PROTOCOL FOR RESEARCH INVOLVING HUMAN RESEARCH

Cervical Spondylotic Myelopathy Surgical Trial

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PROTOCOL FOR RESEARCH INVOLVING HUMAN SUBJECTS

TITLE OF PROJECT: Cervical Spondylotic Myelopathy Surgical Trial (CSM-S Trial)
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Study Sponsor: Patient-Centered Outcomes Research Institute (PCORI)

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II. DESCRIPTION OF STUDY

A. Purpose

1a. To determine if ventral surgery is associated with superior SF-36 PCS outcome at one year follow-up compared to dorsal (fusion or laminoplasty) surgery.

1b. To determine if, compared to pre-operative baseline status, both ventral and dorsal surgery for CSM improve symptoms of spinal cord dysfunction using mJOA.

2. To determine if, from a patient perspective, health resource utilization (out-of-pocket expenses and loss of productivity) for ventral surgery, dorsal fusion, and laminoplasty surgery are different.

3. To determine if cervical sagittal balance post-operatively is a significant predictor of SF-36 PCS outcome.

B. Background

Surgical decompression for CSM can improve its disabling symptoms, but surgical complications are common and many of these complications affect patients' overall health-related quality of life. The optimal surgical treatment, therefore, remains controversial, with disagreement between three main approaches: ventral decompression and fusion, dorsal decompression and fusion, or dorsal laminoplasty. This study aims to test the hypothesis that ventral surgery is associated with superior SF-36 PCS outcome at one year follow-up compared to dorsal approaches and that both ventral and dorsal surgery improve symptoms of spinal cord dysfunction using the mJOA score. A secondary hypothesis is that health resource utilization for ventral surgery, dorsal fusion, and laminoplasty surgery are different. A third hypothesis is that cervical sagittal balance post-operatively is a significant predictor of SF-36 PCS outcome.

C. Specific Location of Study

This is a multi-center trial. Subjects will be entered into the study from 10 separate centers.

D. Probable Duration of Project

Subjects will be recruited into the study over an 18 month period. All subjects will be followed for 5 years with clinical questionnaires.

E. Research Plan

1) Prospective, randomized multicenter trial. Approximately 159 randomized and 91 non-randomized patients would be recruited over 18 months with follow-up through 5 years.

2) Subjects (aged 45-80 years) with CSM (2 or more levels of spinal cord compression from C3 to C7) with 2 or more of the following symptoms/signs, clumsy hands, gait disturbance, hyperreflexia, up going toes, bladder dysfunction, or ankle clonus, will be treated with either ventral decompression/fusion, dorsal decompression with fusion, or dorsal laminoplasty. (Patients <45 years of age do not generally suffer from degenerative arthritis, which is why the lowest age of inclusion is 45).

3) Subjects with C2-C7 kyphosis > 5˚ (measured in standing neutral cervical spine radiograph), a segmental kyphotic deformity defined as 3 or more disc-osteophytes that extend dorsal to a C2-C7 dorsal-caudal line measured on cervical spine CT, structurally significant ossification of the posterior longitudinal ligament (OPLL), previous cervical spine surgery, or significant active health-related comorbidity (Anesthesia Class IV or higher) would be excluded from the study.

4) Each subject will be treated with either a Front Decompression/Fusion or Back of the Neck Decompression with fusion or Laminoplasty as part of standard clinical care. Decompression of the spinal canal to a diameter of at least 13 mm with restoration of cerebrospinal fluid flow around the spinal cord will be the goal, regardless of the approach. Surgical techniques have been standardized. Back of the neck decompression with fusion and laminoplasty are equivalent and preliminary evidence suggests that the outcomes are similar using the SF-36 PCS, which is the same questionnaire being used in this study (see table in Power Analysis section below).

5) Functional outcomes will be determined using well-known quantitative scales (SF-36, Oswestry Neck, mJOA, and EuroQol-5D). These instruments will be administered pre-op, 3 months, 6 months, and at 1 year. Additionally, functional outcomes instruments (SF-36, Oswestry Neck, and EuroQol-5D) will be collected annually at years 2,3,4 and 5.

6) Two independent neuroradiologists will review post-operative imaging at 3 months, and 1 year. Post-operative cervical spine MRI will be performed at 3 months to document satisfactory spinal cord decompression. Cervical spine flexion-extension radiographs will be obtained pre-operatively on all patients and at one year after surgery to assess cervical fusion and/ or radiographic complications. Standing cervical-thoracic-lumbar-sacral films will be obtained on all patients pre-operatively and at one year postoperatively (post-operatively in the randomized group only) to assess cervical as well as overall sagittal balance. A cervical spine CT will be obtained on patients at 1 year who have an NDI score > 30 or whose plain films suggest instability.

7) A study coordinator will collect data at 30 days and at 1 year to document any complications or re-operations. Additionally, the study coordinator will assess whether the patient is having any swallowing complications following surgery.

8) Health resource utilization information (including out-of-pocket expenses) will be obtained using patient diaries along with copies of all medical bills and receipts at 1 month, 3 months, 6 months, and 12 months post-operatively for all of the patients. Participants also will be asked to keep track of days missed from work and days unable to perform usual activities, in addition to days missed from work for medical treatments or evaluations.

F. Data and Safety Monitoring Plan

1) All serious unexpected adverse events (e.g. death within 30 days of operation) will be reported to the IRB within 24 hours. Any appropriate funding agencies or regulatory agencies would be notified as well.
2) Any serious anticipated adverse event (e.g. wound infection, pulmonary embolus) will be reported to the IRB whenever their magnitude or frequency exceeds expectations.
3) All other adverse events (including loss of privacy, significant economic harm) will be reported to the IRB on an annual basis or at the time that re-approval is sought. Any adverse event judged unlikely or unrelated to the study will also be included in an annual report for the IRB.

G. Statistical Considerations

a. Specific data variables being collected for the study.

The data collection sheets will be submitted along with this protocol. There will be several data sheets as follows:

1) Screening/Baseline, 1 Month, 3 Months, 6 Months, and 1 Year Visit Checklist
2) Informed Consent Process
3) Inclusion/Exclusion Criteria
4) Baseline Demographics
5) Spine surgeon's data sheet
6) 30-day and 1 Year morbidity data sheet
7) 1 Month, 3 Months, 6 Months, 1 Year Return to Work Status
8) 3 Month Swallowing Evaluation
9) Initial Hospital Admission Data Sheet
10) 3 Months and 1 Year Radiology
11) End of Study
12) Adverse Event Form
13) Serious Adverse Event Report Form

14) Serious Adverse Event Follow-up Report Form
15) SF-36 questionnaires (pre-op, 3 months, 6 months, 1, 2, 3, 4, and 5 years),
16) Neck Disability Index questionnaires (pre-op, 3 months, 6 months, 1, 2, 3, 4, and 5 years)
17) mJOA, (pre-op, 3 months, 6 months, and1year)
18) EuroQol-5D (pre-op, 3 months, 6 months, 1, 2, 3, 4, and 5 years)
19) Health Resource Utilization Diary (1 month, 3 months, 6 months, 1 year)
20) Report of Second Cervical Surgery
21) Death Form
22) Inpatient Hospital and Rehabilitation Utilization Data Sheet
23) Long term follow-up phone questionnaire (2, 3, 4, and 5 years)

b. Study endpoints.

Subjects will be followed for 5 years. The primary endpoint will be the 1-year change in SF-36 physical component summary score (PCS) at one year. Secondary endpoints will include the 1-year change in mJOA, NDI, and EuroQol-5D scores as well as the observed complication rates, health service utilization, work status, and sagittal balance measurements.

c. Statistical Methods.

Primary analyses will include all subjects randomized using an intent-to-treat approach. The primary endpoint is the 1-year change in Physical Component Summary of the SF-36 (SF-36 PCS) at one year. A likelihood-based analysis using a mixed model will be used to compare SF-36 PCS between groups. This model will adjust for baseline SF-36 PCS, as well as study surgeon using a random effects model. All time points will be included in the model, and each subject will contribute data for the time points at which they were assessed. The model enables a statistical comparison between treatment groups at each time point, though the comparison at the one-year time point will be the primary analysis. The primary advantage of the mixed model, when compared to commonly used methods such as complete case analysis and single imputation (e.g. last observation carried forward), is its flexibility in handling missing data. This analysis will assume that missing data occurs at random (i.e. the missing data value can be dependent on observed data, but independent of unobserved data). The inclusion of all follow-up time points in the model as well as covariates identified to be associated with withdrawal will assist in meeting this assumption and minimizing the risk of bias. Although the assumption for missing data is weaker under the likelihood based analysis compared to complete case analysis, a non-ignorable missing data mechanism is possible. Sensitivity analysis using selection and pattern mixture models will be employed to evaluate the robustness of conclusions to the missing at random (MAR) assumption.

Analysis Plan for Year 2 Outcomes

Year 2 outcomes for SF-36 and other continuous outcomes will be analyzed using linear mixed effects models (lme) that include both first and second year outcomes. The outcomes will be change from baseline. The purpose of the lme is to address missing second year outcomes. Since the year 2 assessments were missing mainly for logistical reasons (at 2 sites, research staff neglected to follow up with participants during specific time intervals), the missing at random (MAR) assumption of the lme is valid. The model will include treatment group, time period, and group*time interaction. To address within-subject correlation, patient id will be a random effect. There will be no adjustment for surgeon, since some surgeons had few patients, and no adjustment for baseline variables, since these were similar between groups. The treatment effect at year 2 will be tested using model contrasts. The year 1 treatment effect will be tested similarly, to confirm previous analyses obtained by t-test and anova. The models will be used to compare the 2 randomized groups and the "as treated groups." We will not address multiple comparisons for the "as treated" analyses because they are considered to be exploratory.

Analysis Plan for Return to Work

The return to work analysis will include all time periods up to 12 months (1, 3, 6, and 12 months). Groups will be compared via Kaplan-Meier plots and log-rank tests. To address multiple comparisons when comparing the as-treated groups pairwise comparisons will be performed at p=0.025 to account for 2 comparisons (DL vs DF and DL vs VF).

Analysis Plan for Health Resource Utilization

The research team has extensive experience conducting economic evaluations, including assessment of musculoskeletal interventions alongside RCTs and will conduct the proposed patient-oriented health resource utilization analysis. We will collect health resource utilization data alongside this RCT. The primary goal of this data collection will be to provide future patients with rigorous, high quality data regarding expected health resource utilization following different surgical procedures for CSM. The collected health resource utilization data will empower patients and will help patients choose the right procedure for their particular social and economic circumstances, as well as inform and be useful to all other stakeholders.

d. Power Analysis.

Sample size for Specific Aim #1a (Ventral surgery is associated with superior SF-36 PCS outcome at one year compared to dorsal (fusion or laminoplasty surgery):
Sample size estimates were calculated based on analysis of covariance model with $\alpha = 0.05$ at 80% and 90% power using Power Analysis and Sample Size software (PASS 2008, NCSS, LLC. Kaysville, Utah). The primary endpoint is the SF-36 PCS. This component of the SF-

36 is derived from the sums of scores of 21 items and thus exhibits distributional behavior commensurate with assumptions for parametric analysis. Our preliminary data suggest standard deviations for SF-36 PCS between 10 and 12 and correlations of baseline with one year SF-36 PCS between 0.6 and 0.7. *The following table describes the total sample size (2:3 ventral-dorsal randomization) required to detect a five point difference in SF-36 PCS one year post-surgery for various combinations of power, standard deviation and one year correlations under a fixed design*.

A minimum sample size of **137** patients provides at least 90% power (see Tables below):

Surgery (N)	Pre-op	Post-Op	Correlation between Pre- and Post-Op	Difference
Ventral (45)	35.5 ± 10.3	44.2 ± 11.7	0.64	+ 8.7 ± 8.2
Dorsal (70)	35.8 ± 11.3	39.8 ± 11.6	0.66	+ 4.0 ± 9.5
Dorsal Fusion (42)	35.0 ± 11.7	39.6 ± 12.4	0.65	+ 4.6 ± 10.0
Laminoplasty (28)	37.0 ± 10.9	40.1 ± 10.6	0.67	+ 3.1 ± 8.8
All patients (115)	35.7 ± 10.9	41.5 ± 11.8	0.64	+ 5.8 ± 9.7

Difference / SD	Correlation	80% Power / 5% Type I error (2-sided)			90% Power / 5% Type I error (2-sided)		
		$N_{Ventral}$	N_{Dorsal}	N	$N_{Ventral}$	N_{Dorsal}	N
5 / SD = 10	0.60	38	56	**94**	50	74	**124**
5 / SD = 10	0.65	40	59	**99**	53	78	**131**
5 / SD = 10	0.70	42	62	**104**	55	82	**137**

The sample size will be inflated by 5% to accommodate multiple significance testing using an Obrien-Fleming stopping boundary. Based on our preliminary data and pilot studies, withdrawal and loss-to-follow-up are not expected to be high. The sample size will be further inflated by 10% to accommodate attrition during the follow-up. Thus, 159 total patients will be recruited and randomized. **Ten high volume surgeons/ centers with the necessary expertise to permit patient randomization (16 randomized CSM cases/ site) have been selected to achieve the goal of enrolling 159 randomized patients over 18 months. An additional 91 nonrandomized patients will be enrolled into the study.**

Sample size for Specific Aim #1b (Compared to pre-operative baseline status, both ventral and dorsal surgery for CSM improve symptoms of spinal cord dysfunction at one year follow-up):

Using the sample size estimate for Specific Aim #1a and assuming ~10% attrition during follow-up, we expect to have 55 ventral surgery and 82 dorsal surgery patients (total = 137 patients) available for analysis. We will be able to detect changes from baseline pre-operative

mJOA status as small as 2.0 points (clinically important difference) for both the ventral surgery cohort and the dorsal surgery cohorts at one year. Assumptions for this sample size analysis include Type I alpha = 0.025, power at 90%, and range of within-subject correlation of 0.60 to 0.70.

H. Economic Considerations

No subject will incur any additional cost for participating in this study. All of the pre- and post-operative CT, MRI, flexion-extenstion x-rays, and pre-operative sagittal balance films are considered standard of care. The post-operative sagittal balance films, which only randomized patients will receive, are not considered standard of care and will be billed directly to the research fund. All costs associated with the adminstration of the study will be assumed by the Patient-Centered Outcomes Research Institute (PCORI) and/or the Lahey Comparative Effectiveness Research Institute.

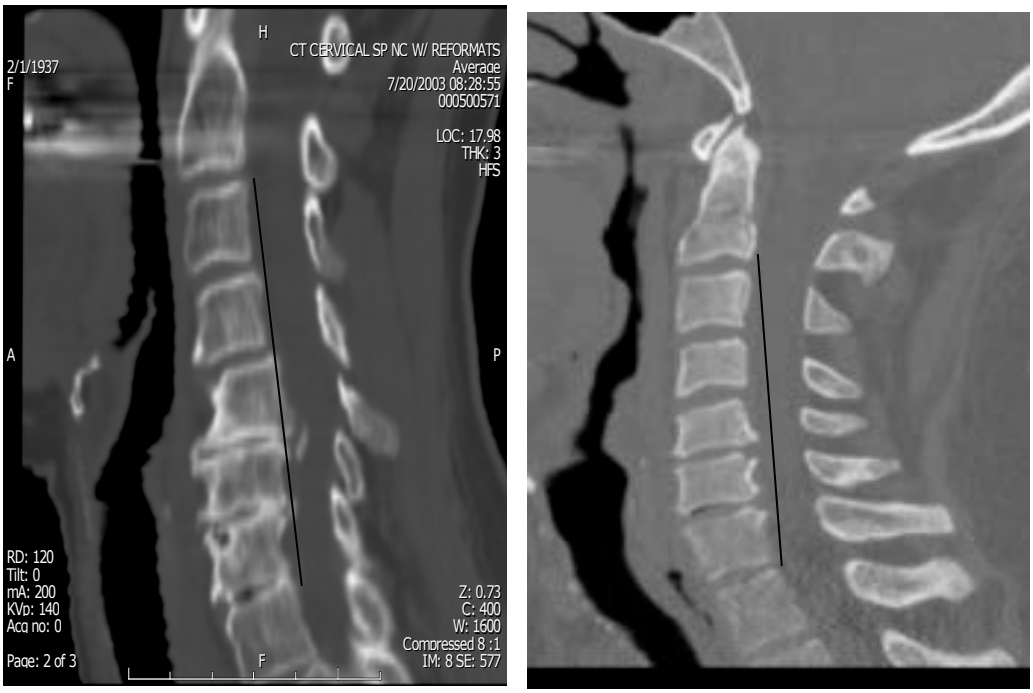
III. HUMAN SUBJECTS

A. Subject Population, Recruitment

Eligibility Criteria: Patients aged 45-80 years with CSM (≥2 levels of spinal cord compression from C3 to C7) presenting with ≥2 of the following symptoms/signs: clumsy hands, gait disturbance, hyperreflexia, up going toes, bladder dysfunction.

Exclusion Criteria: Any of the following: C2-C7 kyphosis>5º (measured in standing neutral cervical spine radiograph), segmental kyphotic deformity (defined by ≥3 osteophytes extending dorsal to a C2-C7 dorsal-caudal line measured on cervical spine CT), structurally significant ossification of posterior longitudinal ligament (OPLL – measured on cervical spine CT), previous cervical spine surgery, or significant active health-related co-morbidity (Anesthesia Class IV or higher).

EXCLUDE INCLUDE



Segmental-Cervical Kyphotic Deformity **Yes** **No**

Figure. Two cases with sagittal CT reconstructed images are depicted. A line is drawn from the dorsal caudal point of C2 to the dorsal caudal point of C7. If 3 or more levels of disc-osteophyte extend dorsal to the line, then the case has a segmental-cervical kyphotic deformity and the case would be excluded from the study. The C2-C7 Cobb angle is 5 degrees lordosis in both cases

Subjects will be enrolled by participating spine surgeons who are investigators in the study. These subjects will be identified within the existing practice of each surgeon. There will be no advertising or any effort to recruit subjects into the study from outside the practice of a study surgeon investigator.

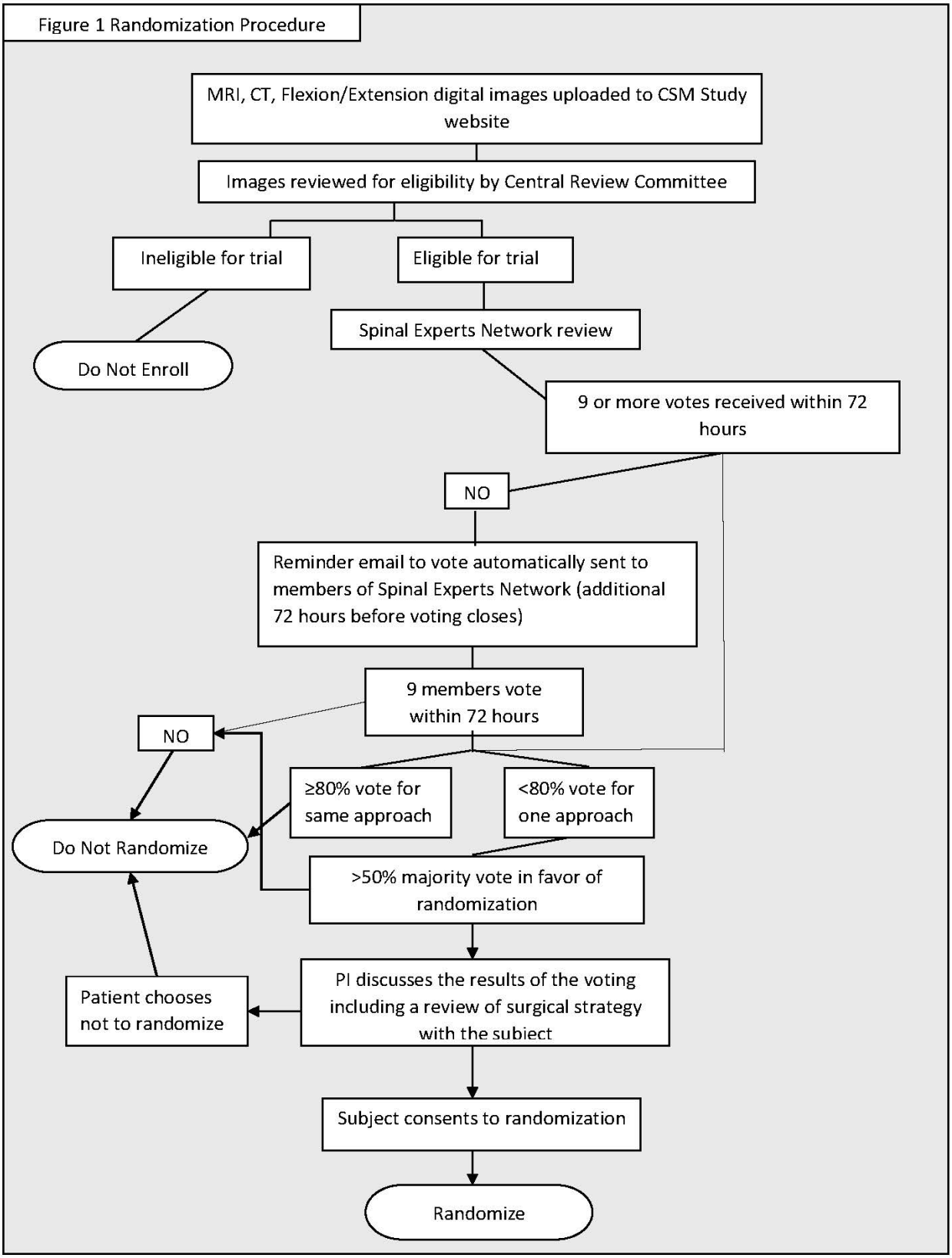
Once a patient has been screened, identified as having CSM, and agreed to participate in the trial by signing consent, the subject will undergo two reviews. The patient's images will first be reviewed by a Central Review Committee (Zoher Ghogawala, MD and Robert Whitmore, MD) to confirm eligibility. If the patient is deemed eligible, their images will then be reviewed by the spinal experts network. The patient's images will be uploaded onto the web-based platform, and an email will be generated and sent to all 15 members (15 CSM surgeon investigators) of the spinal experts panel. Each surgeon will be asked to vote: '**randomize**' or '**do not randomize**' and then to characterize his/her preferred surgical approach as **ventral** or **dorsal**. If after 72 hours, a majority (>50%) of the review panel (with at least 9 votes for a quorum) favor randomization (equipoise) and less than 80% select one approach (ventral or dorsal) over another, then the patient will be eligible for study randomization.

The results of the voting (the number of votes randomize or do not randomize and the number of ventral or dorsal votes) will be available to the patient both to increase patient trust and confidence in the recommendation for randomization, as well as to protect patients from undergoing randomization when one approach (ventral or dorsal) might be superior for that patient.

Patient Randomization (See Figure 1 Below)

Patients will be offered randomization in a subsequent one-hour meeting (following spinal experts review of the case) among study coordinator, surgeon, and patient if two conditions are met:

1) Central Review Committee (Zoher Ghogawala, MD and Robert Whitmore, MD) checked the images and clinical exam findings and found the patient eligible; and
2) Spinal Experts Panel confirmed patient's eligibility (>50% majority vote "randomize" and less than 80% select one approach (ventral or dorsal) over another).
   The patient can either consent to or decline randomization. There will be two categories of patients who have signed an IRB-approved consent to participate in the study:
   1. Randomized cohort: Upon confirmation of eligibility and patient acceptance of randomization, the study coordinator will access the assignment by logging into the secure website (https://pip.acesis.com) with a password and will obtain the randomization assignment from the web-based platform with its pre-programmed blocked (2, 4, or 6 subjects/block) stratified site-specific randomization scheme. Randomized patients will be followed for five years.
   2. Non-Randomized cohort: The non-randomized cohort will consist of all patients who meet entry criteria but for whom equipoise is not confirmed by spinal experts panel. It also will consist of patients who do not consent to randomization. All non-randomized patients will be asked to complete all the study questionnaires and will be followed for five years. The non-randomized cohort will not have an independent radiologist evaluation.



B. Source of Research Material

Subjects will be identified from within the practice of spine surgeon investigators.

C. Consent Procedures

Subjects will be identified by investigator spine surgeons within their practice. Subjects will be registered by the surgeon's office. The subjects will be clearly told by the surgeon that participation is voluntary and that a decision not to participate will not affect their medical care in any way. The patient will sign a consent form with the spine surgeon after having a chance to review the study protocol and consent form with family and others. The subjects will sign the consent with the surgeon during a separate office visit prior to surgery. A spine study coordinator will then contact the patient for more detailed questions regarding registration for the study (e.g. home phone number and home address). The study coordinator will also ask the patient whether he is comfortable enrolling in the study.

D. Risks

All of the subjects in the study will be surgical candidates and would have had surgery recommended even if they were not involved in a study.

E. Protection of Subjects

All subjects will receive standard follow-up by the treating surgeon. All of the surgical procedures are considered standard care and none are considered investigational. The results will be made available to the subjects prior to publication. Any significant findings regarding the overall safety of either procedure at any site will be brought to the attention of all subjects in the study once all of the appropriate IRB committees have been notified. The confidentiality of all subjects will be assured by assigning all subjects a code and by removing all identifying information from questionnaires. Data entered into the study web site will be encrypted using the current industry standard to protect patient confidentiality.

Once the database is analyzed, all patient identifiers will be removed from the final database. The database will be kept at the Lahey Comparative Effectiveness Research Institute. No patient identification would be linked to the data.

F. Data and Safety Monitoring Plan

(As outlined above in Research Plan)

G. Confidentiality

Each subject will be assigned a code number and no identifying information will leave the Lahey Comparative Effectiveness Research Institute. Data from each patient will be

sent to the Lahey Comparative Effectiveness Research Institute or will be entered into the study web site which is encrypted to protect patient confidentiality using the current industry standard. All patient identifiers will be removed from the final database.

H. Potential Benefits

Subjects will be followed closely and might gain from the increased observation. Each subject will be offered a free review of their radiographic images by a panel of spinal experts. The multiple opinions from other surgeons will be used to help educate subjects about their condition. The subjects will have the opportunity to learn about the results of the study through frequent updates available from the Lahey Comparative Effectiveness Research Institute or from the public web page (https://pip.acesis.com).

Society at large might benefit from the results of this study. The study will be useful for spine surgeons to determine if health resource utilization differs among the three surgical procedures for people with cervical spondylotic myelopathy.

I. The Risk-Benefit Ratio

All subjects entered into the study would be surgical candidates for either surgical procedure in the study. All of the surgical procedures used in this study are routine and constitute standard care. No procedure is considered investigational. Therefore, no subject will have any increased risk of physical injury as a result of participation in the study. The subjects will have access to the Study website and will be informed of the results of the study prior to publication. The increased level of observation will possibly benefit some of the subjects. The subjects will know that they are helping society at large because the results of the study will be useful for spine surgeons to help future subjects determine which surgical procedure is best for people with cervical spondylotic myelopathy.

Appendix I: Study Schema