Cervical Spondylotic Myelopathy Surgical Trial: Randomized, Controlled Trial Design and Rationale

BACKGROUND: Cervical spondylotic myelopathy (CSM) is the most common cause of spinal cord dysfunction in the world. There are significant practice variation and uncertainty as to the optimal surgical approach for treating CSM.

OBJECTIVE: To determine whether ventral surgery is associated with superior Short Form-36 Physical Component Summary outcome at the 1-year follow-up compared with dorsal (laminecmytomy/fusion or laminoplasty) surgery for the treatment of CSM, to investigate whether postoperative sagittal balance is an independent predictor of overall outcome, and to compare health resource use for ventral and dorsal procedures.

METHODS: The study is a randomized, controlled trial with a nonrandomized arm for patients who are eligible but decline randomization. Two hundred fifty patients (159 randomized) with CSM from 11 sites will be recruited over 18 months. The primary outcome is the Short Form-36 Physical Component Summary score. Secondary outcomes include disease-specific outcomes, overall health-related quality of life (EuroQOL 5-dimension questionnaire), and health resource use.

EXPECTED OUTCOMES: This will be the first randomized, controlled trial to compare directly the health-related quality-of-life outcomes for ventral vs dorsal surgery for treating CSM.

DISCUSSION: A National Institutes of Health-funded (1R13AR065834-01) investigator meeting was held before the initiation of the trial to bring multiple stakeholders together to finalize the study protocol. Study investigators, coordinators, and major stakeholders were able to attend and discuss strengths of, limitations of, and concerns about the study. The final protocol was approved for funding by the Patient-Centered Outcomes Research Institute (CE-1304-6173). The trial began enrollment on April 1, 2014.

KEY WORDS: Cervical spondylotic myelopathy, Randomized clinical trial, Outcomes


PRINCIPAL INVESTIGATOR

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STUDY SITES

1. Lahey Hospital and Medical Center; site investigator: Subu Magge, MD
2. University of Medicine and Dentistry—New Jersey; site investigator: Robert Heary, MD
Cervical spondylotic myelopathy (CSM) is the most common cause of spinal cord dysfunction in the world. The condition presents insidiously and is defined in terms of its clinical symptoms (gait instability, bladder dysfunction, fine finger motor difficulties) and signs (hyperreflexia, Hoffman sign, ankle clonus, spasticity, alteration of joint position sense). CSM is caused by dynamic repeated compression of the spinal cord from degenerative arthritis of the cervical spine. Proposed mechanisms include axonal stretch-associated injury and spinal cord ischemia from compression of larger vessels and impaired microcirculation. Surgery to decompress and stabilize the spine is often advocated for severe or progressive symptoms, with mixed results. About two-thirds of patients improve with surgery, whereas surgery is not successful in 15% to 30% of cases. In 2000, > 112,400 cervical spine operations for degenerative spondylosis were performed in the United States (100% increase over the past decade), with CSM accounting for nearly 20% of cervical spine operations in the United States. Annual hospital charges for CSM surgery exceeded $2 billion in 2000. In addition, CSM is associated with substantial postsurgical outpatient expenses (eg, physician visits, imaging, physical therapy, medications).

There is significant uncertainty as to the optimal surgical approach for treating CSM. Three alternative surgical approaches currently are widely used in contemporary US surgical practice: ventral decompression and fusion, dorsal decompression and fusion, and laminoplasty. Recently, the Institute of Medicine designated CSM as 1 of the top 100 national health research priorities for comparative effectiveness research. Our previous work suggests that most American cervical spine experts (both orthopedic and neurological surgeons) believe that there is sufficient clinical equipoise to support a comparative randomized clinical trial (RCT) if the study population is carefully defined. Several other important reasons justify a trial of surgical approaches for CSM at this time. First, the complication rate for CSM surgery is high (17% in a recent prospective study). This complication rate is particularly noteworthy in patients >74 years of age who represent a growing segment of the US population. Second, clinical outcomes are unsatisfactory even in up to 30% of cases. Third, ventral surgery might be associated with significantly better health-related quality-of-life outcomes compared with dorsal approaches. Finally, the adjusted 5-year reoperation rate for dorsal surgery (17.7%) has been reported to be significantly higher than for ventral surgery (12.1%; P < .001) by members of our study team.

The CSM-S trial was recently awarded funding from both the NIH (1R13AR065834-01) and the PCORI (CE-1304-6173). The purpose of this article is to describe the rationale for the study and to present the study protocol for the CSM-S trial.

**Rationale for CSM-S Study**

A nonrandomized pilot study enrolled 102 patients comparing ventral and dorsal surgery for CSM. Both ventral and dorsal surgeries were associated with improvement in myelopathy scores, but ventral surgery was associated with superior health-related QOL outcomes compared with dorsal approaches (Figure 1). Poor sagittal balance (C2-C7) was observed more frequently in dorsal surgery cases and was identified as an independent risk factor for poorer health-related QOL outcome after surgery for CSM (Figure 2).

**STUDY GOALS AND OBJECTIVES**

The objective of the CSM-S trial is to compare ventral decompression with fusion vs dorsal surgery for patients with multilevel CSM with the following specific aims:

**Specific Aim 1**

1a. Ventral surgery will be associated with superior Short Form-36 Physical Component Summary (SF-36 PCS) outcome at 1-year follow-up compared with dorsal (laminectomy/fusion or laminoplasty) surgery.

1b. Compared with preoperative baseline status, both ventral surgery and dorsal surgery for CSM will improve symptoms of spinal cord dysfunction as assessed with the modified Japanese Orthopedic Association score.

**Specific Aim 2**

2. From a patient perspective, health resource use (out-of-pocket expenses and loss of productivity) for ventral surgery, dorsal fusion, and laminoplasty surgery will be different.

**Specific Aim 3**

3. Cervical sagittal balance postoperatively will be a significant predictor of SF-36 PCS outcome.
STUDY DESIGN

The study is a multicenter, controlled RCT (www.ClinicalTrials.gov; unique identifier: NCT02076113). The study also includes a nonrandomized arm for patients who are eligible for but refuse randomization. In addition, patients who are eligible but for whom equipoise is not confirmed by the Spinal Experts Panel are entered into the nonrandomized arm.

METHODOLOGY

Subjects

Inclusion Criteria

Inclusion criteria for the trial are age of 45 to 75 years and CSM identified with $\geq 2$ levels of spinal cord compression from C3 to C7 by imaging with magnetic resonance imaging or an equivalent study. Patients will have $\geq 2$ of the following symptoms or signs: clumsy hands, gait disturbance, hyperreflexia, up-going toes, bladder dysfunction, or ankle clonus. Patients will be treated with either ventral decompression with fusion, dorsal decompression with fusion, or dorsal laminoplasty. The Central Review Committee will review imaging to evaluate for radiographic exclusion criteria. In addition, subjects will meet inclusion criteria if a majority of the Spinal Expert Network who review the imaging concur that the case meets randomization criteria and $\geq 80\%$ would recommend the same procedure in a nonrandomized scenario (see below).

Exclusion Criteria

Subjects with C2-C7 kyphosis $>5$ cm (measured in standing neutral cervical spine radiograph), a segmental kyphotic deformity defined as $\geq 3$ disk osteophytes that extend dorsal to a C2-C7 dorsal-caudal line measured on cervical spine computed tomography (CT) or magnetic resonance imaging, structurally significant ossification of the posterior longitudinal ligament, previous cervical spine surgery, or significant active health-related comorbidity (anesthesia class IV or higher) will be excluded from the study. The Central Review Committee will review imaging to evaluate for radiographic exclusion criteria.

Randomization

The randomization scheme will be 2:3 ventral to dorsal. There was significant interest in having outcomes data comparing dorsal laminectomy and fusion (a more commonly conducted procedure in the United States) with dorsal laminoplasty, the most commonly performed procedure for CSM worldwide. We determined that a 3-armed RCT was not feasible. Therefore, we chose to increase the randomization to the dorsal arm and to increase the sample size to allow post hoc nonrandomized comparisons of these 2 dorsal procedures.
Spinal Experts Network Review

One of the most important barriers to performing high-quality RCTs in surgery is patient accrual. Participation in RCTs often is limited by a lack of sufficient equipoise on the part of both the treating surgeon and the patient. We have taken several proactive and innovative steps to improve patient consent to randomization, including the development of a novel Web-based Spinal Experts Network that was demonstrated to facilitate and increase patient enrollment and randomization. In this approach, each expert reviews the radiographic images of eligible patients and makes 2 assessments: the preferred approach and whether for this case there is clinical equipoise for use of either a dorsal or a ventral surgical approach (Figure 3). This provides scientific rigor to the definition of equipoise on an individual-patient basis. It also provides the patient with multiple “second opinions,” increasing the patient’s interest in participating in the RCT and trust in the appropriateness of randomization.

For the CSM-S trial, once a patient has been screened, has been identified as having CSM, and has agreed to participate in the trial by signing consent, the subject will undergo 2 reviews. The patient’s images will first be reviewed by a Central Review Committee (composed of 2 surgeon investigators from the primary site) to confirm eligibility. If the patient is deemed eligible, his or her images will then be reviewed by the Spinal Experts Network. The patient’s images will be uploaded onto the Web-based platform, and an e-mail will be generated and sent to all 15 members (10 CSM surgeon investigators and 5 senior noninvestigator spine surgeons) of the Spinal Experts Panel. Each surgeon will be asked to vote either “randomize” or “do not randomize” and then to characterize his/her preferred surgical approach.

FIGURE 3. A through D, flexion-extension images, sagittal computed tomography, and magnetic resonance imaging images for cervical spondylotic myelopathy case judged to be eligible for study. E, Spinal Experts Panel review. All 9 investigators found the case eligible for randomization. The preferred approach is also shown for each of the voting investigators.
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 <80% select 1 procedure over another, then the patient will be eligible for study randomization (Figure 4).

The results of the voting (the number of votes for randomize/do not randomize and the number of ventral or dorsal votes) will be made available to the patient both to increase patient trust and confidence in the recommendation for randomization and to protect patients from undergoing randomization when 1 approach (ventral or dorsal) might be superior for that patient. Patients will be offered randomization if 2 conditions are met: the Central Review Committee checked the images and clinical examination findings and found the patient eligible, and the Spinal Experts Panel confirmed the patient’s eligibility (>50% majority vote to randomize and <80% select 1 procedure over another).

The patient can either consent to or decline randomization. There will be 2 categories of patients who have signed an Institutional Review Board (IRB)—approved consent to participate in the study:

1. Randomized cohort: On confirmation of eligibility and patient acceptance of randomization, the study coordinator will access the assignment by logging into the secure study Web site (www.csm-study.org) with a password and will

![Figure 4](image-url)
obtain the randomization assignment from the Web-based platform with its preprogrammed blocked (5, 10, or 15 subjects per block) stratified site-specific randomization scheme.

2. Nonrandomized cohort: The nonrandomized cohort will consist of all patients who meet entry criteria but for whom equipoise is not confirmed by the Spinal Experts Panel. In addition, patients who do not consent to randomization will be in this cohort.

**CSM-S Trial Web Site**

In preparation for this trial, we constructed and tested a HIPAA (Health Insurance Portability and Accountability Act)—compliant Web-based platform for the study (www.csm-study.org) (Figure 5). In addition to facilitating direct data entry at each site by local study coordinators, this Web platform provides the mechanism for the Spine Experts Panel to vote on each case. When a new case is enrolled in the study, the patient images are deidentified before being uploaded to the Web site for review. Members of the Spine Experts Network are automatically sent an email when a patient’s images are ready for review. The e-mail will contain a link to the patient case in question, enabling rapid assessment and voting by investigators.

**Study Interventions**

**Surgical Treatment**

All patients will undergo surgery as 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 is the goal, regardless of the approach. Surgical techniques have been standardized, as summarized below.

**Ventral Surgery.** Ventral decompression and fusion will be performed using a multilevel disectomy (including partial or single-level corpectomy) with fusion and plating. Allograft will be used at each disk space, and all compressive osteophytes...
will be removed with the use of the operating microscope. Fixation will be performed with rigid, semi-constrained, or dynamic titanium plates to optimize fusion and to minimize complications.\textsuperscript{26,27} 

\textbf{Dorsal Surgery.}

The surgeon will choose either dorsal laminectomy plus fusion or dorsal laminoplasty.

\textit{Dorsal Laminectomy and Fusion.} Dorsal decompression and fusion will be performed using midline cervical laminectomy with the application of lateral mass screws and rods for rigid fixation.\textsuperscript{11,19} All surgeons will use local bone and allograft as needed to perform a lateral mass fusion, which typically will include 1 level rostral to the levels decompressed.

\textit{Dorsal Laminoplasty.} Laminoplasty will be performed using an open-door approach with the application of plates and screws at each treated level. Ceramic or allograft laminar spacers (surgeon’s choice) can be used with plates and screws to expand the canal diameter.\textsuperscript{28,29}

\section*{OUTCOME MEASURES AND FOLLOW-UP}

\subsection*{Primary Outcome Measure}

The primary outcome measure is the SF-36 PCS score. PCS scores will be calculated using population-adjusted norms to generate normalized scores with a mean $\pm$ SD of 50 $\pm$ 10. The SF-36 (version 2) will be administered in the office by a study coordinator preoperatively and at 3 months, 6 months, and 1 year postoperatively. A clinically meaningful difference in the SF-36 PCS scores will be defined as 5 points.\textsuperscript{30,31}

\subsection*{Secondary Outcome Measures}

Two validated disease-specific outcomes measures (modified Japanese Orthopedic Association\textsuperscript{32} and Neck Disability Index \textit{[NDI]}\textsuperscript{33}) will be measured preoperatively and at 3 months, 6 months, and 1 year postoperatively. Preference-based health-related QOL measures reflecting US population values for calculation of quality-adjusted life-years will be used. Preference-based outcome measures produce a single outcome score on an interval scale anchored at 0 (death) and 1 (perfect health). The assessment of health state preferences will be performed with the EuroQOL 5-dimension questionnaire (EQ-5D).\textsuperscript{34} A separate analysis will compare use of SF-6D and EQ-5D.\textsuperscript{35-37} Preference-based QOL will be assessed with the EQ-5D\textsuperscript{38} and SF-6D\textsuperscript{39} at the same intervals as the primary outcome measure, SF-36 PCS, as will return to work status and disability benefits and payments.\textsuperscript{38} In addition to days missed from work for medical treatments or evaluations, participants will be asked to keep track of days missed from work and days unable to perform usual activities. Major adverse outcomes will be recorded at 30 days and 1 year postoperatively. Health resource use information (including out-of-pocket expenses) will be obtained from patient diaries, along with copies of all medical bills and receipts, at 1, 3, 6, and 12 months postoperatively for all patients. At 1 year postoperatively, full standing sagittal cervical-thoracic-lumbar-sacral radiographs will be obtained to calculate cervical C2-C7 sagittal balance, overall spinal sagittal balance, and cervical C2-C7 kyphosis or lordosis (in randomized patients only).

\section*{SAMPLE SIZE}

Sample size estimates were calculated based on analysis of covariation 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 end point 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 observational data showed a SF-36 PCS difference score of 8.7 for ventral surgery compared with 4.0 for dorsal procedures, with standard deviations between 10 and 12 and correlations of baseline with 1-year SF-36 PCS between 0.6 and 0.7. \textsuperscript{21} Tables 1 and 2 describes the total sample size (2:3 ventral to dorsal randomization) required to detect a 5-point difference in SF-36 PCS 1 year after surgery for various combinations of power, standard deviation, and 1-year correlations under a fixed design. A minimum sample size assuming a 0.70 correlation of 137 patients provides at least 90\% power. The sample size was inflated by 5\% to accommodate multiple significance testing using an O'Brien-Fleming stopping boundary. From our preliminary data and pilot studies, withdrawal and loss to follow-up are not expected to be high. The sample size was further inflated by 10\% to accommodate attrition during the follow-up. Thus, 159 total patients will be recruited and randomized. On the basis of our prior work in terms of both refusal rates and ineligible subjects, we anticipate that 91 nonrandomized patients will be enrolled into the study.

\section*{STUDY SITES AND SURGEONS}

Both orthopedic and neurological surgeon leaders were selected for inclusion in this study on the basis of clinical volume and expertise and their participation in multiple preliminary investigator meetings. The clinical volume for each of the 11 study sites included in this study is summarized in Table 3. All surgeons submitted radiographic evidence of their clinical quality for each of the surgical procedures.

\section*{FOLLOW-UP}

\textbf{Clinical Follow-up (1 Year): End-Point Assessment}

Postoperative clinic visits (outcomes assessment) will occur at 1 month, 3 months, 6 months, and 1 year postoperatively (Figure 6). Health resource use diaries will be completed at all time points. All complications will be reported to the central project manager within 48 hours. The study coordinator will record the following: 1. Thirty-day complications: death, myocardial infarction, pulmonary embolus, rehospitalization, recurrent laryngeal nerve injury, new hoarseness, new neurological deficit (eg, C5 palsy), infection, dysphagia at 30 days resulting in weight loss...
and/or formal swallow evaluation and therapy, esophageal perforation, and reoperation.

2. Delayed complications: reoperation, fusion complication, problems with instrumentation, deformity, and rehospitalization.

Postoperative Imaging Analysis (3 Months and 1 Year)

Postoperative imaging of randomized patients (deidentified and on compact disks) will undergo independent radiographic review at the central reading site (Figure 6). Postoperative cervical spine magnetic resonance imaging will be performed at 3 months to document satisfactory spinal cord decompression. Cervical spine flexion-extension radiographs will be obtained at 1 year after surgery to assess cervical fusion or radiographic complications. Standing cervical-thoracic-lumbar-sacral films will be obtained at 1 year postoperatively to assess cervical and overall sagittal balance. Cervical spine CT scans will be obtained at 1 year if the patient has an NDI >30 or if plain films suggest instability.

5-Year Extended Follow-up

Long-term follow-up will occur annually in years 2 through 5 postoperatively (Figure 6). It will include the SF-36, NDI, and EQ-5D questionnaires, as well as a long-term follow-up phone questionnaire that will address complications (including reoperations) and return to work status.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

All patient questionnaire data will be recorded on IRB-approved case report forms with study identification numbers but without patient identifiers. A HIPAA-compliant data platform Web site has been created to manage the data for the trial. Hard copies of each case report form will be faxed or scanned and sent to the central data management center (Lahey Comparative Effectiveness Research Institute).

Primary analyses will include all subjects randomized with an intention-to-treat approach. The primary end point is the SF-36 PCS at 1 year. A likelihood-based analysis using a mixed model will be used to compare SF-36 PCS scores between groups. This model will adjust for baseline SF-36 PCS and 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, although the comparison at the 1-year time point will be the primary analysis. The primary advantage of the mixed model compared with commonly used methods such as complete case analysis and single imputation (eg, last observation carried forward) is its flexibility in handling missing data. This analysis will assume that missing data occur at random (ie, 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 and 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 with complete case analysis, a nonignorable missing data mechanism is possible. Sensitivity analysis using selection and pattern mixture models will be used to evaluate the robustness of conclusions to the missing-at-random assumption. Analysis of continuous secondary outcomes such as the postoperative sagittal balance and a disease-specific QOL measure, the NDI, will be performed similarly to that described for the primary outcome measure.

### Table 1. Preoperative and Postoperative Short Form-36 Physical Component Summary Scores and Correlations Based on Preliminary Data

<table>
<thead>
<tr>
<th>Surgery (n)</th>
<th>Preoperative</th>
<th>Postoperative</th>
<th>Correlation Between Preoperative and Postoperative</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventral (45)</td>
<td>35.5 ± 10.3</td>
<td>44.2 ± 11.7</td>
<td>0.64</td>
<td>8.7 ± 8.2</td>
</tr>
<tr>
<td>Dorsal (70)</td>
<td>35.8 ± 11.3</td>
<td>39.8 ± 11.6</td>
<td>0.66</td>
<td>4.0 ± 9.5</td>
</tr>
<tr>
<td>Dorsal Fusion (42)</td>
<td>35.0 ± 11.7</td>
<td>39.6 ± 12.4</td>
<td>0.65</td>
<td>4.6 ± 10.0</td>
</tr>
<tr>
<td>Laminoplasty (28)</td>
<td>37.0 ± 10.9</td>
<td>40.1 ± 10.6</td>
<td>0.67</td>
<td>3.1 ± 8.8</td>
</tr>
<tr>
<td>All patients (115)</td>
<td>35.7 ± 10.9</td>
<td>41.5 ± 11.8</td>
<td>0.64</td>
<td>5.8 ± 9.7</td>
</tr>
</tbody>
</table>

### Table 2. Total Sample Size (2:3 Ventral-Dorsal Randomization) Required to Detect a 5-Point Difference in Short Form-36 Physical Component Summary 1 Year After Surgery for Various Combinations of Power, Standard Deviation, and 1-Year Correlations Under a Fixed Design

<table>
<thead>
<tr>
<th>Difference/SD</th>
<th>Correlation</th>
<th>Ventral, n</th>
<th>Dorsal, n</th>
<th>Total, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/SD = 10</td>
<td>0.60</td>
<td>38</td>
<td>56</td>
<td>94</td>
</tr>
<tr>
<td>5/SD = 10</td>
<td>0.65</td>
<td>40</td>
<td>59</td>
<td>99</td>
</tr>
<tr>
<td>5/SD = 10</td>
<td>0.70</td>
<td>42</td>
<td>62</td>
<td>104</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>80% Power/5% Type I Error (2-Sided)</th>
<th>90% Power/5% Type I Error (2-Sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventral, n</td>
<td>Dorsal, n</td>
</tr>
<tr>
<td>50</td>
<td>74</td>
</tr>
</tbody>
</table>
DISCUSSION

The CSM-S RCT is designed to compare the effectiveness of ventral vs dorsal approaches for the surgical management of CSM, a common degenerative condition of the cervical spine associated with significant morbidity for which the optimal surgical treatment for improved long-term function is unknown. The trial is innovative, as are the methods to address clinical equipoise for the individual subject. The Spinal Experts Panel methodology aims to increase trust on the part of patients and in turn increase their willingness to participate in an RCT, and it ensures that for a specific patient there is no consensus among experts as to the best treatment approach. The trial is innovative in its use of stakeholder engagement at the patient, provider, payer and funder levels, which we believe will increase the dissemination of the findings to the relevant groups and increase likelihood of the results to have an impact on clinical care.

NIH-Funded Initial Investigator Meeting

The NIH awarded an R13 grant to fund an initial investigator meeting for the CSM-S trial. The objective was to bring together major stakeholders and investigators to review the current evidence and clinical protocol and to agree on a clinical population to be included in the RCT. The conference was held on January 23-24, 2014, in National Harbor, Maryland (Figure 7), and was conducted by Dr Ghogawala, national study principal investigator (PI), of Lahey Hospital and Medical Center, Burlington, Massachusetts. There were a total of 42 attendees, including the study investigators, radiologists, neurological monitoring experts, health economists, the CSM-S advisory board, all study coordinators, 2 spine patients, a PCORI representative, and a representative from the Centers for Medicare & Medicaid Services. The environment provided an excellent opportunity to discuss the trial protocol and for attendees to address concerns. As a result of the productive discussion at the end of the conference, several major changes were made in the CSM-S protocol:

1. Exclusion criteria were amended. Specifically, developmental narrowed spinal canal was removed from the exclusion criteria, and several other criteria were revised to be more specific.
2. Required radiographic assessments were amended to reduce patient exposure to radiation. Specifically, a routine postoperative CT scan was removed from the protocol. A postoperative cervical CT scan was added at 1 year if the patient’s NDI score is >30 or if plain cervical spine radiographs suggest instability.
3. Ventral-dorsal randomization was amended to a 2:3 randomization (from a 1:1 randomization). The rationale for the 2:3 randomization is to accrue sufficient numbers of dorsal surgery patients to permit exploratory analysis to compare laminoplasty and laminectomy and fusion surgery.

This initial investigator meeting was vital for the trial success. It allowed participating members and important stakeholders to express their expert opinions about the conduct of the trial. It also allowed an opportunity for site study coordinators to attend and to receive formal training.

TRIAL STATUS

Patient enrollment was initiated on April 1, 2014. As of April 30, 2014, 6 patients (3 randomized) have been enrolled from 2 sites. Patient enrollment will occur over an 18-month period with 11 sites participating in enrollment. Seventeen orthopedic spine surgeons and 19 neurosurgeons will enroll patients in this trial.

SAFETY CONSIDERATIONS

All of the subjects in this trial are surgical candidates and would have had surgery recommended even if they were not involved in the

### Table 3. Annual Volume of Surgically Treated Cervical Spondylotic Myelopathy Cases at Each Site

<table>
<thead>
<tr>
<th>Site</th>
<th>Principal Investigator</th>
<th>Ventral, n</th>
<th>Dorsal Laminectomy + Fusion, n</th>
<th>Dorsal Laminoplasty, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lahey Hospital and Medical Center</td>
<td>Subu Magge, MD</td>
<td>52</td>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td>University of Medicine and Dentistry—New Jersey</td>
<td>Robert Heary, MD</td>
<td>15</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>University of Utah</td>
<td>Erica Bisson, MD</td>
<td>36</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Cleveland Clinic Foundation</td>
<td>Edward C. Benzel, MD</td>
<td>23</td>
<td>37</td>
<td>2</td>
</tr>
<tr>
<td>Thomas Jefferson University</td>
<td>Todd Albert, MD</td>
<td>200</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>Massachusetts General Hospital</td>
<td>Jean-Valery Coumans, MD</td>
<td>14</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Washington University—St. Louis</td>
<td>Daniel Riew, MD</td>
<td>12</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>MetroHealth</td>
<td>Michael Steinmetz, MD</td>
<td>45</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Medical College of Wisconsin</td>
<td>Marjorie Wang, MD</td>
<td>45</td>
<td>70</td>
<td>1</td>
</tr>
<tr>
<td>Mount Sinai Medical Center</td>
<td>Tanvir Choudhri, MD</td>
<td>90</td>
<td>58</td>
<td>11</td>
</tr>
<tr>
<td>University of Toronto</td>
<td>Michael Fehlings, MD</td>
<td>57</td>
<td>65</td>
<td>16</td>
</tr>
<tr>
<td>Total annual cases</td>
<td></td>
<td>589</td>
<td>415</td>
<td>99</td>
</tr>
</tbody>
</table>
study. All subjects will receive standard follow-up by the treating surgeon. All surgical procedures are considered standard care, and none are considered investigational. Any significant findings regarding the overall safety of any of the procedures 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 ensured 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.
The Data Safety Monitoring Board will be convened by the Tufts Clinical and Translational Science Institute. An interim analysis is planned when 50% of patients have been enrolled and have completed 1 year of follow-up. The interim analysis will be performed earlier if the Data Safety Monitoring Board identifies any compelling safety concerns.

QUALITY ASSURANCE

There will be several layers of quality control for this study. The NIH-funded initial site investigator meeting included a training session for all study coordinators. It covered data collection and data entry procedures, as well as an opportunity to review all clinical protocols and to answer questions. The data, after being recorded on case report forms and entered into the Web-based platform, will be checked at the central data management site, the Lahey Comparative Effectiveness Research Institute, by the project data manager. In addition, there will be bimonthly Steering Committee meetings with the director of data management, who will supervise audits of the database bimonthly with the project data manager. The PI and biostatistician will supervise the quality control mechanisms at these bimonthly meetings. There will also be site visits to audit the ability of each site to screen and enroll patients and to maintain accurate study records.

EXPECTED OUTCOMES OF THE STUDY

This will be the first randomized study to evaluate the optimal surgical approach to CSM. The results of this study will help surgeons and patients understand the outcomes, complications, and costs associated with the 3 major surgical approaches for this spinal condition.

DURATION OF THE PROJECT

Enrollment is expected to occur over an 18-month period, and patients will be followed up for a total of 5 years postoperatively.
PROJECT MANAGEMENT

The study is being led by the PI, Dr Ghogawala. An advisory committee made up of 5 senior specialists with expertise in clinical trial design and spinal surgery is responsible for reviewing study progress and advising the PI from time to time as to the potential impact of the study results on the quality of surgical care for patients with CSM (Figure 8). The Steering Committee, comprising 5 senior investigators, is responsible for the overall direction and general design and conduct of the study, preparation of study documents, and review of study procedures and progress. A separate Publications Committee will review all manuscripts and set guidelines for authorship.

Study investigators at each site are responsible for recruiting and enrolling patients, reporting adverse events, and completing data collection. Statistical design and analyses are being supervised by Dr Karen Freund of the Tufts Clinical and Translational Science Institute.

ETHICS

The study protocol will undergo review from the IRBs at each of the 11 participating sites. No patients will be enrolled until IRB approval has been obtained at the enrolling site. Written informed consent will be obtained from all eligible patients or next of kin for enrollment in the study.

CONCLUSION

Few surgical treatments are evaluated with RCTs. The CSM-S trial is an innovative study that aims to compare the effectiveness of 3 major surgical approaches to treating CSM using an RCT design. Using a Spine Experts Panel to establish clinical equipoise for randomization might elevate the ethics of this trial by protecting patient’s rights while promoting trust between investigators and patients. All patients who do not consent to randomization will be captured in a nonrandomized cohort. By focusing on patient overall health-related QOL, this study will identify the optimal...
procedure for thousands of patients with CSM and will advance the science of surgical treatment for CSM.

**AQ : 8 Disclosures**

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