller minimum detectable effects (indicating greater power) under the MI procedure described in Section 4.12. These estimates of effect for the NPRS are also consistent with our prior research on patients with acute LBP.