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Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: Empirical Spine
How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_louie.docx.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_todd_f_alamin_md.docx.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_marcia.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. [NCT00316121 - 05-HEALOS-01 - A Prospective, Multicenter, Randomized Study Comparing the Use of HEALOS® to Autograft in a Transforaminal Lumbar Interbody Fusion (TLIF) Approach](#)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

LimiFlex Clinical Trial for the Treatment of Degenerative Spondylolisthesis With Spinal Stenosis

Narrative Summary:

The LimiFlex™ Clinical Trial is a prospective, concurrently controlled, multi-center study to evaluate the safety and effectiveness of decompression and stabilization with the Empirical Spine LimiFlex™ Paraspinous Tension Band compared to decompression and transforaminal lumbar interbody fusion (TLIF) with concomitant posterolateral fusion (PLF) for the treatment of lumbar degenerative spondylolisthesis (Grade I per Meyerding classification) with spinal stenosis. The objective of this data request is to supplement the control group with historically obtained data from qualifying subjects. Note that the original sponsor of the requested study is supportive of this request.

Scientific Abstract:

Background: Degenerative spondylolisthesis (DS) with lumbar spinal stenosis (LSS) is commonly treated with decompression and fusion. Fusion has been shown to be effective, however is associated with significant morbidity and cost. The LimiFlex paraspinous tension band (PTB; Empirical Spine, San Carlos, CA) is an alternative stabilization technique for patients receiving surgical decompression for DS with LSS.

Objective: The objective of this multi-center study is to evaluate the safety and effectiveness of decompression and stabilization with the PTB compared to decompression and transforaminal lumbar interbody fusion (TLIF) with concomitant posterolateral fusion (PLF) for the treatment of DS with LSS.

Study Design: This is a multi-center, prospective, concurrently controlled, non-blinded study. Balance between groups will be achieved through sub classification using propensity scores.

Participants: The prospectively enrolled control group will be supplemented with retrospectively enrolled control subjects recruited from participating study sites, as well as subjects meeting inclusion criteria from the requested HEALOS study data.

Outcome Measures: Non-inferiority of the investigational group will be assessed with composite clinical success criteria including 15 point reduction of oswestry disability index, no new or worsening persistent neurologic deficit, and no device integrity failures.

Statistical Analysis: Non-inferiority will be assessed in a stratified analysis among propensity score-ranked quintiles.

Brief Project Background and Statement of Project Significance:

Degenerative spondylolisthesis is a common clinical condition of the lumbar spine in which there is anterior translation of the superior vertebra relative to the inferior vertebra, with an intact neural arch and degenerative changes of the facet joints. It rarely occurs before the age of 50 years, and it disproportionately affects women, with a female:male ratio of 6:1. Degenerative spondylolisthesis is typically associated with degenerative changes which render the facet joints less resistant to shear forces borne by the segment.

Patients with degenerative spondylolisthesis typically present with symptoms of stenosis, which are relieved surgically with a decompression/laminectomy. Unfortunately, however, the removal of tissue involved in the decompression increases the flexion instability of the spinal segment, and, over time, the listhesis can increase and cause symptoms to recur. Although some studies report good results in patients who receive only a decompression, including two studies which suggest that more limited decompressions preserve sufficient stability without the need for fusion, most suggest that fusion of the segment after decompression provides clinical benefit. Recently, the results of a randomized clinical trial comparing decompressions alone to decompressions and fusion demonstrated that the increasing postoperative segmental flexion in patients with decompression was associated with increasing anterior translation and a poor clinical result. As a result of these findings, the predominant surgical approach in the United States is to treat degenerative spondylolisthesis patients with a decompression and fusion to ensure a good clinical outcome.

Decompression with instrumented fusion, while the standard of care, is still an invasive surgical option and not appropriate or desirable for many patients due to its complication rate and postoperative morbidity. Complications associated with implantation of fusion instrumentation are well understood: these include vascular injury, direct nerve root injury, or disruption of facet joints outside of the segment to be fused. The amount of dissection and retraction of the paraspinal musculature required during the fusion procedure is significantly increased relative to a decompression-alone to allow for the placement of pedicle screws and bone graft. Average blood loss and operative time for instrumented fusion have been reported to be over 600 ml and over 4 hours, respectively. In comparison, current decompression techniques have reported blood loss in the range of 30-50 ml and operative times of less than 2 hours. The additional operative time and exposure results in increased general peri-operative complications associated with their use, including cardiopulmonary complications and infection.

The PTB is designed to allow the surgeon to perform a decompression to treat the presenting symptoms and then apply the device to stabilize the segment. As such, it presents a new stabilization option for patients for whom a surgeon would like to add stability to a decompression without adding the potential risks, morbidity and complications of a fusion.

Specific Aims of the Project:

The primary study objective is to demonstrate the safety and effectiveness of the PTB when used for spinal stabilization, at one level from L1 to S1, in skeletally mature patients following surgical decompression for treatment of lumbar degenerative spondylolisthesis (Grade I per Meyerding classification) with spinal stenosis.

The objective of the present data request is to supplement the control group with historically obtained data from qualifying subjects. Note that the original sponsor of the requested study has been contacted, is supportive of this request, and advised that the data should be requested through the YODA project.

What is the purpose of the analysis being proposed? Please select all that apply.
New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations
New research question to examine treatment safety
Confirm or validate previously conducted research on treatment effectiveness
Confirm or validate previously conducted research on treatment safety
Participant-level data meta-analysis
Participant-level data meta-analysis pooling data from YODA Project with other additional data sources
Research on comparison group

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Detailed Inclusion/Exclusion criteria are published for NCT03115983 on clinicaltrials.gov. Data sources will include prospective investigational and control subjects enrolled at participating study sites; retrospective control subjects included by participating study sites; and historical control patients from the requested YODA data set meeting inclusion/exclusion criteria.

Individual subject level data from the requested study will be screened for inclusion in the broader study. Only data from included subjects will be utilized. Note that the original sponsor of the requested study has been contacted, is supportive of this request, and advised that the data should be requested through the YODA project.

Main Outcome Measure and how it will be categorized/defined for your study:

The main outcome measures utilized in the primary endpoint include Oswestry Disability Index, neurologic exam results, reoperations/revisions, and radiographic device condition. Secondary outcome measures include the individual components of the primary endpoint, as well as Estimated blood loss, Length of procedure, Hospital stay, Return to normal activities of daily living, Work status, Pain medication including narcotics usage, Visual analog scale (VAS) leg pain, Visual analog scale (VAS) back pain, Zurich claudication questionnaire (ZCQ), SF-12 Quality of Life survey, Patient satisfaction and Radiographic fusion status.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

The main predictor independent variable is a Composite Clinical Success (CCS) endpoint evaluated at 24 months follow-up that will assess individual success for patients in the investigational LimiFlex or control fusion arm . To be considered a success, a subject must demonstrate ALL of the following components of the CCS at 24 months:
- 15 point improvement in Oswestry Disability Index (100 point scale)
- Absence of a new or worsening, persistent neurological deficit
- Absence of additional surgical intervention
- Absence of device integrity failures

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Secondary outcomes include:
• Each of the individual components of the composite primary endpoint
• Estimated blood loss and units of blood transfused
• Length of procedure (skin to skin)
• Hospital stay
• Length of time for subject to return to his/her normal activities of daily living
• Work status and days to return to work (as appropriate)
• Medication use for pain, including narcotic usage
• Leg pain as measured on a Visual Analog Scale (VAS)
• Back pain as measured on a Visual Analog Scale (VAS)
• Zurich Claudication Questionnaire (ZCQ)
• Quality of Life through use of the SF-12 Health Survey
• Patient satisfaction
• Radiographic fusion status

Economic parameters will be collected to assess and compare the cost-effectiveness of the investigational and control procedures.

Statistical Analysis Plan:

The treatment arm (LimiFlex Paraspinous Tension Band) is compared to a transforaminal lumbar interbody fusion with concomitant posterolateral fusion with pedicle screw instrumentation (control arm) following decompression. The primary effectiveness analysis is a responder analysis at 24-months post-operative where a subject is a responder if each of the following are satisfied:
• Function - Improvement of at least 15 points (of 100) on the Oswestry Disability Index (ODI) from baseline compared to 24 months
• Neurological status - Absence of a decrease in neurologic status (motor or sensory) at 24 months compared to baseline unless attributable to a concurrent medical condition or other cause unrelated to the device and/ or study procedure
• Surgical Intervention - Absence of additional surgical intervention, in a separate surgery subsequent to the index procedure, defined as revision, removal, reoperation or supplemental fixation/fusion at the instrumented level or levels adjacent to the instrumented level, over the initial 24 months
• Device Integrity - Absence of integrity failures, defined as device breakage, device separation or disassembly, or

device dislocation over the initial 24 months

The primary non-inferiority test will be conducted based on statistically combining within propensity score (PS) subclass comparisons of Month 24 composite clinical success rates between device groups. To conduct the non-inferiority test, the lower bound of a PS subclass adjusted one-sided 95% confidence interval for the difference in success rates will be determined. If this lower bound is larger than -0.125 it will be concluded that the investigational device is clinically non-inferior to control in terms of Month 24 composite clinical success. If the non-inferiority is demonstrated in this way, the same lower bound will be compared to zero and if it exceeds zero, superiority will be claimed. By the closed testing principle, there is no multiplicity adjustment needed for this test of superiority.

Kaplan-Meier survival analysis will be used to characterize and compare failure time distributions between groups stratifying on propensity score quintile where failures include device failure, revisions, reoperations, removals or supplemental fixations for each treatment group. Logistic regression analysis will be used to assess potential factors associated with success or failure of the investigational device including age, gender, BMI, and baseline ODI. Descriptive analyses of continuous secondary endpoints and other relevant variables will include computation of device group specific descriptive statistics including means, standard deviations, medians, minimum, and maximum values. Categorical variables will be summarized using counts and percentages. Specific adverse events and classes of adverse events (e.g., device-related, serious, severity) will be summarized according to the total number of events occurring as well as according to subject specific incidence rates. Counts of the numbers of specific events occurring during discrete time intervals over time and according to severity will be tabulated by device group. Device group differences in classes of adverse events will be summarized using PS subclass adjusted normal distribution based 95% confidence intervals when there are sufficient data to permit this type of analysis. Specific adverse event rates will be summarized using exact 95% confidence intervals for the difference in two binomials but will not account for PS subclass.

As described above, there may be as many as three sources of controls, prospective concurrent controls, retrospective controls, and historical controls or LimiFlex subjects. Primary and secondary effectiveness endpoints will be compared among investigational device subjects, prospective concurrent controls, retrospective controls, and historical controls or LimiFlex subjects, depending upon the number of sources utilized.

Software Used:
I am not analyzing participant-level data / I will not be using these software for analyses in the secure platform

Project Timeline:

Enrollment complete: End of 2019
Primary endpoint completion: End of 2021
Primary analysis complete and FDA submission: 2022
Primary manuscript and results posted to YODA: 2023
Final report (with 5-year follow-up, beyond primary endpoint): 2025

Dissemination Plan:

Several manuscripts are expected from this study: primary and secondary clinical outcomes; economic cost-effectiveness studies; radiographic outcomes; and long-term (beyond primary endpoint) clinical, radiographic and economic outcomes. Target journals, ranked by priority, are as follows:
- The Spine Journal [Spine J]
- Spine [Spine (Phila Pa 1976)]
- The Journal of Neurosurgery: Spine [J Neurosurg Spine]
- Journal of Bone and Joint Surgery [J Bone Joint Surg Am]
- International Journal of Spine Surgery [Int J Spine Surg]

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Supplementary Material:

https://yoda.yale.edu/sites/default/files/2019-4001_yoda_project_research_proposal_direct_data_access_request_2020-01-07.pdf
https://yoda.yale.edu/sites/default/files/response_to_12-23-19_info_request_re_yoda_project_protocol_2019-4001.pdf