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| Title: | Safety and Efficacy of a vertebral body tethering technique for pediatric idiopathic scoliosis |
| Short Title | Vertebral Body Tethering Outcomes |
| Drug or Device Name(s): | Globus Medical Inc.<br>*Reflect/Transition™ Stabilization System*<br>Polyethylene terephthalate (PET) cord |
| FDA IDE | XXX-XX |
| Regulatory Sponsor: | Suken A. Shah, MD |
| eIRB Number: | XX-XXXX |
| Protocol Date:<br>Amendment 1 Date: 4/23/2019<br>Amendment 2 Date: 10/16/2019 | 12/1/2017<br>Amendment 3 Date: 02/17/2020<br>Amendment 4 Date: 06/29/2021 |

Contents

## ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| Adams's Forward Bending Test | Subject stands with their back to the examiner, and bends forward at the waist, with knees in extension. The examiner looks at the horizontal plane of the spine, and measures angle created between a rib hump and the horizontal plane. This is measured with an inclinometer. |
| Adding on | Phenomenon where there is a worsening of the scoliotic curve after spinal fusion. This usually occurs at levels distal to the distal end of the spinal fusion. |
| AE | Adverse event |
| AIS | Adolescent Idiopathic Scoliosis |
| AT | Anterior Tethering |
| Bending/ Bolster x-ray | Coronal radiograph of the entire spine, with the patient positioned in lateral flexion. The lateral flexion is done towards the convex side of the curve, to 'lessen' the appearance of the curve's magnitude. This is done either standing, with the patient bending under their own power; or in the lateral decubitus position, with a pillow or 'bolster' placed at the apex of the convexity of the curve. |
| Coronal spine x-ray | Radiograph of the coronal plane of the entire spine, usually also extending distally to include the femoral head/neck |
| HRQOL | Health-Related Quality of Life |
| JIS | Juvenile Idiopathic Scoliosis |
| Lenke Classification | Standardized classification system for Idiopathic Scoliosis. The system has three components: 1) Main Curve type (1-6), 2) Lumbar spine modifier (A, B, C), 3) Sagittal thoracic modifier (-, N, +) |
| OSP | Office of Sponsored Projects |
| PET | Polyethylene Terepthalate |
| PFT | Pulmonary Function Test |
| PSF | Posterior Spinal Fusion |
| Risser Scale | Indirect measure of skeletal maturity, based on the ossification of the Iliac crest. Graded on a scale of 0-5; 1 being ¼ ossified, and 4 being completely ossified. 0 shows no ossification, and 5 is completely ossified with fusion of the iliac apophysis to the iliac crest. |
| SAE | Serious adverse event – any undesirable experience associated with use of the medical device that results in |
| Sagittal spine x-ray | Radiograph of the entire spine taken in the sagittal plane. |
| Sanders Bone Age | Standardized method of measuring skeletal maturity that is predictive of scoliotic curve progression. This method involves analysis of the ossification centers of the hand, using an AP radiograph of the entire hand. |
| SOC | Standard of Care |
| Thoracic/Lumbar flexion test | Subject stands with trunk erect while measuring tape is placed proximally on the spinous process of C7 and |

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| | distally to S1. The subject then bends forward at the waist, with knees in extension. Following flexion of the vertebrae, using the same bony landmarks, the examiner calculates the difference in distance between the starting and ending positions. |
| Thoracic/Lumbar lateral flexion test | Subject stands erect with the feet flat on the floor. Place one end of a measuring tape on the tip of the middle finger and the other on the floor on a point directly beneath the middle finger. The patient then laterally flexes their trunk. The difference following the lateral flexion motion is measured. |
| TLSO | Thoraco-lumbo-Sacral Orthosis |
| UDI | Unique Device Identification |
| VBT | Vertebral Body Tethering |


## ABSTRACT

Context:

Scoliosis is a condition where the spine is deformed by a curvature in the coronal plane. It is generally associated with a twisting (axial plane) deformity as well. It can have a variety of underlying etiologies and the etiology is used to classify the types of scoliosis. Idiopathic scoliosis is sub-classified in two ways: by age of onset and by magnitude of deformity. Curves between 10 and 25 degrees are considered mild. Curves between 25- and 50 degrees are classified as moderate. Curves greater than 50 degrees are termed severe. The current standard of care for

moderate scoliosis in patients with remaining growth is to utilize a thoracolumbosacral orthosis (TLSO brace) to prevent progression of deformity. The scientific evidence has supported the efficacy of this intervention in avoiding progression of the Cobb angle to 50 degrees or more.

If treated with a TLSO brace, many idiopathic scoliosis patients would conceivably be subjected to years of brace wear and the cost and psychological factors inherent therein. Additional downsides of brace treatment include the potentially negative psychosocial impact of wearing an external sign of deformity during adolescence, a key period of emotional development. Prior research has identified negative psychosocial effects related to wearing a brace in children.

Recent evidence has suggested that certain curve patterns will likely progress to 50 degrees or more, despite treatment with a TLSO brace. Sanders, et al. demonstrated a correlation of Cobb angle (greater than 35 degrees) and skeletal maturity (bone age 4 or less) to the risk of progression to 50 degrees or more, despite TLSO bracing. The evidence supports that the current practice of TLSO bracing is not an effective treatment to avoid progression to 50 degrees in these patients. It is on this population (thoracic Cobb angle greater than 35 degrees, bone age of 4 or less) that we intend to test the safety and efficacy of Anterior Vertebral Body Tethering to avoid curve progression to more than 50 degrees.

Objectives:

The objectives of this study are to assess the safety and efficacy of Anterior Vertebral Body Tethering Surgery (AVBT) to treat Idiopathic Scoliosis.

Study Design:

This is a Phase II, non-randomized, open label study of the anterior insertion of a Polyethylene Terephthalate (PET) cord in pediatric scoliosis. The study will be conducted at a single site- Nemours – Alfred I duPont hospital for Children

Setting/Participants:

This is a single-site, Sponsor-Investigator led phase II clinical trial of Vertebral Body Tethering for pediatric idiopathic scoliosis in children aged 8-16 years. The study will have a retrospective arm to collect data from patients who had the tether surgery prior to approval of the prospective study.

Study Interventions and Measures:

The study intervention is surgical orthopedic implantation of Anterior Vertebral Body Screws with PET cord, by way of thoracoscopic surgery under general anesthesia. The primary outcome measures include assessments of safety of the insertion procedure and of the device, as well as the secondary measure of efficacy by determining the improvement in the angle of deformity. Monitoring will be conducted by a data safety committee, who has extensive training and experience in surgical procedures.

## PROTOCOL SYNOPSIS

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| **Study Title** | Safety and efficacy of a vertebral body tethering technique for pediatric idiopathic scoliosis |
| **Funder** | Departmental Funds |
| **Clinical Phase** | Phase II |
| **Study Rationale** | Anterior surgical approach and instrumentation is an accepted standard treatment for idiopathic scoliosis (IS). This study will assess whether the intervention (Anterior Vertebral Tethering) is a safe and efficacious method of anterior approach surgery for spinal deformity in pediatric scoliosis. |
| **Study Objective(s)** | **Primary**<br>To determine the safety of Anterior Vertebral Tethering surgery<br><br>**Secondary**<br>To determine the efficacy of Anterior Vertebral Tethering surgery |
| **Test Article(s)** | Globus Medical Inc.<br>*Reflect/Transition™ Stabilization System*<br>Polyethylene terephthalate (PET) cord |
| **Study Design** | This is a single center prospective, open-label pediatric clinical device trial with a single surgical intervention with retrospective arm to collect data from patients who already had AVT surgery. |
| **Subject Population Key criteria for Inclusion and Exclusion:** | **Inclusion Criteria**<br>1. Males or females age 8 to 16 years old at time of enrollment (inclusive)<br>2. Diagnosis of Idiopathic Scoliosis<br>3. Sanders bone age of less than or equal to 4<br>4. Thoracic curve of greater than or equal to 35 degrees but not larger than 60 degrees<br>5. Lumbar curve less than 35 degrees<br>6. Spina bifida occulta is permitted<br>7. Spondylolysis or Spondylolisthesis is permitted, as long as it is non-operative, the patient has not had any previous surgery for this, and no surgery is planned in the future<br>8. Completed standard-of-care procedures as outlined in Section 5 |

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| **Subject Population Key criteria for Inclusion and Exclusion:** | Exclusion Criteria<br>1. Pregnancy (current)<br>2. Prior spinal or chest surgery<br>3. MRI abnormalities (including syrinx >4mm, Chiari malformation, or tethered cord)<br>4. Neuromuscular, thoracogenic, cardiogenic scoliosis, or any other non-idiopathic scoliosis<br>5. Associated syndrome, including Marfan Disease or Neurofibromatosis<br>6. Sanders bone age greater than 4<br>7. Thoracic curve less than 35 degrees<br>8. Lumbar curve greater than or equal to 35 degrees<br>9. Unable or unwilling to firmly commit to returning for required follow-up visits<br>10. Investigator judgement that the subject/family may not be a candidate for the intervention |
| **Number Of Subjects** | The study will be conducted at The Nemours – Alfred I duPont hospital for Children, Division of Orthopedics. Subject inclusion will be based on interest of patients that satisfy the inclusion/exclusion criteria that present to the Orthopedic Clinic. The total study enrollment will be 30 subjects. In the retrospective arm we will aim to enroll all patients who had the tether surgery in the past.The study ends when all patients reach skeletal maturity. |
| **Study Duration** | Each subject's active participation will last about 5 years after surgery. The entire study is expected to last at least 8 years. |
| **Study Phases:**<br><br>**Screening** | 1. Screening phase: Subjects will be screened by study staff during a clinical visit in the Orthopedics department. Eligible subjects will be approached and if interested, enrolled during a routine clinical exam. |
| **Study Treatment** | 2. Study Treatment: The subject will undergo surgical intervention using accepted standard-of-care anterior approach using the Globus Medical Inc. *Creo™ Stabilization System*. **Vertebral body tethering using screws and Polyethylene Terepthalate cord (Globus Medical, Inc. Reflect/*Transition™ Stabilization System*) is investigational.** |
| **Post-op Follow-Up** | 3. Post-operative Follow-up: Subjects will be followed at regular time points at 45 and 90 days post-op during the post-operative phase. Patients will also be seen at visits 180, 365, 730, 1095, 1460, 1825 days post-op during the extended follow-up phase. |

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| **Efficacy Evaluations** | The primary efficacy evaluation measurement is thoracic Cobb angle (to nearest degree) at the pre-operative visit to Cobb angle during follow-up, especially at two years post-op (POD 730). |
| **Safety Evaluations** | We will use phase-specific endpoints to measure safety:<br>1) Study treatment phase: Any individual-level intraoperative events including neuromonitoring events (loss or change in neurological signaling or function), unanticipated events during surgery, and SAEs.<br>2) Post-operative active phase: Incidence of infection (within 90 days post-op), pneumothorax, bronpulmonary plug, or any reportable SAE.<br>3) Extended follow-up phase: Incidence of over-correction, implant failure (measured on serial x-ray), incidence of curve progression to >50 degrees at 5 year follow-up, or incidence of secondary surgery or re-operation to correct further spine deformity (not related to trauma or other issues not related to the initial surgery / disease). |
| **Statistical And Analytic Plan** | Cobb angle is a continuous variable. T-test or repeated measures Anova will be used to detect any change in Cobb angle post-operatively. Linear regression will be utilized to assess which variables are associated with change in post-operative Cobb angle. |
| DATA AND SAFETY MONITORING PLAN | The PI and Data Safety group will meet regularly to discuss any safety events. Group's reports will be forwarded to the IRB during continuing review per ORC monitoring guidance. Safety reporting will be according to IRB SOP 408 and governing FDA guidelines. The PI and study team will also comply with all ORC monitoring standards. The PI will meet with the study team regularly to discuss study progress and ensure data fidelity. The first meeting will take place before initiation of the study to discuss the protocol and establish guidelines to monitor the study. The Sponsor-PI will work in conjunction with the DSMB members to prepare an agenda to address the review of the initiation of the trial, reporting of adverse events, stopping rules, etc.<br>Meetings will be held before enrolling the 1st, 5th, 9th and so forth patient. If a Serious Adverse Event (SAE) occurs, a separate meeting will be held. |

The meetings will be held at the Nemours AIDHC Department of Orthopedics using WebEx connectivity for attendees who are not in the office.
Meeting minutes will be recorded by the study coordinator and will become part of the study binder.
DSMB group includes the following members who do not have a financial or other types of conflict of interest related to this study:

1. Michael Wade Shrader, MD

2. Kevin Neal, MD

3. Hossain, Md Jobayer , Ph.D

Dr. Shah will not lead the DSMB meetings, but help to prepare reports/events for the DSMB. Dr. Shah will be present as a participant in the meetings to answer questions by the DSMB personnel, but will not be present for a closed portion of the meeting.
Members of the DSMB are:
Michael Wade Shrader, MD is the director of the Cerebral Palsy program at Nemours – AIDHC department of Orthopedics. He is a board certified orthopedic surgeon with 14 years of experience. He has performed posterior spinal fusion (PSF) surgeries on patients for 14 years.

Kevin M. Neal, MD is the Program Director of Orthopedics Fellowship program at Nemours, Jacksonville. He is board certified orthopedic surgeon with 15 years of experience. Dr. Neal has performed posterior spinal fusion surgeries on pediatric patients for 15 years.

3. Hossain, Md Jobayer, Ph.D is Senior Research Scientist in the Department of Biomedical Research and the Manager of the Biostatistics Core at Nemours, as well as an Adjunct Associate Professor in the Department of Applied Economics and Statistics at University of Delaware. He is a lead or co-author for 103 published articles and more than 160 published abstracts and presentations. He is actively involved in scientific, educational, and research activities. His academic training and extensive work experience in statistics, epidemiology, and biometry.

# 1 BACKGROUND INFORMATION AND RATIONALE

## 1.1 Introduction

Scoliosis is a condition where the spine is deformed by a curvature in the coronal plane. It is generally associated with a twisting (axial plane) deformity as well. It can have a variety of underlying etiologies, and the etiology is used to classify the types of scoliosis. Scoliosis related to conditions affecting the nervous system or muscle function are termed neuromuscular scoliosis. Neuromuscular scoliosis is often related to conditions such as cerebral palsy, muscular dystrophies, spina bifida, or paralysis [1]. Another type of scoliosis is congenital scoliosis; scoliosis related to malformation of the bony structures of the spine. Some syndromes are associated with a high incidence of scoliosis including Marfan syndrome and neurofibromatosis. These forms of scoliosis are termed syndromic scoliosis [2]. Idiopathic scoliosis is scoliosis not due to any of the above mentioned causes. It is a diagnosis of exclusion.

Idiopathic scoliosis is sub-classified in two ways: by age of onset and by magnitude of deformity. Curves between 10 and 25 degrees are considered mild. Curves between 25- and 50 degrees are classified as moderate. Curves greater than 50 degrees are termed severe. Idiopathic scoliosis occurs in 2-3% of the population with decreasing frequency at higher magnitudes of deformity. Idiopathic scoliosis diagnosed before age 3 is classified as infantile idiopathic scoliosis; between 3 and 10, juvenile idiopathic scoliosis; 10 to 18 adolescent idiopathic scoliosis; greater than 18 is adult idiopathic scoliosis. The diagnosis is retained throughout life; a juvenile idiopathic scoliosis patient does not become an adolescent idiopathic scoliosis patient at age 10.

Further classification of surgically treated adolescent idiopathic scoliosis has been derived by Lenke et al. [3], in an attempt to guide treatment. The classification system takes into account factors such as the location of the deformity (thoracic v. lumbar, v. both), number of curves, the flexibility of the deformity, and the sagittal plane. This classification system has been widely adopted in medical literature on the condition.

### 1.1.1 The Principle of Growth Modulation

Although the etiology of idiopathic scoliosis is largely unknown, some genetic factors have been implicated [4]. Biomechanical imbalance leading to asymmetrical spinal growth has also been postulated as the mechanism for progression, though there is limited evidence to link idiopathic scoliosis progression to a biomechanical cause [5]. Many treatments have been proposed to manage the progression of idiopathic scoliosis. Among the various treatment methods used, bracing and surgical fusion remain the most common treatments to alter the natural history of the disease [6]. Although spinal fusion and instrumentation for scoliosis correction has high intermediate success rates with few complications, it is among the most invasive procedures. Loss of motion following fusion and potential for adjacent segment degeneration is a long-term concern.
In the field of limb deformities, the concept of growth modulation by a staple in a growing child (introduced by Blount) is utilized as part of the accepted common practice and as the standard of care for management of limb deformity [7]. It is presumed that compressive implants such as staples inhibit growth according to the Hueter-Volkmann principle [8]. 2

More recently, similar concepts have been applied successfully for spine growth modulation. These devices provide compressive forces on the convex side of the curve utilizing the Heuter-Volkman principle; slowing the growth on the convex side of the curve and enhancing the growth on the concave side. This effect has been demonstrated in animal models [9]. Furthermore, they have shown to preserve motion at the instrumented levels. Radiographic and chemical analysis performed in the animals have shown that disc function is maintained after the application of such a device [9].

### 1.1.2 Current standard of care

#### *1.1.2.1 Moderate Scoliosis (Curves 25-50 Degrees)*

The current standard of care for moderate scoliosis in patients with remaining growth is to utilize a thoracolumbosacral orthosis to prevent progression of deformity. Recent evidence has supported the efficacy of this intervention in avoiding progression of the Cobb angle to 50 degrees or more. In 2010, Katz and colleagues [10] examined the efficacy of bracing and published a study that utilized heat sensors within braces to quantify brace wear compliance. In that study, Katz and colleagues [10] determined the brace success rate to be 82% in patients who wore their brace for more than 12 hours per day. In 2013, Weinstein and colleagues [11] demonstrated an improvement over the natural history with brace treatment and a correlation between hours of brace wear and efficacy of bracing in AIS. The most important difference in the results presented by Weinstein and colleagues [11] and Katz and colleagues [10] and the proposed study is the level of maturity (and therefore natural history) of the treatment population. The average age of initiation of bracing in both the Weinstein et al. and Katz et al. studies was 12.7 years. In a subsequent study of AIS patients treated with bracing, Karol and colleagues demonstrated a more than 5 fold increased risk of bracing failure in Risser 0 patients compared to Risser 1 patients [12].

The study results of Karol et al. and others suggest that there may be a level of skeletal immaturity below which bracing cannot alter the natural history of moderate idiopathic scoliosis [13]. The study reported that 63% of patients with Risser 0 and open triradiate cartilage progressed to the point of requiring a fusion. The efficacy of bracing in this cohort was significantly less than those with closed triradiate cartilages ($P<0.001$). Furthermore, those patients with Risser 0, open triradiate cartilage, and a Cobb angle of 30 degrees or greater had a 74% incidence of progression to fusion. Jarvis and colleagues [14] reported that fusion was avoided in only 49% of those patients with Juvenile Idiopathic Scoliosis (JIS) treated with bracing, which raises the question of whether bracing has any impact the natural history in JIS. Charles et al. further stratified JIS by Cobb angle [15]. The study showed that curves more than 30 degrees prior to the puberty growth spurt progressed to a magnitude requiring surgery in 100% of cases despite bracing.

If treated with a brace, many idiopathic scoliosis patients would conceivably be subjected to years of brace wear and the cost and psychological factors inherent therein. Additional downsides of brace treatment include the potentially negative psychosocial impact of wearing an external sign of deformity during adolescence, a key period of emotional development. Prior research has identified negative psychosocial effects related to wearing a brace in children [16]. Such ramifications were further explored in a recent study by Misterska and colleagues [17], who found that the patients experienced a moderate level of 3

stress specifically related to brace wear despite only low stress levels related to perceived spinal deformity. From a patient reported outcome point of view, the treatment is worse than the disease.

#### *1.1.2.2 Severe Scoliosis (Curves 50 Degrees and Greater)*

Spinal fusion is the current standard of care for curves at or near 50 degrees in AIS and JIS. Posterior spinal fusion (PSF) involves a midline approach to the back, placement of spinal anchors (usually pedicle screws), and fusion with bone graft across the posterior laminae. The course of treatment is predictable and safe. Newton et al. reported on the treatment of the most common subtype of AIS – Lenke 1 curves – which comprise about half of all AIS cases. He reported that a posterior spinal fusion will require a 4 hour surgery with a 5 day hospital stay with a blood loss of approximately 800cc [18]. Anterior Spinal Fusion is often utilized as well and this may involve a thoracotomy (open procedure) or thoracoscopy. Thoracoscopic anterior spinal fusion also has consistent outcomes in terms of radiographic results and expected course of treatment [19].

## 1.2 Name and Description of Investigational Product or Intervention

### 1.2.1 Vertebral tethering

Vertebral Body Tethering (VBT) will be performed via an anterior thoracoscopic approach (see "Surgical Technique" below). This surgical approach is utilized as a common approach for the current standard of care anterior-type spinal fusion [19, 20]. Thoracoscopic anterior approaches do not seem to carry any increased risk over other approaches for spinal fusion, namely posterior spinal fusion and open anterior spinal fusion. The reason it is not uniformly utilized is that the fusion is less reliable in this approach with the pseudo-arthrosis rate in thoracoscopic surgery reported at 11% v. 3% in posterior spinal fusion [18]. This concern is irrelevant in VBT as fusion is not the goal.

### 1.2.2 Implant

The implants utilized comprise of two components from Globus Spine, Inc., the *Creo*™ and Reflect/*Transition*™ *(aka Reflect)* systems. The *Creo*™ system is designed and indicated to be used in anterior thoracoscopic spinal fusion for spinal deformity. We anticipate placing centering staples and screws in a manner identical to how they are approved for use. However, rather than performing a discectomy, placing bone graft, and placing a rigid rod, we will place a flexible Polyethylene Terephthalate (PET) cord (Globus Spine, Inc. Reflect/*Transition*™ *Stabilization System*). The cord is approved as part of a posterior spinal stabilization system. Currently, no other company has an approved device for the use we are proposing for this clinical study. Zimmer Spine, Inc. has a posterior PET cord as part of their *Dynesis*® system but they do not have an anterior thoracoscopic implant system that it can be used with. Some surgeons have suggested modifying posterior screws from the *Dynesis*® system for anterior use for vertebral tethering but these screws do not have sizing for pediatric indications, as the *Creo*™ system does. Furthermore, the *Dynesis*® system does not have a centering/stabilizing staple, which is a common component of anterior spinal instrumentation systems.

### 1.2.3 Surgical Technique

The surgical technique has been described by Samdani, et al. [21, 22]:
The patient is intubated with a double lumen endotracheal tube with fiber optic assistance. A Foley catheter is placed. The patient is positioned in a lateral decubitus position with the operative (convex curve) side facing up. The operative flank is prepped and draped from midline anteriorly to midline posteriorly. Flouroscopic assistance is utilized to mark out the location of the various vertebra and three 5mm incisions are made to insert the ports in triangular fashion. The apex incision is made at the anterior axillary line at the 5th intercostal space. The other two incisions are made at the midaxillary line at the 3rd intercostal space and the 8th intercostal space. Through the first port a camera is introduced, harmonic scapel through the second, and endoscopic "peanut" is placed through the third incision. The pleura is dissected off the vertebral bodies laterally along the length of the curve, and anteriorally to the rib heads. Care is taken to identify and coagulate the segmental vessels. A 15mm port is then inserted over the most cephalad vertebral body ready to be tethered. Over the anterior aspect of the most cephalad vertebral body, a 3 prong staple (*Creo™ Stabilization System*, Globus Spine, Inc.) is introduced while maintaining caution that the staple is not introduced in the foramen. Using fluoroscopy the position of the staple is confirmed, and then a 5.2mm tap is used to create a screw hole under fluoroscopic guidance. The tap is begun on the convex side of the curve towards the convex side, across the anterolateral portion of the vertebral body. Next, an appropriately sized screw (*Creo™ Stabilization System*, Globus Spine, Inc.) is placed, with position of the screw confirmed by fluoroscopy. Utilizing the same skin incision, the 15mm port is moved to the next intercostal space. The vessel ligation, staple placement, tap, and screw placement are then repeated at the next vertebral body- moving cephalad to caudad. Generally, up to 3 intercostal spaces can be accessed through the same skin incision. Patients who are instrumented to L3 require a mini-open retroperitoneal approach.

After all of the screws are placed, the caudal 15mm port is used to pass the PET cord (Reflect/*Transition™ Stabilization System*, Globus Spine, Inc.) through the tulips of all of the screws. The set screw (*Creo™ Stabilization System*, Globus Spine, Inc.) is then placed on the most caudal screw tulip using a T-handle pusher. The set screw is locked in place using a locking cap (*Creo™ Stabilization System*, Globus Spine, Inc.), thereby securing the PET cord on the most caudal screw. Correction is achieved by tensioning the PET cord and through translation of the spine. Once the correction achieved is satisfactory to the surgeon, the set screws are tightened on each screw tulip- moving caudad to cephalad. Flouroscopic images should be obtained after each screw is tightened, to confirm curve correction. These fluoroscopic images also confirm that there is no pulling out, plowing, or other untoward changes in the screw placements in the vertebral bodies.

Once all screws have been tightened, global AP and Lateral X-rays of the spine should be performed to confirm correction of the curvature. Once satisfactory correction is

confirmed in this manner, the PET cord should be trimmed, to leave about 2cm at either end to accommodate any future adjustment if necessary. An attempt should be made to re-approximate the pleura, though this is difficult with the implant. A chest tube should be placed in one of the 5mm port sites. The hemithorax is then irrigated, the lung is re-inflated under direct vision, and the incisions are closed in layers.

### 1.3 Findings from Non-Clinical and Clinical Studies

#### 1.3.1 Clinical studies

When anterior spinal fusion is selected it is more often performed in cases where only one curve, the thoracic or the lumbar curve, requires a fusion [23]. We are proposing similar indications and applications for vertebral tethering – a single thoracic curve requiring treatment. Anterior spinal fusion provides good clinical and radiographic results. The approach for anterior spinal fusion for AIS is most often performed with thoracoscopic guidance. The thoracoscopic approach is less invasive than its alternative, an open thoracotomy. Newton et al. reported on 5 year results of thoracoscopic anterior fusion showing that Cobb angle correction averaged 56% [20, 24], and total lung capacity at 91% of expected. These results were not different than the 2 year outcomes in the same patients, suggesting that any slight negative impact of anterior thoracoscopy did not lead to a progressive decline in pulmonary function. Furthermore, although open anterior spinal fusion is associated with a significant decline in objective measurements in pulmonary function, thoracoscopic anterior surgery was not different in its impact on pulmonary function than posterior spinal fusion [25, 26]. Faro et al. demonstrated that pulmonary function declines 3 months after both open and thoracoscopic anterior scoliosis surgery but recovers by 1 year post-op in thoracoscopic surgery but not in open anterior surgery [27].

In a comparison of the three approaches for fusion of the thoracic spine for AIS (open anterior, thoracoscopic anterior, and posterior), Newton et al. in another study reported that Cobb angle correction (57%) was similar in all groups, blood loss and incidence of transfusion was greater but surgical time was less in the posterior group, and SRS-22 scores were equivalent [18]. Furthermore, they reported decreased pulmonary function in the open anterior groups but similar PFTs in posterior and thoracoscopic patients. Lonner et al. also addressed the impact of surgical approach on pulmonary function [23]. The authors reported a decrease in forced expiratory volume in 1 second (FEV1) and functional vital capacity (FVC) as a percent of expected by 4-5% but an increase in total lung capacity (TLC) of 3% **(Tables 1 and 2)**. These changes are of minimal clinical significance.

Table 1: Demographics (Adapted from Lonner et al, 2015)

| Approach Type | N | Sex Distribution | Mean Age at Surgery (Range)* | Mean Numbers Levels Fused | Lenke Curve Type |
|---|---|---|---|---|---|
| Thoracotomy | 68 | 61 female, 7 male | 14.3 (10-21) | 6.6 | 1 |
| Thoracoscopic | 44 | 39 female, 5 male | 13.9 (10-18) | 6.1 | 1 |
| Thoracoabdominal | 19 | 18 female, 1 male | 14.8 (13-18) | 4.1 | 5 |

*Not significantly different.

Table 2: Mean Percent-predicted Values Preoperatively to Follow-up (Adapted from Lonner et al, 2015)

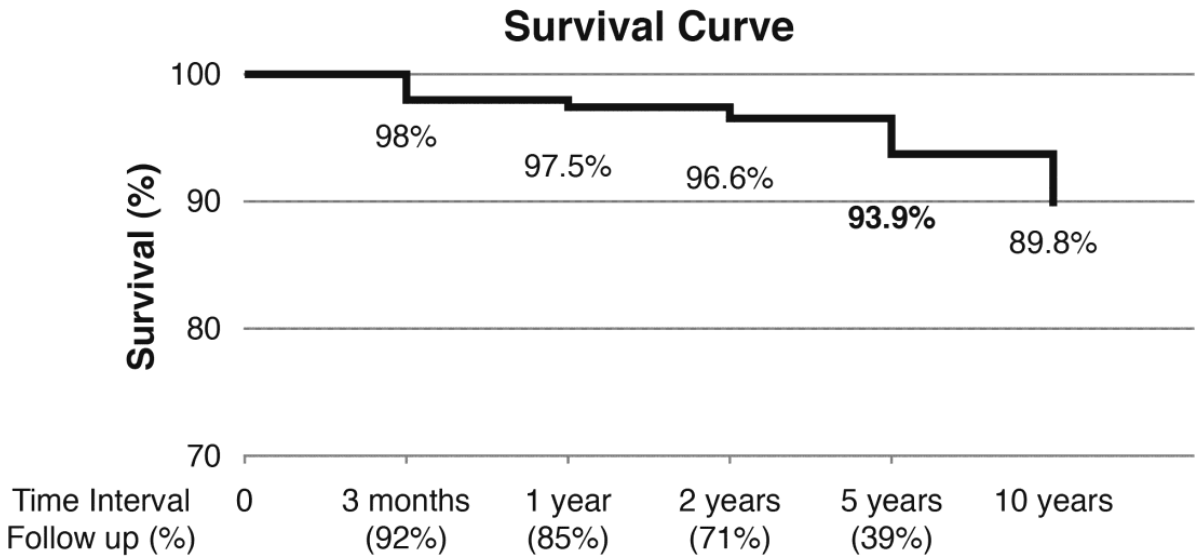
| | **Percent predicted FEV1** | **Percent predicted FVC** | **Percent predicted TLC** |
|---|---|---|---|
| Thoracotomy | | | |
| Mean preoperative | 83.3 | 88.1 | 85.6 |
| Mean follow-up | 72.3 | 75.1 | 77.6 |
| □ *(Pre-post)* | -11.0 | -13.0 | -8.0 |
| P | <0.001 | <0.001 | ≤ 0.001 |
| | | | |
| Thoracoscopic | | | |
| Mean preoperative | 82.5 | 87.2 | 85.0 |
| Mean follow-up | 78.1 | 82.5 | 88.2 |
| □ | -4.4 | -4.7 | 3.2 |
| P | <0.004 | NS | NS |
| | | | |
| Thoracoabdominal | | | |
| Mean preoperative | 90.3 | 93.7 | 94.7 |
| Mean follow-up | 83.5 | 87.7 | 95.1 |
| □ | -6.8 | -6.0 | 0.4 |
| P | NS | NS | NS |

FEV1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity; NS, non-significant; TLC, total lung capacity

There is room for improvement over the outcomes of posterior spinal fusion. In particular, the durability of the procedure is coming into question. Posterior pedicle screw constructs came into

popularity in the early 2000's and new 10 year post-op data is demonstrating a concerning trend. The Harms Study Group, a multicenter consortium of scoliosis practitioners and researchers have recently shown that almost 10% of AIS fusions require revision surgery by 10 years post-op and that this trend is progressive [28] **(Figure 1).**

Figure 1: Re-operation rates ("Survival Curve") of posterior spinal fusion over time. (Personal Communication from Peter Newton)




Other authors have also reported on high long term re-operation rates following AIS fusion surgery ranging from 4.6% to 19% [29-31]. One theory is that a fusion imparts increased stress on unfused segments below a fusion. Marks et al. have shown that patients will retain total lumbar motion after a posterior spinal fusion by increasing motion in the unfused areas [32]. The authors postulate that increased motion may lead to degeneration of discs and facet joints. These findings of supraphysiologic motion below a posterior spinal fusion may explain some of the decreasing durability of posterior spine fusion. Green et al. have studied the health of intervertebral discs below a spinal fusion at an average of 11.8 years following posterior spinal fusion [33]. The authors found that disc degeneration was occurring in 85% of patients and the discs when graded by the Firman scale, an objective validated measure of disc degeneration [33]. Vertebral tether surgery will allow for continued motion of the instrumented levels and thus avoid the long lever-arm effect of a long fusion that may be contributing to early degeneration. Additional reports have questioned the durability of posterior spinal fusion. Upasani et al. reported on increased pain in patients at 5 years post-spinal fusion compared to at 2 years [34]. Lastly, posterior spinal fusion in patients who have not had their pubertal growth spurt, the population in whom we are proposing vertebral tethering, are at increased risk of complications and re-operation. Sponseller et al. reported that patients with open triradiate cartilages undergoing spinal fusion surgery have an increased rate of "adding on" (development of deformity below a fusion) and the response of the uninstrumented lumbar curve is less predictable [35].

Ideally, longitudinal outcomes of current standards of care including anterior thoracoscopic and posterior pedicle screw instrumented fusion would be used as a standard against which new technology can be compared. However, such data is a half century away. Furthermore, the pace of change and improvement in spinal deformity instrumentation and surgery tells us that change is inevitable [36].

### 1.3.2 Non clinical studies

There have been several animal studies of vertebral tethering. Peter Newton and colleagues at The University of California at San Diego and Rady Children's Hospital have performed spinal tethering studies in bovine and porcine models [37-39]. The first study the authors published was in an immature bovine model [38]. They utilized a stainless steel tether. They demonstrated those animals who had a sham surgery without placement of the tether did not develop a curvature while those with placement of two rods did develop a curve. This was offered as a proof of concept that tension of a tether could alter growth and change alignment. In the porcine model, the investigators demonstrated the ability of a spinal tether to induce deformity in immature animals proportionally to the duration it was left in place, offering further evidence of the effect of growth in contributing to the deformity rather than tension of the implant alone [40]. Further evidence of the effect of growth driving the change in alignment was offered in a subsequent study of the bovine model [37]. They demonstrated equivalent deformity magnitude after 12 months between groups in which the tether was tensioned and those in which it was placed without tension.

## 1.4 Relevant Literature and Data

The natural history of scoliosis after maturity has been described in several populations treated non-operatively and followed longitudinally. One cohort is from Scandinavia and was reported by Danielsson and Nachemson [41]. The other is from Iowa and was reported by Weinstein and colleagues [42, 43]. Nachemson reported a cohort of 117 scoliosis patients with a variety of types of scoliosis including those classified as congenital scoliosis, neuromuscular scoliosis, post-infectious scoliosis, and idiopathic scoliosis [44]. Decreased life expectancy was reported in this group. A subsequent sub-analysis of only the idiopathic scoliosis patients in this group revealed that there was no increase in mortality compared to the general population. Weinstein et al. reported a group of idiopathic scoliosis patients treated with observation [43]. They showed that, despite an increase in back pain symptoms, there was no increase in mortality rates compared to the aged matched general population. Furthermore, they identified Cobb angle greater than 50 degrees as a predictor of continued progression in adulthood. Greater than 85% of these patients progressed at a rate of ~1.1 degrees per year. Weinstein demonstrated a Cobb angle greater than 50 degrees as a factor predictive of further progression in adolescents in a subsequent study [42]. This forms the basis for current indications of surgical fusion for curves greater than 50 degrees. Conversely, curves less than 30 degrees at the end of growth did not progress nor did they exhibit any pain or pulmonary dysfunction. The desire to keep curves below thirty degrees forms the recommendation for initiation of brace management in curves that are 25- 30 degrees.

### 1.4.1 Curves below 50 Degrees With A High Likelihood of Progression to 50 Degrees

Further studies have elucidated which curves in immature patients will progress to 50 degrees before reaching skeletal maturity. Rather than taking a reactive approach to these curves, we propose early treatment of this population with vertebral tethering. Dimeglio et al. demonstrated that immature patients with idiopathic scoliosis with a Cobb angle of 30 degrees or greater prior to their pubertal growth spurt will universally progress to 50 degrees by the end of growth [45].

Dimeglio suggests several measures for identifying the onset of 10 pubertal growth spurt including the changes of various bone growth centers remote from the spine. These include the appearance (radiographically) of the sesamoid bone in the thumb, the presence of two distinct ossification centers in the olecranon (elbow), and an open tri-radiate cartilage (hip socket). Sanders et al. have also demonstrated a correlation of risk of progression to a Cobb angle of 50 degrees between markers of skeletal maturity and Cobb angle [46]. They developed an easily applied scoring system of 1-7 to a hand x-ray. The advantage of a hand x-ray is that it encompasses a large number of growth centers, does not require additional training of radiology personnel, and is remote from more radiosensitive organs. The maturity based progression assessment derived by Sanders assigns a risk of progression to a Cobb angle of 50 degrees or more. It is this risk of progression to 50 degrees on which we base or treatment decision for Vertebral Body Tethering. **Table 3** illustrates that there is significant risk for progression if a patient's curve is above 35 degrees, and is a Sanders stage of 4 or less. Therefore our inclusion criteria for this study are set to include patients with curves above 35 degrees and a Sanders stage of 4 or less.

We have selected an upper limit of 60 degrees due to the theoretical concern of achieving higher amounts of correction during periods of limited growth. In retrospective series by Samdani et al., the average Cobb angle of treated curves was 44 degrees [21, 22].

Table 3: Projected risk of progression of scoliosis to above 50 degrees, based on curve magnitude and bone age. (From Sanders, et al. 2008)

**TABLE III Logistic Projection of the Probability of Lenke Type-1 and Type-3 Curves Progressing to Surgery Assuming a >50° Threshold*†**

| Curve | Stage 1 | Stage 2 | Stage 3 | Stage 4 | Stage 5 | Stage 6 | Stage 7, 8 |
|---|---|---|---|---|---|---|---|
| 10° | 2% (0% to 40%) | 0% (0% to 15%) | 0% (0% to 0%) | 0% (0% to 0%) | 0% (0% to 0%) | 0% (0% to 0%) | 0% (0% to 1%) |
| 15° | 23% (4% to 69%) | 11% (1% to 58%) | 0% (0% to 2%) | 0% (0% to 0%) | 0% (0% to 0%) | 0% (0% to 0%) | 0% (0% to 7%) |
| 20° | 84% (40% to 98%) | 92% (56% to 99%) | 0% (0% to 14%) | 0% (0% to 1%) | 0% (0% to 1%) | 0% (0% to 1%) | 0% (0% to 26%) |
| 25° | 99% (68% to 100%) | 100% (92% to 100%) | 29% (3% to 84%) | 0% (0% to 5%) | 0% (0% to 5%) | 0% (0% to 2%) | 0% (0% to 64%) |
| 30° | 100% (83% to 100%) | 100% (98% to 100%) | 100% (47% to 100%) | 0% (0% to 27%) | 0% (0% to 22%) | 0% (0% to 11%) | 0% (0% to 91%) |
| 35° | 100% (91% to 100%) | 100% (100% to 100%) | 100% (89% to 100%) | 0% (0% to 79%) | 0% (0% to 65%) | 0% (0% to 41%) | 0% (0% to 98%) |
| 40° | 100% (95% to 100%) | 100% (100% to 100%) | 100% (98% to 100%) | 15% (0% to 99%) | 0% (0% to 94%) | 0% (0% to 83%) | 0% (0% to 100%) |
| 45° | 100% (98% to 100%) | 100% (100% to 100%) | 100% (100% to 100%) | 88% (2% to 100%) | 1% (0% to 99%) | 0% (0% to 98%) | 0% (0% to 100%) |

*Unshaded cells correspond with combinations of curve size and maturity stage for which surgery would be a plausible treatment if >50° at maturity is accepted as the threshold for surgical treatment. Shaded cells correspond with combinations for which surgery would not be a plausible treatment. †Cells with wide 95% confidence intervals (shown in parentheses) correspond with groups that had too few patients for accurate estimates (or groups that had no patients) and should be interpreted with caution.

### 1.5 Compliance Statement

This study will be conducted in full accordance with all applicable Nemours Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, 314 and 812 and the Good Clinical Practice: Consolidated Guideline

approved by the International Conference on Harmonization (ICH). All episodes of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with Nemours IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

## 2 STUDY OBJECTIVES

The purpose of the study is to determine the safety and efficacy of Anterior Vertebral Body Tethering surgery on patients with Idiopathic Scoliosis.

### 2.1 Primary Objective (or Aim)

The primary objective is to assess the safety of Anterior Vertebral Body Tethering surgery in the immediate post-operative period.

### 2.2 Secondary Objectives (or Aim)

The secondary objective is to assess the post-operative correction of the scoliotic curve, as measured by Cobb Angle on Coronal (AP/PA) radiograph of the spine.

# 3 INVESTIGATIONAL PLAN

## 3.1 General Schema of Study Design

### 3.1.1 Screening Phase

Subjects will be screened from patients presenting to the orthopedic clinic for routine clinical care. Patients who satisfy the inclusion and exclusion criteria will be approached and presented information about the clinical study. Those subjects and families who are interested in pursuing the clinical study will be enrolled by providing informed consent/assent.
Subjects who learn about the study through social media and contact Nemours for additional information will be directed to have a scoliosis clinical appointment After that they will follow the same research procedure as the subjects who present in the orthopedic clinic for scoliosis care. This phase will last 1 day

### 3.1.2 Study Intervention (Surgery)

Enrolled patients who have completed the pre-operative course for anterior spine surgery (Pre-operative SOC and Pre-operative study procedures) will undergo the study intervention comprising implantation of anterior vertebral body screws and PET cord under general anesthesia. This phase will last 1 day (day of surgery). This surgical episode is estimated to last about 5.5 hours; 2.5 hours of anesthesia induction and preparation, 2.5 hours of surgery, and 30 minutes of emergence from anesthesia.

### 3.1.3 Post-operative follow-up

The Post-operative follow-up phase of the study will last approximately 90 days, beginning with the day after the surgical intervention. This period has 2 set time points for follow-up, which will occur during standard-of-care clinical follow-up visits for spine patients receiving surgical intervention. The two time-points are a POD-45 clinical visit, and a POD-90 clinical visit. During these two clinical visits physical exams, radiographs, and AE / SAE data will be collected. POD 2-44 will be monitored for known complications and AE / SAEs only, as there will be no clinical outcomes data to collect during this time. This data will be abstracted from the medical records. In addition, the patient will be under SOC post-operative care for patients who have undergone Anterior Spinal Surgery. Data from any SOC interventions will also be abstracted from the medical record.

## 3.2 Allocation to Treatment Groups and Blinding

The study will not be blinded, as the patient must make an informed decision to undergo the intervention, and the surgeon must perform the intervention. Introduction of a sham or placebo group would be impractical and unethical in this context. The study will only enroll one cohort- the Anterior Tethering (Intervention) cohort.

## 3.3 Study Duration, Enrollment and Number of Sites

### 3.3.1 Duration of Study Participation

The subject will be followed for at least 10 visits over a 5-year (1825 day) period: 1 day for recruitment /consent, 1 day for the study intervention (surgery), 1 day for each visit: POD45, POD90, POD180, POD365, POD730, POD1095, POD1460, and POD1825. These visits follow the schedule for a patient's standard-of-care follow-up for anterior spinal surgery. Any off-study

visits within the study window will not be captured, unless they are related to an AE / SAE. There is a three-week grace period for post-operative study visits, and a 90 day grace period for extended follow-up visits, making the maximum study participation time 1825 + 90 days after the day of surgery.

### 3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at Nemours – Alfred I duPont Hospital for Children.
As this is a registry of an approved device being used in an off-label method, we do not have a maximum number of patients or target enrollment. Based on a broad review of patient visits over the past year, we may expect to enroll up to 15 patients per year. These patients will be followed up clinically until skeletal maturity. The total number of enrolled subjects in both retrospective and prospective arms will be 30.

## 3.4 Study Population

### 3.4.1 Inclusion Criteria

1) Males or females age 8 to 16 years old at time of enrollment (inclusive)

2) Diagnosis of Idiopathic Scoliosis

3) Sanders bone age of less than or equal to 4

4) Thoracic curve of greater than or equal to 35 degrees, but no bigger than 60 degrees

5) Lumbar curve less than 35 degrees

6) Spina bifida occulta is permitted

7) Spondylolysis or Spondylolisthesis is permitted, as long as it is non-operative, the patient has not had any previous surgery for this, and no surgery is planned in the future

8) Completed standard-of-care procedures as outlined in Section 5

9) Subject consent and (if applicable) assent

### 3.4.2 Exclusion Criteria

1) Pregnancy (current)

2) Prior spinal or chest surgery

3) MRI abnormalities (could include syrinx >4mm, Chiari malformation, or tethered cord)

4) Neuromuscular, thoracogenic, cardiogenic scoliosis, or any other non-idiopathic scoliosis

5) Associated syndrome, including Marfan Disease or Neurofibromatosis

6) Sanders bone age greater than 4

7) Thoracic curve less than 35 degrees

8) Lumbar curve greater than or equal to 35 degrees

9) Unable or unwilling to firmly commit to returning for required follow-up visits

10) Investigator judgement that the subject/family may not be a candidate for the intervention

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

## 4 STUDY PROCEDURES

### 4.1 Screening Phase

#### 4.1.1 Visit 1 (Screening & Pre-operative Visit)

- Medical record and x-ray review
- Hand x-ray to define bone age
- Informed consent / assent
- Physical Exam (research- including Adam's Forward bending test (degrees), thoracic and lumbar flexion (cm), thoracic and lumbar lateral flexion (cm)
- Clinical photos
- Pregnancy Test (Urine or Blood) as applicable
- CBC blood test
- SRS 30 Questionnaire

### 4.2 Study Treatment Phase (Surgery)

#### 4.2.1 Visit 2 (Surgical Intervention)

This phase includes the surgical intervention- Vertebral Body Tethering through anterior thoracoscopic approach under general anesthesia. This process is described in Section 2. Data from the surgery will be abstracted by medical record review for adverse events or complications. Intraoperative data (including radiographs) will also be abstracted from the medical record / surgical logs. Results from the surgery and inpatient stay will be abstracted at the time of discharge, except for those events which fall under the reporting guidelines of AE/SAEs. All AE/SAEs will be reported according to reporting guidelines listed in Section 8.

### 4.3 Post-surgical Follow-up Phase

This phase will include monitoring for post-operative complications / SAE, as well as two SOC clinical visits in this phase, where the subject will also undergo a research visit. Information from standard-of-care procedures will also be abstracted from the medical records and radiology databases.

#### 4.3.1 Visit 3 (POD 45)

- Medical record review and abstraction
- X-ray review and abstraction
- Physical Exam (research)
- Complications Review

#### 4.3.2 Visit 4 (POD 90)

- Medical record review and abstraction
- X-ray review and abstraction
- Physical Exam (research)
- Complications Review

### 4.4 Extended Follow-up Phase

This phase will include monitoring for post-operative complications/SAE, as well as three SOC clinical visits in this phase, where the subject will also undergo a research visit. Information from

standard-of-care procedures will also be abstracted from the medical records and radiology databases.

**4.4.1 Visit 5 (POD 180)**
- □ Medical record review and abstraction
- □ X-ray review and abstraction
- □ Physical Exam (research, including Adam's Forward bending test (degrees))
- □ SRS 30 Questionnaire
- □ Complications Review

**4.4.2 Visit 6 (POD 365)**
- □ Medical record review and abstraction
- □ X-ray review and abstraction
- □ Physical Exam (research- including Adam's Forward bending test (degrees), thoracic and lumbar flexion (cm), thoracic and lumbar lateral flexion (cm)
- □ SRS 30 Questionnaire
- □ Clinical Photos
- □ Hand x-ray to define bone age
- □ Complications Review

**4.4.3 Visit 7 (POD 730)**
- □ Medical record review and abstraction
- □ X-ray review and abstraction
- □ Physical Exam (research- including Adam's Forward bending test (degrees), thoracic and lumbar flexion (cm), thoracic and lumbar lateral flexion (cm)
- □ SRS 30 Questionnaire
- □ Hand x-ray to define bone age
- □ Clinical Photos
- □ Complications Review

**4.4.4 Visit 7 (POD 1095)**
- □ Medical record review and abstraction
- □ X-ray review and abstraction
- □ Physical Exam (research- including Adam's Forward bending test (degrees), thoracic and lumbar flexion (cm), thoracic and lumbar lateral flexion (cm)
- □ SRS 30 Questionnaire
- □ Hand x-ray to define bone age
- □ Clinical Photos
- □ Complications Review

**4.4.5 Visit 7 (POD 1460)**
- □ Medical record review and abstraction
- □ X-ray review and abstraction
- □ Physical Exam (research- including Adam's Forward bending test (degrees), thoracic and lumbar flexion (cm), thoracic and lumbar lateral flexion (cm)
- □ SRS 30 Questionnaire
- □ Hand x-ray to define bone age
- □ Clinical Photos
- □ Complications Review

**4.4.6 Visit 7 (POD 1825)**

 Medical record review and abstraction
 X-ray review and abstraction
 Physical Exam Exam (research- including Adam's Forward bending test (degrees),thoracic and lumbar flexion (cm), thoracic and lumbar lateral flexion (cm)
 SRS 30 Questionnaire
 Hand x-ray to define bone age
 Clinical Photos
 Complications Review

**4.5 Unscheduled Visits**

Unscheduled clinic visits will be made through the departments / hospitals clinical schedulers. As part of clinical care, physical evaluations and tests may be conducted. At these visits, the only research procedures performed will be medical record / radiographic record abstraction and complications review.

**4.6 Subject Completion/Withdrawal**

Subjects may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study treatment or visit schedules, AEs, or due to non-compliance. However, in order to collect important study-related data for this investigational device, as much as is feasible, the Investigator will make efforts to follow-up subjects who do not strictly adhere to timely visit schedules. The Investigator may do this via emails, phone calls, or letters. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

**4.6.1 Early Termination Study Visit**

Subjects that withdraw from the study prior to study completion will have all data collected to date kept on file. Subjects who wish to have their data removed from the study must submit a written request addressed to the site's PI. A 'Study Completion CRF' will be filed for each subject.

## 5 STUDY EVALUATIONS AND MEASUREMENTS

**Patients will undergo standard of care for adolescent idiopathic scoliosis before research procedures are initiated.**

**New visit includes the following:**

- Medical history
- Vitals
- Standing x-rays (pre-op Coronal / Sagittal / Bending Bolster Film)
  Cobb angle (measurement of spinal curve)
- Hand x-ray to determine skeletal maturity age
  Sanders score (0-7) to be used
  0 pre-pubertal skeletal maturity
  7 skeletal maturity
- Clinical Photo

Follow-up Visit(s)

- Medical history
- Vitals
- Standing x-rays (pre-op Coronal / Sagittal Film)
  Cobb angle (measurement of spinal curve)
- Clinical Photo

Pre-op operative discussion for surgical indication

1. Pain
2. Thoraco-lumbar orthosis inadequately managing curve progression

### 5.1 Screening and Monitoring Evaluations and Measurements

#### 5.1.1 Pre-operative Visit

##### *5.1.1.1 Screening*

- Potential subject identified by treating surgeon (match I/E criteria, surgical candidate)
- Informed Consent / Assent
- Review Inclusion / Exclusion Criteria, Complete I/E Checklist
- Subject Screening CRF

##### *5.1.1.2 Pre-operative Medical Record / Radiograph Review*

- Name
- Age
- Race
- Sex
- Ethnicity
- Date of Birth
- MRN
- Diagnosis
- Clinical and Surgical History (including history of pregnancy)
- Radiographic information and reports (including pre-op Coronal / Sagittal / Bending Bolster Films; Spine MRI)
- Clinical photos
- PFT Data (if available)

***5.1.1.3 Pre-op Physical Examination***

- Standing Height
- Weight
- BMI – (reported as %) as calculated by the medical record
- Trunk flexibility measurements (standardized): Adam's Forward bending test / Inclinometer (degrees), thoracic and lumbar flexion (cm), thoracic and lumbar lateral flexion (cm)
- Data abstracted from clinical care exam (medical records, radiology reports, pulmonology tests)
- SRS 30 Questionnaire

### 5.1.2 Surgical Intervention and Post-operative Course

#### *5.1.2.1 Intraoperative Data (abstracted from medical record)*

- Operative time (Surgical Start time, Surgical End time)
- Intra-operative estimated blood loss
- Blood products utilized: cell saver (cc) given, other transfused blood products (cc)
- Number of portals
- Implant tracking Information:
  - Brand and model information of each implanted device
  - Part number, lot number, and UDI **of device components: PET cord, set screws, vertebral screws, staples.**
  - Type and size of screws used
  - Length of PET cord used
- The extent of annulectomy (complete or partial) and the presence of pleural closure
- Whether a thoracoplasty was performed will be noted along with number of ribs and whether the pleura was cut or not (internal vs external thoracoplasty – if used)
- Posterior based Discectomy
- First Assistant information
- Antibiotic use
- Type and Dose of antifibrinolytic
- Time-Exposure of Flouroscopic X-ray during procedure
- Total intraoperative radiation dose

#### *5.1.2.2 Post-surgical Data (abstracted from medical record)*

- Chest tube drainage on day #1 - #5, and total collected
- Postoperative day of extubation as well as chest tube removal will be noted
- Postoperative day the patient was converted entirely to oral pain medication
- Visual Analogue Scores (measures the intensity of a child's pain experience) at discharge will be recorded. This is used to record the amount of back pain a patient is experiencing.
- Day of discharge will be recorded
- The use of a postoperative brace and the number of months utilized will be recorded
- Complications will be recorded: Post-operative complications will be recorded and status will be updated until resolved. This data collection methodology will be standardized via the complication form in the patient's study binder.
- Post-op Drain: type and drainage amounts daily until d/c of drain.
- Data abstracted from medical records, radiology reports, and surgical logs

### 5.1.3 POD-45 and POD-90 Follow-up

#### *5.1.3.1 Post-Operative Visit*

- Medical and radiographic record review

- Standing Height
- Weight
- BMI
- Trunk flexibility measurements (standardized): **Adam's Forward bending test (degrees) only**
- Data abstracted from clinical care exam (medical records, radiology reports, pulmonology tests)

### 5.1.4 POD-180, POD-365, POD-730, POD 1095, POD 1460, POD 1825 Follow-up

#### *5.1.4.1 Extended Follow-up Visit*

 Medical and radiographic record review
 Standing Height
 Weight
 BMI
 Trunk flexibility measurements (standardized): Adam's Forward bending test (degrees), thoracic
and lumbar flexion (cm), thoracic and lumbar lateral flexion (cm)
 Data abstracted from clinical care exam (medical records, radiology reports, pulmonology tests)
 Clinical photos for all of the extended follow-up visits except POD-180
 SRS 30 Questionnaire

### 5.1.5 Laboratory Evaluations

#### *5.1.5.1 Pregnancy Testing: Performed at Pre-op Visit only*

A urine or blood pregnancy test will be performed for female subjects older than 11 years of age, or any female who has begun menses will be required to complete a urine or blood sample pregnancy test. Results of such testing will be provided to the study participant, unless it is determined that she is unable to understand the significance or implications of a positive test result. In this case, the parent (s) will be informed of the positive result. In the event of pregnancy, the participant will not receive the study intervention. Participants who are found to be pregnant will be advised to contact family planning counseling services.

### 5.1.6 Other Evaluations, Measures

 Sanders Bone Age: Attached as Supplement 1
 Adam's Forward Bending Test: Subject stands with their back to the examiner, and bends forward at the waist, with knees in extension. The examiner looks at the horizontal plane of the spine, and measures angle created between a rib hump and the horizontal plane. This is measured with an inclinometer.
 Thoracic/Lumbar Flexion test: Subject stands with trunk erect while measuring tape is placed proximally on the spinous process of C7 and distally to S1. The subject then bends forward at the waist, with knees in extension. Following flexion of the vertebrae, using the same bony landmarks, the examiner calculates the difference in distance between the starting and ending positions.
 Thoracic/Lumbar Lateral Flexion test: Subject stands erect with the feet flat on the floor. Place one end of a measuring tape on the tip of the middle finger and the other on the floor on a point directly beneath the middle finger. The patient then laterally flexes their trunk. The difference following the lateral flexion motion is measured.
 SRS 30: Attached as Supplement 2

## 5.2 Safety Evaluation

Subject safety will be monitored by recording all AEs and SAEs, and will be recorded on the complication form in the patient's study binder. The evaluation of safety is a primary objective of

this research study. There will be a clear classification of "device-related" adverse events. Device-related adverse events are those events directly related to the integrity, safety, or biomechanics of the device components: **PET cord, staples, set screws and vertebral screws.** This can include variables like device breakage or device migration. Other adverse events which are considered not device-related are those that are related to the act of surgery and medical recovery. The type of events will be documented on the CRF.

### 5.3 Efficacy Evaluation

The mode of efficacy evaluation for this procedure will be measurement of Cobb Angle. Cobb Angle is a coronal plane radiographic measurement of curvature of the spine. This angle will be recorded for the pre-operative coronal spine radiograph, as well as all subsequent serial radiographs. The change in Cobb angle (reduction) will be the primary evaluator of efficacy. 'Overall study success' of the intervention will be defined by a final Cobb angle of less than or equal to 50 degrees by the time subject reaches skeletal maturity.

# 6 STATISTICAL CONSIDERATIONS

## 6.1 Primary Endpoint

The primary endpoint is the rate of Adverse Events/SAEs in Anterior VBT Surgery.

## 6.2 Secondary Endpoints

The secondary endpoint is change in post-operative Cobb angle compared to pre-operative Cobb angle, measured on coronal radiograph of the spine.

## 6.3 Statistical Methods

### 6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender). Categorical data analysis methods such as chi-square will be used for dichotomous variables and repeated measures Anova or t-test for continuous data (such as differences in Cobb angle). Logistic regression analysis will be conducted to analyze various factors associated with adverse events in anterior tethering surgical procedure.

### 6.3.2 Safety Analysis

The safety endpoint will be factors associated with the adverse events in patients that have undergone Anterior VBT Surgery. Variable reporting for adverse event will be dichotomous. Descriptive statistics will be used to report number and type of adverse events. Further, chi-square or fisher-exact test analysis will be used to identify variables that correlate with adverse events following anterior tethering surgery. Further, logistic regression will be conducted to clarify which variables are associated with adverse outcomes. Odds ratio along with confidence intervals will be reported.

**All subjects will begin the safety analysis at Study Day 0 (day of surgery).** Intraoperative and post-intervention medical events or signs and symptoms of the complications arising after the start of study intervention will be captured using list of common events associated with Anterior VBT Surgery. Adverse signs, symptoms, and/or laboratory abnormalities already existing prior to the baseline visit will be captured in the medical history assessment.
The date of onset, severity, and end date (if relevant) will be documented.

Medical events resulting from any procedure performed in the study will be collected as adverse events (AEs). The event description, date of onset, end date, severity, and outcome will be documented for the study-related AEs. The frequencies of AEs by type, body system, severity and relationship to study intervention will be summarized. SAEs (if any) will be described in detail. A distinction will be made between those AE/SAEs which are “device-related”, those which are “not device-related”, and those which are “uncertain to be related”. “Device-related” complications will include any events directly related to the integrity, safety, or biomechanics of the PET cord. Device-related AE incidence will be summarized along with the corresponding exact binomial 95% two-sided confidence intervals. 22

### 6.3.3 Efficacy Analysis

The primary analysis will be based on an intention to treat approach and will include all subjects who have undergone the intervention.

The endpoint used for efficacy will be change in post-operative Cobb angle compared to pre-operative Cobb angle, measured on coronal radiograph of the spine. Considering change in Cobb angle is a continuous variable, repeated measures Anova or t-test will be used to detect any change in Cobb angle post-operatively. Linear regression will be utilized to assess which variables are associated with change in post-operative Cobb angle.

### 6.4 Sample Size and Power

The purpose of this study is to longitudinally follow a cohort of patients treated with a novel use of an implant, to explore safety and efficacy of the implant. The regulatory status of such an implant requires that we obtain an IDE. There is no comparative group and thus no effect size or power analysis associated with the work.

### 6.5 Interim Analysis

The study team will perform interim analyses based on the stopping rules listed in section 6.6 (below). If any of these rules are met, the study will halt enrollment until appropriate measures can be put in place to reduce patient risk. All reporting of AE/SAEs during the study will adhere to the guidelines in Section 8 (Safety Management).

### 6.6 Stopping Rules

The stopping rules for this study will be based on the prevalence of SAEs. There is special consideration given to SAEs that are found to be "device-related", as outlined below.

#### 6.6.1 Stopping rules for any SAE related to the study procedure (surgery)

- SAE in all of the first 5 patients or
- SAE in 7 of first 10 patients or
- SAE in >50% of patients after 20 cases

#### 6.6.2 Stopping rules for SAEs that are device-related

Definition of Terms:

- Screw failure – screw and/or centering staple have loosened from the vertebra AND require re-operation
- Tether failure – the tether has broken or lost tension. Diagnosed at any time point after 3 months by increased angulation at a disc space on standing PA or increase in disc wedging on side bending x-ray to the side away from the implant. Also, it is only an SAE if noted before maturity AND overall Cobb worsens compared to the first erect measurement
- Implant re-operation - any problem with the implant that requires re-operation including re-operation for overcorrection with any of the following: a removal of all or part of the implant, loosening of the tension on the implant, or spinal fusion.

Stopping Points

- Screw failure stopping point: 3 of first 5 cases, 5 of first 10, or 25% of patients beyond 20 cases
- Tether failure stopping point: 3 of first 5 cases, 5 of first 10, or 25% of patients beyond 20 cases
- Implant failure re-operation stopping point: occurs in 4 of first 5 cases or greater than 50% of cases beyond 10 cases

# 7 STUDY DEVICE

## 7.1 Description

The device is the use of Polyethylene Terephthalate (PET) cord with pedicle screws and staples for vertebral body tethering. The PET cord is part of a 510k-cleared implant system distributed by Globus Medical, Inc. called the Reflect/Transition™ Stabilization System. The pedicle screws and staples are part of a 510k-cleared implant system distributed by Globus Medical, Inc. called the CREO™ Stabilization System. Both systems are classified as Class II under 21 CFR 888.3070, and are manufactured and distributed according to manufacturer guidelines and in compliance with 21 CRF 820. The combined use of screws, staples, and Polyethylene Terephthalate cord for vertebral body tethering is investigational.

The entire system is supplied at Nemours as part of routine surgical treatment. The system supplied also includes hydroxyapatite-coated titanium alloy Ti6Al4V (ASTM F136) or alloy Ti6Al4Nb (ASTM F1295) pedicle screws, polycarbonate urethane spacers and bumpers, titanium alloy spools, end spools, and set screw ends**. The only article being used from this system is the PET cord.** The rest of the system will be discarded according to the appropriate NEMOURS Operation Room policies and procedures.

## 7.2 Packaging

The device is part of a commercially marketed system from Globus Medical, Inc. As such, the device is packaged according to manufacturer guidelines and in compliance with 21 CFR 820.130.

## 7.3 Labeling

The device is part of a commercially marketed system from Globus Medical, Inc. As such the device will be labeled according to manufacturer guidelines and in compliance with 21 CFR 801. Specific device label parameters will be tracked by the study team to comply with FDA standards for investigational device tracking. Those parameters include:

o Manufacturer of device

o Model name of device

o Device Part Number

o Device Lot Number

o Unique Device Identification (UDI)

o Length of PET cord used

All parts of the tethering system (vertebral screws, set screws, staples and PET cord) will be labeled and tracked in the same manner.

# 8 SAFETY MANAGEMENT

## 8.1 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

## 8.2 Adverse Event Reporting

Unanticipated problems related to the research involving risks to subjects or others that occur during the course of this study (including SAEs) will be reported to the IRB in accordance with Nemours IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

## 8.3 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention). The occurrence does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
We will use the Clavien-Dindo Classification system [47], as well as the Comprehensive Complication Index (based off of the Clavien-Dindo system) [48] to classify and analyze patient adverse events. **Grade I and Grade II events will be considered AEs. (See Appendix 1 for classification table)**

## 8.4 Definition of a Serious Adverse Event (SAE)

An SAE is any adverse event that results in any of the following outcomes:
□ death,

□ a life-threatening event (at risk of death at the time of the event),

□ requires inpatient hospitalization or prolongation of existing hospitalization,

□ a persistent or significant disability/incapacity, or

□ a congenital anomaly/birth defect in the offspring of a subject.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A distinction should be drawn between serious and severe AEs. A severe AE is a major event of its type. A severe AE does not necessarily need to be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but

would not be considered serious. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be considered serious.
We will use the Clavien-Dindo Classification system [47], as well as the Comprehensive Complication Index (based off of the Clavien-Dindo system) [48] to classify and analyze patient adverse events. **Grade III (a/b), Grade IV (a/b), and Grade V events will be considered SAEs. (See Appendix 1 for classification table)**

### 8.4.1 Relationship of AE/SAE to study intervention or device

The relationship of each Event to the study intervention should be characterized using one of the following terms in accordance with NEMOURS IRB Guidelines: **definitely, probably, possibly, unlikely or unrelated**. In this case, the "study intervention" in considered to be the surgical intervention and implantation of the medical device (*Anterior vertebral body tethering surgery under general anesthesia with spinal cord monitoring*). This includes (but is not limited to) induction of anesthesia, incision and surgical approach, device implantation, and recovery. **For each SAE, the PI and Safety Officer will make a case-by-case determination on the relationship of the SAE to the study procedure, which will be documented in the study documents.**

There will be further classification of the Event as either "device-related", "not device-related", or "uncertain to be device-related". Device-related adverse events are those events directly related to the integrity, safety, or biomechanics of the implanted device. This can include variables like device breakage or device migration. Other adverse events which are considered not device-related are those that are related to the act of the surgery and medical recovery (anesthesia, incision and surgical approach, post-operative recovery, etc.). This distinction will be indicated in the study documents. **For each Event, the PI and Safety Officer will make a case-by-case determination on whether the Event is "device related", "not device related", or "uncertain". An event which is classified as "device related" will be considered an Adverse Device Effect. Adverse device effects have special reporting guidelines, as outlined below.**

### 8.4 Recording plan for AE / SAEs

Surgery and Post-operative Phase (Day 0 – POD 90):
For these phases, all AEs (including SAEs) will be noted in the study records and reported per IRB and FDA requirements outlined below. The subjects will be encouraged to contact the office with any concerns, and the medical record will be monitored by study staff for indications of AEs.
Extended Follow-up Phase (POD 91-POD 1825):
For this phase, all SAEs will be recorded (regardless of cause). Only AEs which are deemed "device related" will be recorded on study documents and reported per IRB and FDA requirements outlined below. The subjects will still be encouraged to contact the office with any concerns, and the medical record will be monitored by study staff for indications of SAEs or device-related AEs.

Only the AE/SAEs indicated above will be recorded in a patient-specific study binder, kept in the secure Orthopedics research office. The binder will contain a full description of the event, including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event. Hard copies of the primary documents (medical record notes) describing the event and any associated treatment will be printed and kept in the patient-specific study binder. A redundant copy of adverse events will be kept in the study REDCap database and will be maintained by the study team separately from the patient-specific study binder. The study binder will serve as the official record of all Events.

**8.6 IRB/IEC Notification of SAEs and Other Unanticipated Problems**

The Investigator will promptly notify the IRB of all on-site unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the eIRB system and in accordance with the timeline below. External SAEs that are both unexpected and related to the study intervention will be reported promptly after the investigator receives the report. External events that do not change the risk to subjects or result in a change to the research protocol will be reported to the IRB following IRB recommendations.

**REPORTING REQUIREMENTS TO THE IRB**

| **Type of Unanticipated Problem** | **Initial Notification (Phone, Email, Fax)** | **Written Report** |
|---|---|---|
| Internal (on-site) SAEs Death or Life Threatening | 24 hours | Within 2 calendar days |
| Internal (on-site) SAEs All other SAEs | 7 days | Within 7 business days |
| Unanticipated Problems Related to Research | 7 days | Within 7 business days |
| All other AEs | N/A | Brief Summary of important AEs may be reported at time of continuing review |

**8.4.1 Follow-up report**

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

**8.7 Investigator Reporting Requirements to IRB, FDA, and Sponsor**

**INVESTIGATOR REPORTING TO THE FDA / DEVICE MANUFACTURER**

| Type of Report | Description of Report | Submit to: | Timeline |
|---|---|---|---|
| *Unanticipated Adverse Device Effects* | Report of any unanticipated adverse device effect | IRB and FDA | Within 10 working days after investigator first leans of effect. |
| *Withdrawal of IRB approval* | If IRB withdrawn from study site | Sponsor | Within 5 working days |
| *Progress Report* | FDA Form 3419 | IRB, FDA, Sponsor | Regular intervals, no less than yearly |
| *Deviations from the investigational plan* | If deviation of investigational plan occurred in order to protect subject's life or physical well-being (i.e. during an emergency) | IRB, Sponsor | Within 5 working days |
| *Informed Consent* | If investigator used device without obtaining informed consent | IRB, Sponsor | Within 5 working days |
| *Final Report* | Complete and final investigative report | IRB, Sponsor | Within 3 months of study completion or study termination |
| *Other Reports* | Any access or reports on request | IRB, FDA | Per request |
| *Voluntary Reports* | At discretion of investigator.<br><br>**Voluntary adverse event reporting is done through Form 3500A.** | IRB, FDA | As deemed by investigator |

## 8.8 Sponsor Reporting Requirements to FDA and IRB

**SPONSOR REPORTING TO THE IRB / FDA**

| Type of Report | Description of Report | Submit to: | Timeline |
|---|---|---|---|

| | | | |
|---|---|---|---|
| *Unanticipated Adverse Device Effects* | Report of any unanticipated adverse device effect | FDA and reviewing IRB(s) | Within 10 working days after sponsor first receives notice. May submit further reports at FDA requests |
| *Withdrawal of IRB approval* | If IRB withdraws approval of investigation or part of the investigation | FDA and reviewing IRB(s) and participating investigators | Within 5 working days of receipt of notice |
| *Withdrawal of FDA approval* | If FDA withdraws approval | Reviewing IRB(s) and participating investigators | Within 5 working days of receipt of notice |
| *Current Investigator List* | Current list of names and addresses of all participating investigators | FDA | 6 month intervals |
| *Progress Report* | FDA Form 3419 | FDA and reviewing IRB(s) | Regular intervals, no less than yearly |
| *Recall and Device Disposition* | If Sponsor requests return, repair, or disposal of device, and why | FDA and reviewing IRB(s) | Within 30 working days after request is made |
| *Final Report* | Complete and final investigative report | FDA and reviewing IRB(s) | 1. Notify FDA within 30 working days<br>2. Submit final report to FDA and IRBs within 6 months |
| *Informed Consent* | If investigator used device without obtaining informed consent | FDA | Within 5 working days of receipt of notice |
| *Significant risk device determination* | IRB determination of significant risk of the medical device | FDA | Within 5 working days of receipt of notice of the determination |
| *Other* | Any access or reports on request | FDA and reviewing IRB(s) | Per request |

**8.9 Medical Emergencies**

If a medical emergency occurs in the hospital system, it will be reported following the above guidelines and timeline. If no emergencies are identified through chart review, subjects will be asked at designated follow-up if they have sought medical care for any reason between research visits. Any events will be reported through the above policies and procedures. Subjects who contact the study team or clinical offices regarding a medical emergency will be referred to the appropriate health care professional to manage their emergency, and contact will be documented in the medical record.

# 9 STUDY ADMINISTRATION

## 9.1 Data Collection and Management

1. Confidentiality:
A master list will be maintained separately from the coded data collection sheet and will contain the subject ID number, name, MRN, date of birth and dates of service. The list will be password-protected so that only the study staff will have access. Data will be collected on each subject using the subject's Study ID number. Data will be managed and stored using the research-focused electronic data capture system REDCap, under an agreement with the software's development consortium, led by Vanderbilt University. REDCap supports two secure, web-based applications designed exclusively to support data capture for research studies. REDCap is a PHP web application served by Apache Tomcat over a 128-bit SSL connection using a signed certificate. The application relies on a study-specific data dictionary defined in an iterative self-documenting process that will be conducted by all members of the research team. The data dictionary is the foundation for custom case report form design and validated coding of variables. Authentication of research staff will be performed via LDAP using Nemours's enterprise Active Directory service. The application generates a complete audit trail of user activity, provides reporting, and has an automated export mechanism to common statistical packages (SAS, SPSS, Stata, R/S-Plus).
A patient-specific study binder will be kept for each enrolled patient. The study binder will contain adverse event information, as well as signed consent forms and paper forms collected during testing, as well as all relevant documentation. These will be stored in a locked research office.

2. Security:

The master sheet will be a password protected excel file kept in the secure orthopedic research drive at each institution. The REDCap MySQL database is replicated in real time to a completely redundant instance of MySQL. The redundant instance is available for restoration of the primary database or for manual failover in the case of primary database failure. Time-stamped backup files are made from the replicated database daily by NEMOURS Research Information Systems using automated backup routines. Backup files are encrypted and transferred to a secure file server accessible only to designated personnel. A rolling seven-day window of backup files is maintained in an immediately available online state, with a larger window maintained in a compressed file archive available at a reduced speed of access. Daily destructive database backup files are stored on the database server and are deleted only after successful backup of the entire database to file. In the event of data error, loss or corruption, Research personnel will work with Nemours Research Information Systems to determine the most appropriate recovery strategy. Data and backups are stored in the NEMOURS Research Information Systems Storage Area Network (SAN). Access to the SAN directories where data are stored will be limited to Research Information Systems personnel, with authentication performed using NEMOURS's enterprise Active Directory service. The data from the application will be compiled on a secured survey web platform that is encrypted using AES 256 bit encryption. The data collected on paper forms during testing will be secured in the patient-specific study binders in a locked research office.

3. Anonymization, de-identification or destruction:

Data will be collected on each subject using the subject's Study ID number. Study personnel will store a list connecting the subject's PHI to study ID. All PHI collected from this study (master

sheet) will be destroyed 6 years after study closure. All other de-identified data will be retained for 6 years following study closure.

### 9.2 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and that the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. No identifiable data will be used for a future study without first obtaining IRB approval.

### 9.3 Regulatory and Ethical Considerations

#### 9.3.1 Data and Safety Monitoring Plan

The PI will monitor data and safety throughout the duration of the study and will report any adverse events in accordance with IRB policies. The PI, Safety Monitor, and study team will perform interim safety analyses as outlined in Section 6.6. Safety monitoring will be handled internally by the study Safety Monitor and NEMOURS Office of Research Compliance (ORC). We will also submit reports to the FDA, device manufacturer, or both as per medical device reporting requirements specified in 21CFR803.

#### 9.3.2 Risk Assessment

This section outlines risks associated with the study procedures.

##### *9.3.2.1 Surgical Procedure: Anterior-approach thoracoscopic vertebral body tethering (greater than minimal risk)*

1. Investigational devise risks:

Implant failure (tether breakage, lost tension, screw pullout, screw fracture) overcorrection of curve, failure of correction, progression of curve and need for conversion to spinal fusion. Reoperation for any of the above listed reasons.

2. Anesthesia Risks:

Anesthesia effects alone or with the effects of surgery can be life threatening. Injury to the eyes, lips, teeth, nerves and/or spinal cord, increased or decreased blood pressure, irregular heartbeat, abnormal reaction to anesthesia agents. Some other known risk, side effects and potential complications include nausea and vomiting after surgery, excessive bleeding requiring blood transfusions. There are certain (very rare) risks of anesthesia including stroke, blindness, and long-term learning disability, which are unpredictable, not well understood and still being studied by doctors.

3. Surgery Risks:

Infection, bleeding, allergic reaction, significant scarring, need for additional surgery, and even death or disability. Some other known risks, side effects and potential complications include neurological deficit, visceral, or vessel injury, blindness, need for transfusion of

blood products, back pain, pulmonary insufficiency, pain and unforeseen medical complications. Risks associated with radiation exposure from fluoroscopy and X-rays.

4. Spine surgery risks:
Implant malposition, implant failure (rod breakage, screw pullout, screw fracture), progression of curve above or below corrected spinal region, pseudoarthrosis (non-union), need for additional surgery, vertebral body damage, paralysis, and allergic reaction to implants. Reoperation for any of the above listed reasons.

*It should be noted that the above risks are the same risks that are present for standard-of-care surgery for spinal surgery. All appropriate clinical care procedures and pathways followed for standard-of-care spine surgeries will take place for these subjects.*

***9.3.2.2 Other Potential Risks (No greater than minimal risk study procedures):***

- Review of medical records: There is a risk of breach of confidentiality and privacy as a result of medical record review. This risk is minimized as detailed in Section 9.
- Administration of questionnaires: The questionnaires have the potential to make subjects feel uncomfortable.
- Reproductive Risks:
  Girls deciding whether or not to be in this study may already have started having periods or may begin having periods while they are in this study. Therefore, we need to tell you some important facts. We often do not know the effects of research procedures (such as drugs or tests) on unborn babies. Your child should not plan to become pregnant while participating in this study. If sexually active, your child should use effective birth control to prevent pregnancy while participating in this study. As appropriate, the study doctor will discuss issues of possible sexual activity and use of effective birth control privately with your child.

Nemours have the following mitigation strategies in place to minimize the risks listed above:

1. Investigational device risks

Your Nemours surgeon is highly experienced with vertebral body tethering technique and will employ his knowledge and skills to prevent any risk associated with the investigational device.

2. Anesthesia risks

To minimize the possibility of the all anesthesia related risks, the patient will undergo a pre-operative evaluation by the Anesthesia team. You and your child will have an opportunity to discuss these risks with the anesthesiologist.

3.Surgery risks

Nemours Orthopedic surgeons and surgeon's assistants are American Orthopedic board certified doctors who strive to minimize all type of risks. To minimize the surgery risk and the risk of

infection on particular all Nemours Standard Operating procedure regarding sterile procedures and institutional policies on infection prevention will be followed to prevent infection. The patient will be placed on Nemours Orthopedics Standard Operating Procedure for pre- and post-operative antibiotic regimen for spine surgery patients.

To minimize the bleeding every reasonable effort will be made by the surgical staff to reduce blood loss. Expected Blood Loss during surgery will be recorded on the clinical research form. To reduce the need of banked blood transfusion Cell Saver machine will be used to filter lost patient's blood and transfuse back to the patient.

To reduce and minimize the pain levels, Nemours pain team will be consulted for pain management in the time following the surgery, to best manage post-operative pain.

To monitor for surgery risks related to neurology there will an Intra-operative Neuromonitoring in the Operating room. After surgery, the patient will be monitored for pneumothorax by inpatient hospital staff. If a pneumothorax is found, it may cause elongation of the patient's hospital stay, or require medical / surgical intervention. After surgery, the patient will be monitored for presence of a bronchopulmonary plug by inpatient hospital staff. If a bronchopulmonary plug is found, it may cause elongation of the patient's hospital stay, or require a medical / surgical intervention. Nemours uses low dose x-ray machine for all spinal x-rays to reduce the amount of radiation patient receives. The widely-accepted ALARA (as low as reasonably acceptable) principle will be used to ensure surgeons are imparting the lowest radiographic dose possible onto the patient during fluoroscopy.

4. Spine surgery risks

Your Nemours surgeon- Suken Shah, MD- is a pediatric spine surgeon who performs an average of 50 spine surgeries per year. His assistants are clinical fellows who are board certified orthopedic surgeons. They will use their knowledge and skills to eliminate or minimize any of the surgery related risks.

5. Other Potential Risks 9.3.2.2 (No greater than minimal risk study procedures)

- Nemours make all efforts to protect patient's privacy. Study data are stored in locked cabinets and password protected computers.
- Subjects will be allowed to skip questions which they are not comfortable answering without compromising their participation in the study.
- Because girls can become pregnant even when using birth control, we will be doing pregnancy tests during the study. The results of any pregnancy test done during the study will be made available only to your child. By law, all minors have a right to confidentiality when discussing issues of pregnancy and birth control with a doctor. This information will be discussed with you only if your child agrees. If there is any chance that pregnancy could have occurred during the study, the study doctors must be told immediately. Anyone who is pregnant may be taken out of the study right away. You and your daughter should be aware that, if this happens, others are likely to realize that she is pregnant. We encourage open honest communication between parents and their children regarding issues of sexual activity and possible pregnancy. It is also important for you to let the study doctor know if a young girl starts having periods during this study so that appropriate precautions can be taken from that point onward.

### 9.3.3 Potential Benefits of Trial Participation

There is some direct benefit to trial participation. First, studies have shown that there is a lower surgical risk in anterior-approach spine surgery compared to the posterior approach [19]. Vertebral Body Tethering has the theoretical potential for improvement over the outcomes of posterior spinal fusion. In particular, the durability of the posterior spinal fusion is coming into question. Posterior pedicle screw constructs came into popularity in the early 2000's and new 10 year post-op data is demonstrating a concerning trend. The Harms Study Group, a multicenter consortium of scoliosis practitioners and researchers have recently shown that almost 10% of AIS fusions require revision surgery by 10 year post-op and that this trend is progressive [28]. Other authors have also reported on high long term re-operation rates following AIS fusion surgery ranging from 4.6% to 19% [29-31]. One theory is that a fusion imparts increased stress on unfused segments below a fusion. Marks et al. have shown that patients will retain total lumbar motion after a posterior spinal fusion by increasing motion in the unfused areas [32]. The authors postulate that increased motion may lead to degeneration of discs and facet joints. These findings of supraphysiologic motion below a posterior spinal fusion may explain some of the decreasing durability of posterior spine fusion. Green et al. have studied the health of intervertebral discs below a spinal fusion at an average of 11.8 years following posterior spinal fusion [33]. The authors found that disc degeneration was occurring in 85% of patients and the discs when graded by the Firman scale, an objective validated measure of disc degeneration, demonstrated an average decrease from 1.1 pre-op to 1.8. Vertebral tether surgery will allow for continued motion of the instrumented levels and thus avoid the long lever-arm effect of a long fusion that may be contributing to early degeneration. Additional reports have questioned the durability of posterior spinal fusion. Upasani et al. reported on increased pain in patients at 5 years post-spinal fusion compared to at 2 years [34]. Lastly, posterior spinal fusion in patients who have not had their pubertal growth spurt, the population in whom we are proposing vertebral tethering, are at increased risk of complications and re-operation. Sponseller et al. reported that patients with open triradiate cartilages undergoing spinal fusion surgery have an increased rate of adding on (development of deformity below a fusion) and the response of the un-instrumented lumbar curve is less predictable [35].

The basic science literature suggests that this study intervention has the potential benefit to preserve motion of the spine in long-term follow-up, compared to traditional PSF [37-39].

Indirectly, participation in this trial will benefit the scientific community as a whole. Results from this trial will guide standard practice in a novel approach to spinal surgery in the pediatric population.

### 9.3.4 Risk-Benefit Assessment

The known risks and direct (and indirect) benefits will be presented to the patients by the investigators without bias. The investigators believe that benefits outweigh the risks based on all current knowledge and literature on the subject.

## 9.4 Recruitment Strategy

Subjects will be recruited by the investigator and clinical staff of the Orthopedic Clinic. Potential subjects who may satisfy the inclusion / exclusion criteria will be identified by the clinic staff, and will contact a study team member. The study team member will use the "Screening CRF" to assess preliminarily whether a potential subject may meet I/E criteria. Then, the study team

member will confer with the PI and/or investigators to determine whether the patient should be approached to offer the clinical trial to the subject and family. Potentially eligible patients will then be approached for informed consent/assent.

### 9.5 Informed Consent/Assent and HIPAA Authorization

Eligible patients will then undergo consent / assent during their orthopedic visit. This will take place in a private exam room in the clinic. The study will be explained to the patients / families and they can decide whether to participate in the study. Subjects and their families will be given the opportunity to ask questions and may take as long as they need to make a decision.

A patient advocate will be present while you are discussing the study with the research team and before you decide whether to consent for your child's participation in this study. The patient advocate's name is Gina Hennessy who is an orthopedic nurse practitioner. Her role in this study is to answer any questions you have or discuss study options with you in an impartial manner.

### 9.6 Payment to Subjects/Families

No payment will be given to subjects or families.

## 10 PUBLICATION

Following the completion of subject enrollment, data collection, and analysis, a manuscript will be prepared and submitted to an appropriate journal in order to contribute to the literature on this topic.

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# 12 APPENDIX

## 12.1 Appendix 1: Clavien-Dindo complications classification system (from Dindo, *et al.*)

**TABLE 1.** Classification of Surgical Complications

| Grade | Definition |
|---|---|
| Grade I | Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions |
| | Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside |
| Grade II | Requiring pharmacological treatment with drugs other than such allowed for grade I complications |
| | Blood transfusions and total parenteral nutrition are also included |
| Grade III | Requiring surgical, endoscopic or radiological intervention |
| Grade IIIa | Intervention not under general anesthesia |
| Grade IIIb | Intervention under general anesthesia |
| Grade IV | Life-threatening complication (including CNS complications)* requiring IC/ICU management |
| Grade IVa | Single organ dysfunction (including dialysis) |
| Grade IVb | Multiorgan dysfunction |
| Grade V | Death of a patient |
| Suffix "d" | If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication. |

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.