1.0 PROTOCOL

Study Design Overview: This is a Phase III Clinical Trial. Our overall goals are to evaluate the effectiveness of nonoperative and operative interventions in patients with adult symptomatic lumbar scoliosis (ASLS) and to identify important clinical and radiographic determinants of change in patient-reported HRQOL. To accomplish these goals, a 5-year cooperative, multi-center longitudinal randomized study with a concurrent observational cohort is proposed.

Specific Aim #1: Compare the outcomes of surgery and nonoperative treatment in patients aged 40 to 80 with ASLS defined as a lumbar curve with a coronal Cobb measurement of 30° or more, and either of the following: Oswestry Disability Index (ODI) score of 20 or more; or Scoliosis Research Society Quality of Life (SRS-QOL) instrument score of 4.0 or less, in the domains of pain, function and/or appearance.
Null Hypothesis: Nonoperative and operative treatment groups will have similar outcomes at follow-up.

Specific Aim #2: Evaluate the impact of patient factors (age, gender, socioeconomic status, education) and comorbidities [mental health, body mass index (BMI) and bone mineral density (BMD)] on adverse events and treatment outcomes for both the non-operative and operative arms. Incorporate these variables into a prediction model to help identify those patients most likely to benefit from either a surgical or non-operative approach.
Hypothesis: Age, gender, socioeconomic status, education, and comorbidities will have an impact on the final result at 2-4 years post-intervention.

From the adult section of the SDSG, we will utilize five centers that have consistently enrolled the most ASLS patients. From 2004 through 2006 these five centers enrolled 155 non-operative and 141 operative patients meeting the ASLS criteria Each center has committed to the enrollment of at least 10 patients per year, and across all 5 sites we expect to average 20 patients per year, to reach a targeted enrollment of 300 patients over 3 years.

As summarized in the flow chart shown in Figure 1 eligible patients at each site will be informed about the study and will be able to participate in one of two ways. Those agreeing to randomization will be randomized to operative or non-operative care, while those willing to participate in the study but not accepting random treatment assignment will be followed in a prospective observational cohort. The primary outcome measure will be longitudinal change in disease-specific quality of life as measured by the Scoliosis Research Society-Quality of Life (SRS-QOL) subscore.

We plan to recruit a total of 300 patients into the trial. Based on our preliminary data, we expect 90% participation and about 30% randomization, resulting in a total of about 82 in the randomized trial and 188 in the observational cohort. While we will perform both intent-to-treat and as treated analysis, intent-to-treat analysis of the randomized trial will provide the most internally valid, un-confounded estimate of the effect of surgery, while the inclusion of the prospective observational cohort will help assess the external validity of the results and include a much broader spectrum of patients with ASLS than an RCT alone.

1.1 Eligible Participants: This is a study of patients

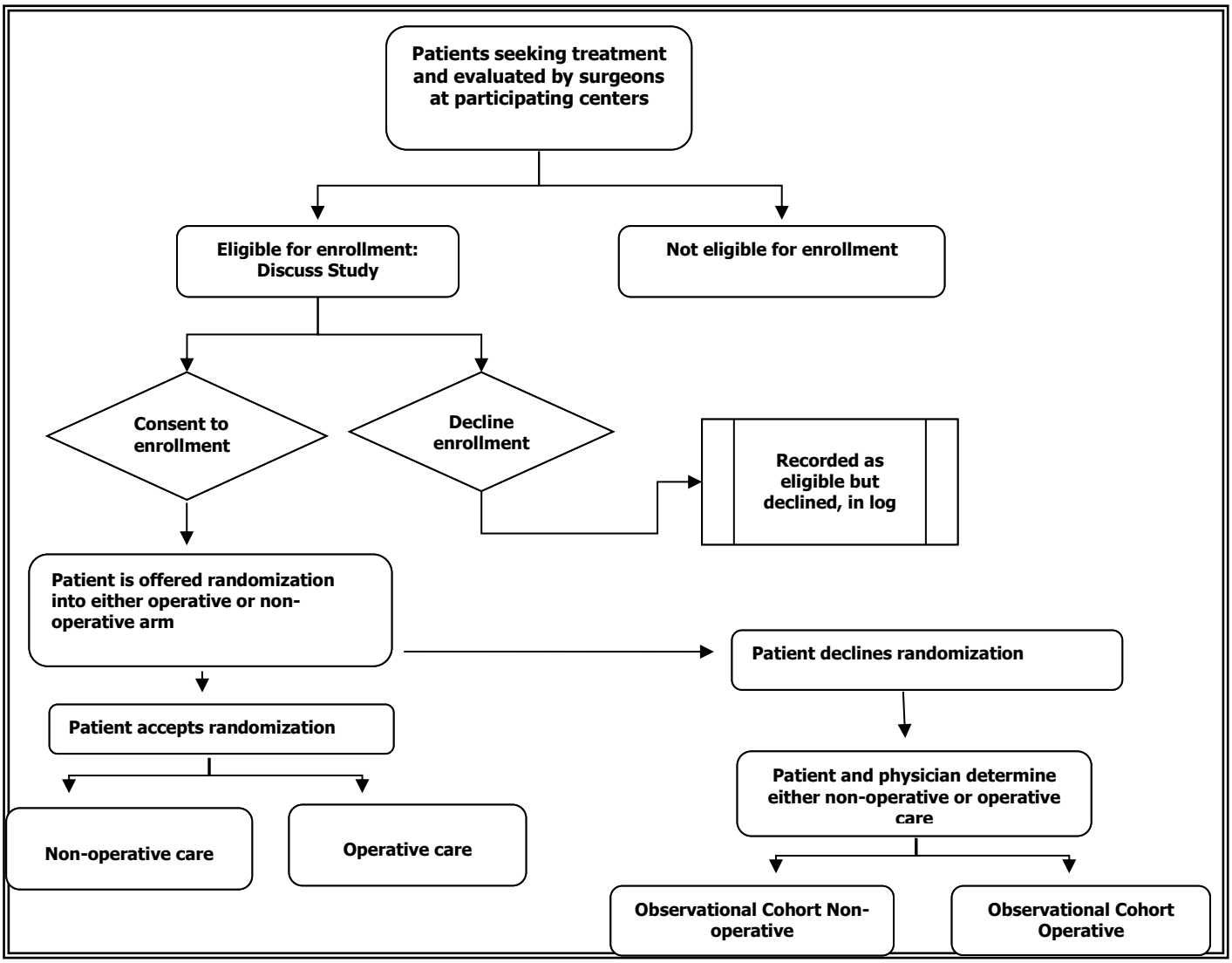
- aged 40 to 80 years with
- ASLS defined as
    - lumbar curve with a coronal Cobb measurement ≥ 30°, and
    - **either of the following**:
        - Oswestry Disability Index (ODI) score ≥ 20 ***or***
        - SRS-QOL score ≤ 4.0 in the domains of pain, function and/or appearance.
- *If assigned to surgical intervention* (by randomization or patient preference), the intervention plan would include, at a minimum, the Cobb levels of the Thoracolumbar/lumbar spine.

Patients 81 years or older are not eligible for inclusion, as most providers would not recommend major surgical procedures of this nature for these patients in this age group due to the increased risk of perioperative morbidity and mortality. Eligibility for participation is not restricted based on gender, ethnicity or principle language.

Excluded from participation are patients with any of the following factors:

- Substantial cardiac, pulmonary, renal or metabolic disease that, in the judgment of the surgical team, would preclude performing an operative procedure without undue risk of morbidity and mortality
- Concomitant high-grade spondylolisthesis (Grade $\geq$3)
- Prior thoracic or multiple level lumbar laminectomy or decompression [single or two level lumbar decompression (e.g., herniated disc) will not be an exclusion]
- Prior thoracic or lumbar fusion
- Osteoporosis evidence by a dual-energy x-ray absorptiometry (DEXA) T-score <-3.0 at the femoral neck for patients considered to be at risk (post-menopausal females, males $\geq$ 60 years of age, steroid dependent rheumatoid arthritics, status post organ transplantation, etc.). Patients may be randomized prior to obtaining DEXA results. Non-Surgical patients may initiate non-surgical treatments prior to completion of DEXA (if required) as non-surgical treatments will not affect DEXA results BUT DEXA must be completed and results entered within 3 months of enrollment. Surgical patient must have DEXA prior to surgical intervention. Waivers will be provided for patients meeting inclusion criteria who have had bilateral total hip replacements only if t score of spine and wrist are provided.
- Neuromuscular scoliosis (e.g., spinal muscular atrophy, cerebral palsy, Parkinson's Disease, post-polio syndrome, Charcot Marie Tooth disease)
- Congenital scoliosis in the lumbar spine. Congenital anomalies of the cervical or thoracic spine are acceptable.
- Spine tumor, infection or connective tissue disorder
- Cognitively impaired or unable/unwilling to comply with follow-up
- Pregnancy or planning on conceiving during time of study involvement
- Ankylosing Spondylitis
- Past history of vertebroplasty or kyphoplasty of the thoracic or lumbar spine

Figure 1: Patient flow and Triage



1.2 Identification and Enrollment: Site investigators and/or research coordinators will identify potential study participants based on patient history, physical exam, radiographs and HRQOL scores. See Section 19 Administrative Forms: Screening Checklist. Patients meeting inclusion/exclusion criteria will be offered study participation. Potential patients will view a short video regarding study participation.

Eligible patients not consenting to study participation will be entered into the electronic database in a de-identified manner. Age, gender, inclusion criteria and reason for declining participation will be documented.

1.3 Randomization and Observational Cohort Assignments: Patients consenting to randomization will be randomized 1:1 to the non-operative or operative intervention arms. A permuted randomized block approach[1] with blocks of size 4, 6 and 8 and stratified by site, age group (2 levels: 40-59 years of age, 60-80 years of age), gender and Cobb angle-based severity (2 levels: 30-54°, 55-100°) will be used to ensure representative treatment assignment across these demographic and disease-specific categories with approximately balanced assignment totals at interim intervals as well. Based on preliminary data, we anticipate that 57% of participants will be in the younger age category and 43% in the older age category.

Patient loss to follow-up can affect the randomization balance and quality. When a patient is lost to follow-up prior to treatment or because of an administrative error, such as qualifying a patient for inclusion in

the study when, in fact, study inclusion criteria were not met or exclusion criteria were initially missed, these patients will be removed from the study along with all study data. The guidelines for removing a patient from the study will follow the ICH guidelines; subjects who fail to satisfy an entry criterion will be excluded from the analysis under the following circumstances:

1. the entry criterion was measured prior to randomization;
2. the detection of the relevant eligibility violations can be made completely objectively;
3. all subjects receive equal scrutiny for eligibility violations; and
4. all detected violations of the particular entry criterion are excluded.

The study management plan is explicitly designed to minimize these events. Specifically, there will be electronic registration by site coordinator with explicit inclusion and exclusion criteria assessment on the enrollment form and review of registration by the Project Manager (PM) at Washington University.

In the observational cohort, the choice of nonoperative vs. operative care will be made by the patient guided by the provider's recommendation and presentation of existing data regarding nonoperative and operative care based on the following parameters: Patients with clinical symptoms of pain and functional limitations that are well controlled with non-operative care will be encouraged to pursue nonoperative care. Patients who have not demonstrated access or utilization to previous nonoperative care for their symptoms will be directed to non-operative care as an initial treatment. Enrollments into the observational arms will be closed when each arm's sample size is reached in order to achieve equal numbers of patients in each arm at the conclusion of the study.

1.4 Study Interventions: Regardless of study cohort participation (randomized or observational), interventions will not be implemented until the PM has confirmed appropriate enrollment. Nonoperative interventions will then be implemented as soon as possible. Due to the length and complexity of spinal deformity procedures, available dates for elective operative procedures may range from 1 to 6 months. Therefore, operative intervention will take place within six months of treatment assignment but baseline assessments, specifically MD assessment, patient reported HRQOL and treadmill tests must be completed within 6 months prior to intervention. Standardized protocol guidelines for nonoperative and operative treatment, as detailed below, will be followed by all sites.

1.4.1 Non-operative Techniques: To standardize non-operative treatments, sites will utilize one physician from their center with experience and expertise in non-operative management of spinal conditions (physiatrist, rheumatologist, or internist). For patients who live far from the enrolling center, referral to a local physiatrist will be made with a letter of introduction and a review of the proposed treatment plan from the study physician. A copy of the non-operative guidelines will be provided to all supervising nonoperative physicians.

The strategy for non-operative care for all non-operative patients will include:

1. **Physical Therapy**: Physical therapy will consist of treatment guided by one or a combination of: core stabilization, resistance training, directional preference, movement based, manual therapy, treatment-based group classification, aquatic therapy. Modalities will consist of strengthening arms and legs, improving aerobic conditioning, improving strength of spinal extensor muscles and teaching patients to avoid maneuvers that axially load or flex the lumbar spine. Physical therapy will include a combination of the following: water aerobics and/or reasonable forms of aerobic conditions. Strengthening of spinal extensor muscles will include upper and lower extremity muscles and avoidance of axial loading and flexion of the lumbar spine. Modalities for spine pain will include ultrasound, massage and transcutaneous electrical nerve stimulation (TENS) units.
2. **Injection Therapies**: Injections including epidural steroid and selective nerve root blocks will be used for patients with a significant component of radicular pain. Patients with back pain from facet joints will be offered facet blocks and medial branch ablation. This care pathway will be ordered by the enrolling physician, and enacted by a specialist in injection therapies. For leg pain, if a specific lumbar nerve root appears to be involved, a selective nerve root injection will

be considered. If leg pain is diffuse and involves both lower extremities, an epidural steroid will be considered.

3. **Pain Management**: Medications including non-steroidal anti-inflammatory drugs (NSAIDs) and narcotic analgesics will be used as appropriate. Medications will be started with non-steroidal and/or mild narcotics and only increased if necessary.
4. **Complementary and Alternative Approaches**: Patients in this study may access alternative healthcare resources including massage, acupuncture, acupressure and behavioral programs in an effort to improve pain and function. Alternative modalities will be made available to patients on a referral basis and the use of these modalities will be recorded for all patients. Weight loss will be strongly encouraged for body mass index (BMI) >27.

At each follow-up visit, patients will document the extent to which they have utilized these 4 modalities.

1.4.2 Operative Techniques: Operative treatments have been standardized across all study centers. Each center and surgeon will follow these guidelines. Therefore, surgical interventions should be completed at the study center so the kinds of operative treatment the patients receive will be relatively uniform from center to center and from surgeon to surgeon.

1. Extent of fusion: All spinal reconstruction cases will include at a minimum the Cobb levels of the curve. Additionally, the surgical reconstruction should include a balanced (neutral in rotation and stable, meaning centered on the center sacral line) vertebral segment at each end. All degenerative, rotated or listhetic segments will be included in the reconstruction.
2. Anterior release and inter-body grafting of the lumbar and thoracolumbar curves may be considered when the curve is rigid (i.e., does not reduce by 50% on push, side bending films, or supine films).
3. Pedicle subtraction and Smith-Petersen osteotomy can be performed as an alternate to anterior release for coronal or sagittal correction in rigid deformities.
4. All symptomatic spinal cord or nerve root compression will be addressed surgically with decompression.
5. Iliac bone graft and/or local bone will be used for fusion. This may be supplemented with bone growth factors and allograft.
6. Segmental instrumentation (pedicle screw, hook, and rod) will be utilized for all reconstructions. A universal goal will be to achieve at least 1.5 fixation points per level and dual fixation points at the top and bottom of the construct. Only rigid instrumentation systems will be implanted. No Dynamic Stabilization Devices will be used. No artificial disc replacements will be used in the lumbar spine.
7. Anterior structural support will frequently/usually be considered at L4-L5 and L5-S1, either as an anterior lumbar inter-body fusion (ALIF), posterior lumbar inter-body fusion (PLIF) or transforaminal lumbar inter-body fusion (TLIF) approach in patients being fused to the sacrum.
8. With fusion to the sacrum, 4-point sacropelvic fixation will be utilized in all circumstances, either in the form of four sacral screws or two sacral screws and two iliac screws.
9. Decompression/laminectomies will be warranted for segments with substantial spinal stenosis, both centrally and in the lateral recesses and in some cases in the foramen, when those stenotic segments are judged to be substantially stenotic and contributing to the patient's symptoms.
10. Surgeon judgment will be trusted on the fractional curve below. Most lumbar scoliosis consists of a curve that more or less goes from T10 to L3 or L4 with another curve that goes the other way between L3 or L4 and the sacrum. It will be expected that in most cases both these curves will be addressed and fused and instrumented. There may be some exceptions. There may be some cases in which the fractional curve is not included and there may be some cases in which the main curve is not included and only the fractional curve is included. If both curves are not

included, it would be helpful for the surgical team to give a description of why the decision was made to include only one of the two curves.

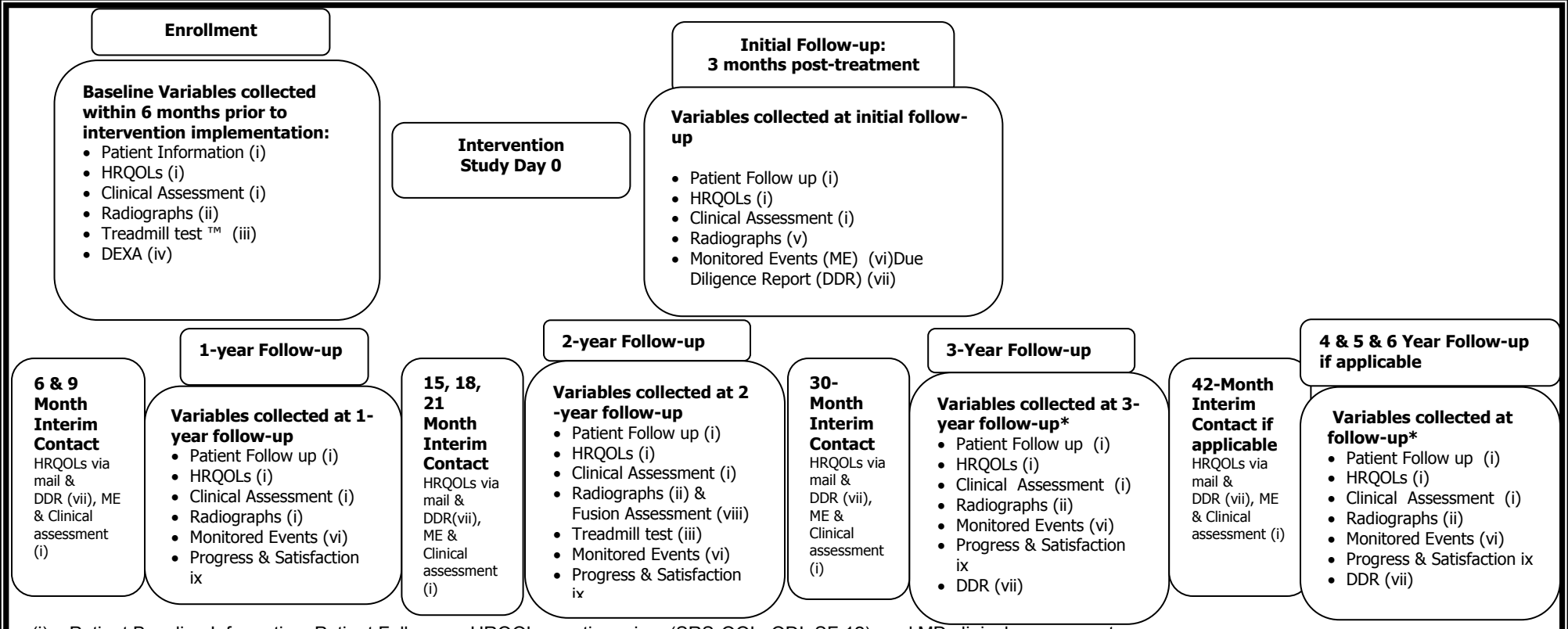
If a consented patient is later not able to return to the original study center or a participating center for surgical intervention, *it is expected that the patient will continue in the study and participate as fully as possible.*

Surgical summary data will not be collected or posted to the database unless the surgery was performed by one of the participating investigators. If the surgery is not performed by a participating investigator, a Monitored Events report will be completed to reflect 1. SAE (Hospitalization) and if applicable, intervention cross over and 2. Discontinued treatment/Follow up continued.

All follow up data will be collected by mail and telephone contact. Sites will complete MD assessments by phone and follow up on any due diligence report reaching contact threshold. Sites should try to obtain copies of radiographic images annually.

Sites and patients will be reimbursed for 'long distance' follow up as outlined in the MOOP, Section 25.

1.5 Schedule of Events and Data Collection: Table 1: Schedule of Events



(i) Patient Baseline Information, Patient Follow-up, HRQOL questionnaires (SRS-QOL, ODI, SF 12), and MD clinical assessment.
(ii) Standing long cassette coronal (AP) and sagittal (lateral) radiographs of entire spine from C7 to femoral heads.
(iii) If Non-Surgical patient crosses over to Surgical arm & surgery is prior to reaching 21 mo follow up, 2 year treadmill test (TM) is to be delayed until the patient is 2 year s/p CROSSOVER surgical procedure. If patient crosses over and surgery is between 21 & 30 mo follow up, pt will be complete TM prior to surgery and asked to complete a 3rd TM when 2 years out from crossover surgery. See Appendix for a description of the standardized treadmill test.
(iv) DEXA within 24mo of enrollment for all post-menopausal females, males > 60 years of age, any steroid dependent participant unless, is taking FDA approved drug for treatment of osteoporosis, has history of fracture in the past year, has taken steroids on long term basis or most recent DEXA scan t score was -**2**.5 or worse, in which case, DEXA in the past 12 months of intervention is required.
(v) Standing long cassette radiographs for operative intervention only.
(vi) Monitored Events (ME) including: Serious Adverse Events, Crossovers and Withdrawal from Study Participation
(vii) Due Diligence Report (DDR) ran by PM after follow up data entered.
(viii) Fusion Assessment: In addition to Standing AP & lateral radiographs, obliques (right & left) images of the surgical site and, if fused to the sacrum, a Ferguson AP L5-S1 will be obtain for patients treated surgically at those centers were these radiographs are collected as standard care.
(ix) Progress & Satisfaction questionnaire as reported by the patient at annual visits and at time of crossover or revision surgery.
The only difference between nonoperative & operative interventions is no x-rays are obtained at the initial (3 month) follow-up & Fusion Assessment is not applicable in the nonoperative arm.

1.5.1 Data Collection and Forms: (Please note, all Case Report Forms are located in Section 26). This is a five year study (with 2 year extension) in which all patients will have a minimum of 2 year follow up. Additional 3, 4, 5 & 6 year follow up will depend upon when patient entered the study.
If enrolled Year 1, participation in the study will be for 6 years.
If enrolled Year 2, participation in the study will be for 5 years.
If enrolled Year 3, participation in the study will be for 4 years.
If enrolled Year 4, participation in the study will be for 3 years.
If enrolled Year 5, participation in the study will be for 2 years.

Patient Baseline Information: Baseline covariates will include: age, gender, medical history, socioeconomic status, and education level. In addition, we will capture patient symptoms, characterizing the percent of back pain and leg pain through numerical rating scales (NRS).

HRQOL: Two HRQOL questionnaires will be collected (SRS-QOL, ODI) at baseline and specified follow-up intervals (3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 60 and 72 months post-intervention). In addition, the SF 12 will be completed at baseline and annually. All questionnaires will be administered by the site research coordinator either at the time of the office visit or by mail.

- SRS-QOL: The SRS-QOL is a disease-specific instrument for the measurement of health status in patients with spinal deformity. Age-gender norms exist for the non-deformity adult population. The SRS-QOL questionnaire has been fully validated in adult spinal deformity patients. It is reproducible, reliable, and sensitive to change. The questionnaire has four domains: pain, function, self-image and mental health. Domain values and subscore (a summary over the 4 domains) are reported as an average score for each domain (1-5). A score of 5 implies no pathology and a score of 1 implies maximum pathology. There are 2 satisfaction questions scored in similar fashion: 5 implies maximum satisfaction and 1 implies maximum dissatisfaction. There are 7 historical recall questions asked post-treatment to assess patient feelings regarding QOL improvement and to document satisfaction.
- Oswestry Disability Index: The ODI is a disease-specific measure of disability associated with back pain. The instrument is a 10-item questionnaire that has been validated and is reproducible and reliable. Norms exist for a population without back pain, and thresholds have been established for defining a clinically significant difference in scores. The ODI scoring is on a 0-100 point scale (0 implies no pathology and 100 implies the maximum pathology).
- Short Form-12: The SF-12 is a self-administered, generic HRQOL measure derived from the Rand Health Insurance Long Form. The SF-12 is validated for the U.S. with age and gender normal values. This instrument provides mental and physical component scales (MCS, PCS) for translating health status and changes in health status between cohorts of patients with distinct disorders. Previous studies in adult scoliosis have used the SF-12 to measure HRQOL.

All three of these outcomes instruments will be available in Spanish. The Spanish translated HRQOLs have been validated.

Progress & Satisfaction questionnaire. This is a brief, four item questionnaire for the patient to document satisfaction with treatment and treatment assignment. This questionnaire will be completed at the time of the office visit or by mail. The questionnaire is also completed at the time of crossover and prior to any revision surgery.

Functional Treadmill test: All patients will have a standardized functional treadmill test performed at baseline and 2 years post-treatment. This test is performed routinely at Washington University and has been published in *The Journal of Bone & Joint Surgery*. (See Appendix for details).
If a Non-Surgical patient crosses over to the Surgical arm and tentative surgery date is prior to 21 month follow up, 2 year post intervention treadmill test will be delayed until the patient is *2 year s/p CROSSOVER surgical procedure.*

If Non-Surgical patient crosses over to Surgical arm and tentative surgery date is between 21 and 30 month follow up, post intervention TM will be obtained prior to crossover surgery. These patients will be asked to complete a 3rd treadmill test 2 years after CROSSOVER surgical procedure. If the patient is agreeable, a separate, supplemental consent will be obtained for 3rd treadmill test. Patient and site (physical therapist) will be reimbursed for all three treadmill tests.

MD Clinical and Radiographic Assessment: The physician and/or research coordinator will complete clinical assessments capturing pertinent neurologic and/or physical findings and comorbidities at baseline and clinical follow-up appointments (required at 3, 12, 24, 36, 48 & 60 months post-intervention with capability to compete as needed at all study intervals). Baseline clinical assessment will include recording of comorbidities, BMI and bone mineral density (BMD). Baseline BMD (femoral neck t score) will be captured by Dual energy X-ray absorptiometry, or DEXA, which is most widely used and accepted as an accurate, economic and noninvasive predictor of BMD for postmenopausal females, males 60 years or older, or any patient in which it is clinically indicated (e.g. steroid dependent, post organ transplantation, etc.) DEXA machines have a standard reference (called NHANES III) that can be used for all machines, regardless of manufacturer. BMD obtained via qualitative CT, peripheral DEXA scan or ultrasound is not acceptable. Since degenerative spinal conditions and scoliosis may alter the results of the DEXA BMD femoral neck t scores will be recorded. Waivers will be provided for patients meeting inclusion criteria who have had bilateral total hip replacements only if t score of spine and wrist are provided.

Specified radiographic parameters (coronal and sagittal balance; coronal and sagittal Cobb measurements) based on long cassette radiographs will be captured at baseline and clinical follow-up appointments (3 months for operative arm only and at 12, 24, 36, 48 & 60 months post-intervention for both arms). Fusion mass will be assessed by reviewing right and left obliques and Ferguson AP L5-S1 (if fused to the sacrum) at two years post intervention for patients treated surgically, if considered standard care at the participating centers.

Medical History & Medication Log: This is a source document to capture baseline medical problems. It will be reviewed at each clinical follow-up to ensure accurate capture and reporting of any adverse events. Data collected on this source document will be used to complete Monitored Events and MD Clinical Assessment CRFs.

Surgical Summary: For patients managed operatively, a surgical summary will be completed by the surgeon at the time of intervention. Data captured will include, but not be limited to: blood loss, length of surgery, surgical approach, and vertebral levels involved. Equally important will be the reporting of any intra-operative adverse events, as well perioperative adverse events occurring prior to discharge. Procedural codes (CPT codes) will also be reported.

Patient Intervention Follow-Up: All participants will complete a comprehensive description of the nonoperative modalities used, and the frequency of use will be detailed (3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 60 & 72 months post-intervention). These assessments will be part of the standard questionnaires given at each study follow-up. Patient diaries will be used as memory aids but will not be used for primary data collection. Any adverse events stemming from nonoperative or operative treatments will be recorded along with changes in health history.

Monitored Events: Sites will complete a Monitored Events Case Report Form (CRF) at each clinical follow-up appointment to report: Serious or Unexpected but reasonably related adverse events (AEs), Crossover to the other intervention, or exiting the study. In addition, sites will complete this form as applicable with each patient contact, including telephone calls.

Due Diligence Report: This report will be run by the Project manager after each follow up visit data has been entered into database. The report will calculate differences in previously reported HRQOL value. Any patient with a decrease of -0.5 in the SRS domains or an increase of 10 or more points in the ODI score warrant further investigation.

The primary outcome variable will be the change in SRS-QOL subscore because the literature supports this questionnaire as a more disease-specific tool for assessment of spinal deformities. The concurrent validity of the SRS-QOL function domain compared favorably to the SF-12 PCS (r=0.73) and the ODI (r=0.87), as did the SRS-QOL mental health domain compared to the SF-12 MCS (r=0.87). Thus, the SRS-QOL is especially suited to our study population and research questions. Changes in ODI and SF-12 will also be assessed as they are frequently used measures of QOL and will facilitate comparison of our findings with those of others.

1.5.2 Data Collection Procedures: Site research coordinators will identify, consent and enroll eligible participants in the study. After obtaining patient consent, the site coordinator will electronically register participants through a secure Web site. Registration information will include demographic information and documentation of inclusion criteria to minimize inappropriate enrollment. Randomization software will generate an intervention assignment upon completion of registration for patients agreeing to randomization. Site coordinators will notify the PM of patient enrollment via alpha pager. Site coordinators will provide questionnaire packages at study entry (all patients), at 3 months post-treatment and at each annual post-treatment clinical visit. In addition, questionnaire packets will be mailed to participants at 6, 9, 15, 18, 21, 30, 42 & 72 months post-intervention to enhance patient tracking. A self-addressed, stamped envelope will be provided for return of questionnaires. Therefore, patients will complete HRQOL at baseline and every 3 months post-intervention for the first 2 years, every 6 months years 3 & 4 and annually thereafter.

Radiographic images will also be electronically uploaded to the database for measurement, future retrieval and review. An independent, blinded, experienced orthopedic spine surgeon will perform radiographic measurements at baseline and at annual follow-up visits. The surgeon will be blinded to patient, site and surgeon identification and he will not enroll or treat any study participants, thus eliminating the potential threat for bias if sites measured their own patient films. In addition, the blinded surgeon will assess fusion mass on participants receiving surgical treatment by reviewing radiographic images (standing AP and lateral, right and left oblique views of the surgical site, and, if fused to the sacrum, a Ferguson AP L5-S1). Results will be recorded on the Radiographic Assessment form and entered into the database. In addition, Clinical Assessment forms will be completed at baseline and annual follow-up visits to document physical and medical findings, including adverse events and complications.

Data capture will occur via REDCap, a secure Web-based data input interface available in each participating center's research facility. This Web-based secure data capture, data storage and data transmission system is maintained by Washington University. To improve data accuracy, double data entry will be implemented. Immediate data clarifications will be generated at the time of data entry for missing responses, out-of-range responses, and/or inconsistencies in responses that break established validity rules. The REDCap application is fully HIPAA-(Health Insurance Portability Accountability Act) compliant and will have thorough testing and validation processes in place. Baseline data will be entered within 24 hours of enrollment, before study interventions are activated. Follow-up data will be entered within 1 week of a patient's visit.

Site coordinators and PIs will receive a monthly Upcoming Events Report via email. This report will be generated by the PM and include any patient who will be due for a clinic visit in the upcoming 3 months. Site coordinators will have the capability to run this report more frequently, if they choose. This will allow site coordinators adequate time to contact and arrange for appropriate scheduling, including functional treadmill testing at the 2-year follow-up. The report will also include all patients who will require HRQOL mailings in the upcoming month. Site coordinators will be responsible for mailing, tracking return of and entering data from the questionnaires. Failure to obtain and store data on patients within a 1-week period of the expected encounter windows will be monitored by the PM through weekly database queries. The PM will follow up with the site coordinator to further investigate these situations. Weekly reports of patients with past due follow-up will be sent to the site coordinator and PI.

Patients will be encouraged to return to the primary center for examination, radiographs and questionnaires at the designated intervals. If the patient is unable to return to the center, they will be

encouraged to complete questionnaires and radiographic studies locally and mail them to the primary center at the intervals required by the study protocol.

Acceptable windows for data collection are as follows:

Baseline data must be completed prior to intervention initiation, specifically:

- Site and patient completed forms, functional treadmill test completed within 6 months prior intervention initiation,
- Radiographs (standing AP and lateral entire spine) completed within 6 months prior to intervention and
- DEXA scan of femoral neck* (if applicable) completed within 24 months prior to enrollment and prior to intervention** *UNLESS patient meets any of the following criteria, in which DEXA must be completed 12 months prior to intervention:*
    - Taking an FDA approved drug for the treatment of osteoporosis
    - History of fracture in the past year
    - Has taken Prednisone on a long term basis
    - Most recent DEXA scan t score was -2.5 or worse.

  *Waivers will be provided for patients meeting inclusion criteria who have had bilateral total hip replacements only if t score of spine and wrist are provided.

  ** *Patients enrolled in the NON surgical arm may initiate non-surgical treatment measures but must have DEXA completed (if required) within 3 month*

Initial follow-up is to be completed 30 to 120 days post intervention.

Interim questionnaires/assessments will be mailed and posted to database +/- 30 days of scheduled event (6, 9, 15, 18, 21, 30, 42, 72 months post intervention).

One year follow-up must be completed11 months to 1 year 4 months post intervention.

Two year follow-up cannot be captured prior to 2 year anniversary date and up to 4 months post anniversary date.

Three year follow-up will be captured 2 year 11 months to 3 year 4 months post intervention.

Four year follow-up will be captured 3 year 11 months to 4 year 4 months post intervention. Patients who reach the 4 year milestone prior to end of current grant funding (Aug. 30, 2016) will be asked to sign a revised informed consent to include 5 year clinical visit and 72 month interim mailing if applicable).

1.5.3 Patient Compliance: To enhance patient compliance and participation, the site coordinators will mail interim questionnaires to all study participants at 6, 9, 15, 18, 21, 30, 42, & 72 months post-intervention. These will be completed in addition to the HRQOL questionnaires obtained at baseline and post-intervention clinical appointment visits (3, 12, 24, 36, 48 & 60 months). Furthermore, participants will be reimbursed for time and travel associated with completion of HRQOLs questionnaires, treadmill tests, radiographic and clinical exams.

In the event that subjects do not return for a scheduled follow-up visit, or fail to return mailed questionnaires in a timely manner (within four weeks of mailing), site coordinators will contact subjects via telephone and/or e-mail. After two failed attempts, site coordinators will send a U.S. Postal Service certified letter to the subject's last known address. Address change service will be requested with all mailings. If certified mailings are returned undeliverable with no forwarding address, site coordinators will notify the PM, who will then conduct Internet searches and fee-based searches, such as ChoicePoint, to locate missing subjects.

Any patient deciding not to return to &/or continue treatment at the study will continue to be followed by mail and telephone, if the patient is willing. A monitored events report will be completed to document this change in patient and treatment status (Discontinued treatment/Follow up continued). Sites will mail QOLs to patients at interim and clinical follow up intervals. Site will follow up with patient if Due Diligence Report reaches contact threshold, to clarify any questionable patient information, &/or follow up on any questionnaires not returned. Site will ask patient to mail x-rays at annual milestones, as outlined in the protocol. Follow up MD assessments will only document treatments actually prescribed/recommended the Study PI (not MD from outside institutions).

1.6 Project Manager (PM). In addition to confirming appropriate participant study enrollment the PM will be responsible for tracking and monitoring productivity at all centers to further ensure complete and accurate data. It will be the responsibility of this individual to strive for 100% follow-up in both nonoperative and operative arms of the study.

The PM will have 24 hour/day access to the data collected and stored on study patients. The PM will query the database on a daily basis to monitor each site's productivity (enrollment and follow-up). Likewise, the sites will have access to the PM via alpha pager.

Responsibilities of PM:

- Develop an operations manual.
- Provide detailed training of site coordinators upon study initiation at start-up meetings and throughout the remainder of the study via conference calls and site visits. Conference calls with the PM and site coordinators will be held weekly until all sites are actively participating and comfortable with the study protocol, with decreasing frequency as study needs dictate.
- Visit each site at the time of, or soon after, the first subject has been enrolled to ensure completeness of protocol procedures.
- Conduct monitoring visits to the sites once per year during active enrollment.
- Ensure the appropriate inclusion/exclusion of each patient in the study.
- Maintain a list of study participants (site, cohort and intervention arm).
- Maintain a list of eligible participants who decline study participation and reason for decline.
- Track and ensure complete data entry on all patients. Contact site coordinator and work to resolve any issues for patients whose visits have not occurred during the specified interval window.
- Create and provide monthly site reports for upcoming study events due (clinical visits and questionnaire mailings).
- Review each Protocol Variances with Lead Investigator. Action plans for each variance will be determined based on the individual variance.
- Perform random checks of critical parameters on films measured by the independent observe. Discrepancies >10 degrees in Cobb measurements or 10mm in linear measurements will be resolved through discussions with PM and independent observer. Measurements will include:
    - Major Cobb angle of the lumbar curve
    - Sagittal Cobb angle from T12 to the sacrum
    - Sagittal Cobb angle from T5 to T12
    - Sagittal Cobb angle from T10 to L2
    - C7 plumb relative to the sacrum (coronal balance) on standing long cassette radiographs
    - C7 plumb relative to the sacrum (sagittal balance) on standing long cassette radiographs
- Troubleshoot potential site issues through, but not limited to:
    - Tracking frequency and type of data clarifications generated,
    - Tracking unresolved data clarifications,
    - Tracking data collection and entry within appropriate interval windows.

1.1 Schedule of Events

	Visit 0	Day 1	FU 1	FU 2	FU 3	FU 4	FU 5	FU 6	FU 7	FU 8	FU 9	FU 10	FU 11	FU 12	FU 13	FU 14
Visit Description	Screening/ Baseline	Intervention	3mo	6mo	9mo	12mo	15mo	18mo	21mo	24mo	30mo	36mo	42mo	48mo	60 mo	72 mo
Study Visits (months)	-6 mo to -1day except as noted	Day 0	30 to 120 days	+/-30 days	+/-30 days	11mo to 16mo	+/-30 days	+/-30 days	+/-30 days	24mo to 28mo	+/-30 days	35mo to 40mo	+/-30 days	47mo to 52mo	59 mo to 64mo	+/-30 days
Informed Consent	x															
Upright AP/lateral radiographs entire spine C7 to sacrum*	-6mo to -1day		x*			x				x**		x		x	x	
History & Physical exam	x					x				x		x		x	x	
Patient Baseline CRF	x															
Medical History & Medication Log	x		x			x				x		x		x	x	
ODI	x		x	mail	mail	x	mail	mail	mail	x	mail	x	mail	X	x	Mail
SRS-30	x		x	mail	mail	x	mail	mail	mail	x	mail	x	mail	x	x	mail
SF-12	x					x				x		x		x	x	
Progress & Satisfaction						X				X		X		x	x	
MD Baseline Clinical Assessment CRF	x															
Treadmill test	x									X****						
DEXA***	-12mo to -1day															
Randomization	x															
Surgical Summary CRF		x														
Non Operative Summary Source Document		x														
Patient Follow up Information			x	mail	mail	x	mail	mail	mail	x	mail	x	mail	x	x	mail
Due diligence report			x	x	x	X	x	x	x	X	x	X	x	x	x	x
MD Follow up Clinical Assessment CRF			x	x	x	x	x	x	x	x	x	x	x	x	x	x
Monitored Events CRF		X	X	x	x	X	x	x	x	X	x	X	x	X	x	x

CRF = Case Report Form
*Surgical Arm only
**Fusion Assessment, Surgical Arm only
***See Protocol, pg 3 & 9 for details
****See Protocol, pg 7-8 for details