Title:	**Safety and Feasibility of a Vertebral Body Tethering Technique for Pediatric Idiopathic Scoliosis**
NCT#:	NCT03194568
Short Title:	Vertebral Body Tethering Outcomes
Drug or Device Name(s):	Anterior Vertebral Tether Device From the *Creo® Stabilization System*, *Transition™ Stabilization System*, and *SILC™ Fixation System* of Globus Medical, Inc.
FDA IDE:	G170023
Regulatory Sponsor:	**Patrick J. Cahill, MD**
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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 the 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), and 3) sagittal thoracic modifier (-, N, +).
ORC	Office of Research Compliance
PET	Polyethylene Terephthalate
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

	death, is life-threatening, requires inpatient hospitalization, or prolongs existing hospitalization.
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 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 in which 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 50 degrees.

Objectives:

The objectives of this study are to assess the safety and feasibility of anterior vertebral body tethering surgery to treat idiopathic scoliosis.

Study Design:

This is a pilot study, non-randomized, open label study of the anterior insertion of an Anterior Vertebral Tether Device in pediatric scoliosis. The study will be conducted at a single site - The Children's Hospital of Philadelphia.

Setting/Participants:

This is a single-site, Sponsor-Investigator led pilot study of vertebral body tethering for pediatric idiopathic scoliosis in children aged 8-16 years.

Study Interventions and Measures:

The study intervention is surgical orthopedic implantation of the Anterior Vertebral Tether Device, 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 feasibility by determining the ability to successfully implant the investigational device. Monitoring will be conducted by a Safety Officer, who has extensive training and experience in surgical procedures.

PROTOCOL SYNOPSIS

Study Title	**Safety and Feasibility of a Vertebral Body Tethering Technique for Pediatric Idiopathic Scoliosis**
Funder	Departmental Funds
Clinical Phase	Pilot Study
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 feasible method of anterior approach surgery for spinal deformity in pediatric scoliosis.
Study Objectives	**Primary** • To determine the safety of anterior vertebral tethering surgery in patients who have been recommended to have surgical intervention. **Secondary** • To determine the feasibility of anterior vertebral tethering surgery in patients who have been recommended to have surgical intervention.
Test Articles	Anterior Vertebral Tether Device Globus Medical, Inc. *Transition™ Stabilization System* *SILC™ Fixation System* *CREO® Thoracolumbar Stabilization System*
Study Design	This is a single center prospective, open-label pediatric clinical device trial with a single surgical intervention.
Subject Population **Key criteria for Inclusion and Exclusion:**	**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 and less than or equal to 60 degrees 5. Lumbar curve less than 35 degrees 6. Patient has already been identified for and recommended to have surgical intervention 7. Spina bifida occulta is permitted

Subject Population Key criteria for Inclusion and Exclusion:	8. 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 9. Completed standard-of-care procedures as outlined in Section 5 **Exclusion Criteria** 1. Pregnancy (current) 2. Prior spinal or chest surgery 3. MRI abnormalities (including syrinx greater than 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 or greater than 60 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
Number Of Subjects	The study will be conducted at The Children's Hospital of Philadelphia, Division of Orthopedics in up to 40 subjects. Subject inclusion will be based on interest of patients who present to the orthopedic clinic and satisfy the inclusion/exclusion criteria.
Study Duration	Each subject's active participation will last post-operatively and until approximately two years after skeletal maturity. The entire study is expected to last at least 10 years.
Study Phases: **Screening** **Study Treatment**	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. 2. Study treatment: The subject will undergo surgical intervention using an accepted standard-of-care anterior approach using components from Globus Medical Inc. products, the *Creo® Stabilization System, Transition™ Stabilization System, and SILC™ Fixation System*. The investigational device is identified as the Anterior Vertebral Tether Device, comprising the staples, screws and locking

	caps from *Creo*® and the PET cord from the *Transition*™ *Stabilization System* and *SILC*™ *Fixation System*.
Post-op Follow-Up	3. Post-operative follow-up: Subjects will be followed at regular time points at 21, 45, and 90 days post-op during the post-operative phase. Patients will also be seen at visits 180, 365, and 730 days post-op during the extended follow-up phase. Long-term follow-up, beyond two years post-operatively, will occur through chart review of subjects, through two years beyond attaining skeletal maturity, which will be conducted under a separate study.
Efficacy Evaluations	The exploratory therapeutic 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 and Feasibility Evaluations	We will use phase-specific endpoints to measure safety and feasibility: 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. 2) Post-operative active phase: Incidence of infection (within 90 days post-op), pneumothorax, bronchopulmonary plug, or any reportable SAE. 3) Extended follow-up phase: Incidence of over-correction, implant failure (measured on serial x-ray), incidence of curve progression to more than 50 degrees at two 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). Additional follow-up, through two years beyond skeletal maturation, will be conducted by periodic chart review. 4) Feasibility will be assessed by the capacity to successfully implant all components of the anterior vertebral tether device in subjects.
Statistical And Analytic Plan	The enrollment target of 40 subjects for this initial study of the device is based primarily on feasibility rather than statistical concerns. As such, analyses will be primarily descriptive for safety and feasibility. The Cobb angle, the exploratory therapeutic endpoint, will be evaluated as a continuous variable.
Data And Safety Monitoring Plan	The PI and Safety Officer will meet regularly to discuss any safety events. Safety Officer reports will be forwarded to the IRB during continuing review per CHOP Office of Research Compliance 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 CHOP Office of Research Compliance monitoring standards. The PI will meet with the study team regularly to discuss study progress and ensure data fidelity.

TABLE OF STUDY PROCEDURES									
Study Phase		**Pre-op / Screening**	**Surgery**	**Post-Operative Phase**				**Extended Follow-up Phase**	
Visit Number		**1**	**2**	**N/A**	**3**	**4**	**5**	**6**	**7**	**8**
Study Days		**Pre-op**	**0**	**1-44 (or until discharge)**	**21 (+/- 21 days)**	**45 (+/- 21 days)**	**90 (+/- 21 days)**	**180 (+/- 90 days)**	**365 (+/- 90 days)**	**730 (+/- 90 days)**
Clinical Care (SOC) Evaluations:										
All procedures included here are standard-of care for a surgical orthopedic spine patient	*X-ray: Hand Bone Age*	*								
	X-ray: AP/PA and Lateral Spine	*X*			*	*X*	*X*	*X*	*X*	*X*
	X-ray: Bending bolster films	*X*				*	*	*	*	*
	MRI: MRI Spine (can be obtained at any time prior to pre-op)	*X*								
	Pulmonary Function Test	*							*	*
	History and physical exam with height and weight	*X*			*X*	*X*	*X*	*X*	*X*	*X*
	Anaesthesia Evaluation	*X*								
	Pregnancy Test (as applicable)	*X*								
	Bloodwork	*X*	*X*	*X*						
	Post-operative inpatient management by treating physician and inpatient staff		*X*	*X*						
	X-ray: AP/PA and Lateral Spine (performed at discharge)			*X*						
Research Evaluations:										
Medical Record Review		X	X		X	X	X	X	X	X

Review Inclusion/Exclusion Criteria	X								
Informed Consent/Assent	X								
Study Specific Physical Exam	X				X	X	X	X	X
SRS 30 Questionnaire (completed by subject)	X						X	X	X
Clinical Photographs	X						X	X	X
Anterior tethering surgery under general anaesthesia with spinal cord monitoring		X							
Intraoperative fluoroscopy (< 1hr)		X							
Complications Evaluation		X	X	X	X	X	X	X	X
KEY:									
X = Procedure is performed at that visit									
* = Optional standard-of-care procedure, performed at discretion of treating physician									
Italics = Procedures which are performed as standard-of-care									
Bold = Procedures with greater than minimal risk									
NOTE: Long-term follow-up through two years after skeletal maturity will take place under a separate observational research protocol									

1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

Scoliosis is a condition in which 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 vs. lumbar vs. 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].

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 Hueter-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 care for moderate scoliosis in patients with remaining growth is in a state of clinical equipoise. Almost all practitioners utilize one of three strategies: immediate spinal fusion, observation with delayed fusion once a curve reaches fifty degrees, and bracing. Based on evaluation of the current body of literature and his clinical experience, he selects immediate fusion for those in whom bracing will be ineffectual in preventing progression to 50 degrees or more. The sponsor-investigator does utilize observation with delayed fusion in those patients in whom progression to 50 degrees is a high probability. Evidence from Charles et al. and Sanders et al. have provided evidence to predict which patients will have inevitable progression to 50 degrees and beyond by stratifying skeletal maturity and Cobb angle. The practice of fusion of curves less than 50 degrees is supported by a query of the Harms' Study Group database on fusion for AIS. This consortium is the largest registry for AIS fusions and is made up of the most prominent thought leaders in the field. The registry demonstrates that the thoracic Cobb angle of patients who have under gone fusion averages 56 degrees (std. dev. 13 degrees). Furthermore, a delay in spinal fusion can lead to the need for a longer spinal fusion that may be inclusive of the lumbar curvature [10-11].

The sponsor investigator utilizes bracing in his practice in those patients in whom bracing has a probability of altering the natural history. Support of bracing as a general invention derives from recently published studies. In 2010, Katz and colleagues [12] 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 [12] 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 [13] demonstrated an improvement over the natural history with brace treatment and a correlation between hours of brace wear and efficacy of bracing in adolescent idiopathic scoliosis (AIS).

The prospective studies of bracing have led to analysis of various subpopulations treated with bracing and published literature suggests that bracing in ineffectual for those patients who are early in the skeletal maturation process. The most important difference in the results presented by Weinstein and colleagues [13] and Katz and colleagues [12] 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 from the Katz et al. study, Karol and colleagues demonstrated a more than five-fold increased risk of bracing failure in Risser 0 patients compared to Risser 1 patients [14]. 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 [15]. 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 [16] 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 on the natural history in JIS. Charles et al. further stratified JIS by Cobb angle [17]. 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.

For these reasons, the practice of the Sponsor-Investigator is to perform a spinal fusion in those patients with a curve less than 50 degrees who would have a high likelihood of progression to a Cobb angle beyond 50 degrees and in whom bracing would likely fail. The decision making by the PI exactly mirrors the inclusion criteria: a) those patients who meet the parameters for inclusion would otherwise be offered a spinal fusion, and b) those who do not meet the inclusion criteria would be recommended bracing or observation.

Additional negative aspects of brace management in inappropriate populations are coming to light. 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. Brace treatment includes 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 [18]. Such ramifications were further explored in a recent study by Misterska and colleagues [19], who found that the patients experienced a moderate level of 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 four hour surgery with a five day hospital stay with a blood loss of approximately 800cc [20]. 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 [21].

1.2 Name and Description of Investigational Product or Intervention

1.2.1 Vertebral Body Tethering

Vertebral body tethering (VBT) will be performed via an anterior thoracoscopic approach (see "Surgical Technique" below). This approach is safe and effective at achieving access to the spine for the purposes of instrumentation, and has predictable perioperative course and little to no long-term impacts on health and function. This surgical approach is utilized as a common approach for the current standard of care anterior-type spinal fusion [21, 22]. 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% vs. 3% in posterior spinal fusion [20]. This concern is irrelevant in VBT as fusion is not the goal.

1.2.2 Implant

The implants utilized are comprised of components from Globus Medical, Inc., the *Creo*® *Stabilization System, Transition*™ *Stabilization System, and SILC*™ *Fixation System* systems. The *Creo*® system is designed and indicated to be used in anterior thoracoscopic spinal fusion for spinal deformity. We anticipate placing centering staples, screws and locking caps from the *Creo*® system 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 (from the Globus Medical, Inc. *Transition*™ *Stabilization System* or *SILC*™ *Fixation System*). The cords are approved as part of posterior spinal stabilization systems. The implanted investigational device will be composed of the staples, screws and locking caps from the *Creo*® system and the PET cord from the *Transition*™ *Stabilization System* or *SILC*™ *Fixation System*, and will be referred to in this IDE application as the Anterior Vertebral Tether Device (AVTD). 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. In August 2019, the FDA approved The Tether™ – Vertebral Body Tethering System, developed by Zimmer Biomet Spine.

1.2.3 Surgical Technique

The surgical technique has been described by Samdani, et al. [23, 24]:

> 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. Fluoroscopic 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 scalpel 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 anteriorly 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 Medical, 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 concave side, across the anterolateral portion of the vertebral body. Next, an appropriately sized screw (*Creo® Stabilization System*, Globus Medical, 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 (*Transition™ Stabilization System* or *SILC™ Fixation System*, Globus Medical, Inc.) through the tulips of all of the screws. The set screw (*Creo® Stabilization System*, Globus Medical, 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 Medical, 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. Fluoroscopic 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. At this juncture, the implantation of the investigational device, the Anterior Vertebral Tether Device, composed of staples, screws and set screws from the *Creo® Stabilization System,* and the PET cord from the *Transition™ Stabilization System* or *SILC™ Fixation System*, is complete. 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 [25]. We are proposing similar indications and applications for vertebral body 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 five year results of thoracoscopic anterior fusion showing that Cobb angle correction averaged 56% [22, 26], and total lung capacity at 91% of expected. These results were not different than the two 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 [27, 28]. Faro et al. demonstrated that pulmonary function declines three months after both open and thoracoscopic anterior scoliosis surgery but recovers by one year post-op in thoracoscopic surgery but not in open anterior surgery [29].

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 [20]. Furthermore, they reported decreased pulmonary function in the open anterior groups but similar pulmonary function tests (PFTs) in posterior and thoracoscopic patients. Lonner et al. also addressed the impact of surgical approach on pulmonary function [25]. 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.*

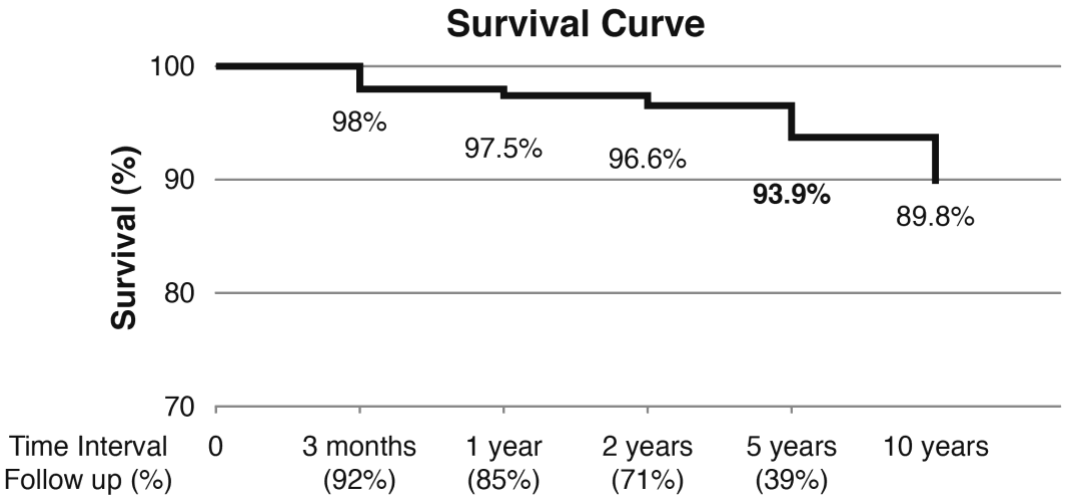
Table 2: Mean Percent-predicted Values Preoperatively to Follow-up (adapted from Lonner et al, 2015)

	Percent predicted FEV1	**Percent predicted FVC**	**Percent predicted TLC**
Thoracotomy			
Mean pre-operative	83.3	88.1	85.6
Mean follow-up	72.3	75.1	77.6
Δ (Pre-post)	-11.0	-13.0	-8.0
P	<0.001	<0.001	≤ 0.001
Thoracoscopic			
Mean pre-operative	82.5	87.2	85.0
Mean follow-up	78.1	82.5	88.2
Δ	-4.4	-4.7	3.2
P	<0.004	NS	NS
Thoracoabdominal			
Mean pre-operative	90.3	93.7	94.7
Mean follow-up	83.5	87.7	95.1
Δ	-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, has recently shown that almost 10% of AIS fusions require revision surgery by 10 years post-op and that this trend is progressive [30] **(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% [31-33]. 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 [34]. 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 [35]. The authors found that disc degeneration was occurring in 85% of patients when graded by the Firman scale, an objective validated measure of disc degeneration [35]. 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 five years post-spinal fusion compared to at two years [36]. 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 [37].

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 [38].

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 [39-41]. The first study the authors published was in an immature bovine model [40]. 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 [42]. Further evidence of the effect of growth driving the change in alignment was offered in a subsequent study of the bovine model [39]. 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 [43]. The other is from Iowa and was reported by Weinstein and colleagues [44, 45]. 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 [46]. 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 [45]. 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 [44]. 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 Liklihood 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 [47]. Dimeglio suggests several measures for identifying the onset of

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 [48]. 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 our 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 [23, 24].

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 Children's Hospital of Philadelphia 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. 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 The Children's Hospital of Philadelphia 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 feasibility 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 patients recommended for surgery in the immediate post-operative period.

2.2 Secondary Objectives (or Aim)

The secondary objective is to assess feasibility by determining the ability to successfully implant the investigational device in study subjects who have been recommended for surgical intervention.

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 who have been indicated for scoliosis surgery by the treating physician. 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. This phase will last one 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 staples, anterior vertebral body screws, locking caps and PET cord (the Anterior Vertebral Tether Device) under general anesthesia. This phase will last 1 day (day of surgery). This surgical intervention 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 three set time points for follow-up, which will occur during standard-of-care clinical follow-up visits for spine patients receiving surgical intervention. The three time-points are a POD 21 wound check, POD-45 clinical visit, and a POD-90 clinical visit. During these three clinical visits physical exams, radiographs, and AE/SAE data will be collected depending on the visit. 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.

In unique circumstances, the Investigator may determine it is necessary for the Subject to be seen for a follow-up visit(s) at an outside institution due to geographic, travel, other restrictions. In such a case the Investigator will communicate with the physician evaluating the Subject at the outside institution and Subject to ensure all necessary data points and AE/SAE information are captured. If possible copies of the Subject's medical record for this visit will be obtained by the study team.

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 eight visits over a two year (730 day) period: one day for recruitment/consent, one day for the study intervention (surgery), one day for each visit: POD21, POD45, POD90, POD180, POD365, and POD730. 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 initial study participation period 730 + 90 days after the day of surgery. Long-term follow-up through at least two years following skeletal maturity will take place through a separate observational study.

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

The study will be conducted at The Children's Hospital of Philadelphia.

This study is a clinical investigation of the anterior vertebral tethering procedure in up to 40 subjects using the investigational device elements as described within this protocol. Based on a broad review of patient visits over the past year, we may expect to enroll about 5-10 patients per year.

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 and less than or equal to 60 degrees
5) Lumbar curve less than 35 degrees
6) Patient has already been identified for and recommended to have surgical intervention
7) Spina bifida occulta is permitted
8) 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
9) Completed standard-of-care procedures, as outlined in the Table of Study Procedures
10) 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 greater than 4mm, Chiari malformation, or tethered cord)
4) Neuromuscular, thoracogenic, cardiogenic scoliosis, or any other non-idiopathic scoliosis
5) Associated syndrome, including Marfan syndrome or neurofibromatosis
6) Sanders bone age greater than 4
7) Thoracic curve less than 35 degrees or greater than 60 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)

- Informed consent/assent
- Medical record and x-ray review for eligibility screening (research)
- History and physical exam with height and weight
- Research specific physical exam (research)
- Anesthesia evaluation
- Pulmonary function test (completed at treating physician's discretion)
- Bloodwork (outlined in Section 5.1.6)
- Pregnancy test, as applicable
- X-ray: bending bolster, AP/PA, lateral spine, and hand bone age
- SRS 30 Questionnaire (research)
- Clinical photographs (research)
- Medical record and x-ray information abstraction (research)

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 and fluoroscopic guidance. This process is described in Section 2.

Data from the surgery will be abstracted by medical record review for adverse events or complications. Intra-operative 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 three SOC clinical visits in this phase, where the subject will also undergo a research visit. This phase also includes all inpatient recovery in the post-operative period, which includes post-operative bloodwork and radiographs. Information from SOC procedures will also be abstracted from the medical records and radiology databases.

4.3.1 Visit 3 (POD 21)

- X-ray: AP/PA and lateral spine (completed at treating physician's discretion)
- History and physical exam with height and weight
- Medical record review and abstraction (research)
- Complications review (research)

4.3.2 Visit 4 (POD 45)

- X-ray: AP/PA and lateral spine
- X-ray: Bending bolster films (completed at treating physician's discretion)
- History and physical exam with height and weight
- Research specific physical exam (research)
- Medical record review and abstraction (research)
- X-ray review and abstraction (research)
- Complications review (research)

4.3.3 Visit 5 (POD 90)

- X-ray: AP/PA and lateral spine
- X-ray: Bending bolster films (completed at treating physician's discretion)
- History and physical exam with height and weight
- Research specific physical exam (research)
- Medical record review and abstraction (research)
- X-ray review and abstraction (research)
- Complications review (research)

4.4 Extended Follow-up Phase

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

4.4.1 Visit 6 (POD 180)

- X-ray: AP/PA and lateral spine
- X-ray: Bending bolster films (completed at treating physician's discretion)
- History and physical exam with height and weight
- Research specific physical exam (research)
- Medical record review and abstraction (research)
- X-ray review and abstraction (research)
- Complications review (research)
- Clinical photographs (research)
- SRS 30 Questionnaire (research)

4.4.2 Visit 7 (POD 365)

- X-ray: AP/PA and lateral spine
- X-ray: Bending bolster films (completed at treating physician's discretion)
- Pulmonary function test (completed at treating physician's discretion)
- History and physical exam with height and weight
- Research specific physical exam (research)
- Medical record review and abstraction (research)
- X-ray review and abstraction (research)
- Complications review (research)
- Clinical photographs (research)
- SRS 30 Questionnaire (research)

4.4.3 Visit 8 (POD 730)

- X-ray: AP/PA and lateral spine
- X-ray: Bending bolster films (completed at treating physician's discretion)
- Pulmonary function test (completed at treating physician's discretion)
- History and physical exam with height and weight
- Research specific physical exam (research)
- Medical record review and abstraction (research)
- X-ray review and abstraction (research)
- Complications review (research)
- Clinical photographs (research)
- SRS 30 Questionnaire (research)
- Study completion CRF (research)

4.5 Long-Term Follow-up Phase

We are planning a long-term follow-up phase (LTFU) through approximately two years after each subject reaches skeletal maturity. Following the extended follow-up phase (approximately two years post-operative), the LTFU will be an observational study involving chart review. This will be performed under a separate research study. Device-related SAEs and relevant data to assess safety and feasibility endpoints up to two years after skeletal maturity will be reported in accordance with FDA requirements.

4.6 Unscheduled Visits

Unscheduled clinic visits will be made through the department's/hospital's 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.

4.7 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 and study team will make efforts to follow-up subjects who do not strictly adhere to timely visit schedules. The Investigator and study team 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.

Subjects who are withdrawn from the study during the post-operative follow-up phases due to AEs/SAEs, such as tether failure or implant re-operation, will no longer be followed at study-specific visits. These subjects have the option to consent and allow for continued monitoring by medical and radiographic record review through the end of the two-year Extended Follow-up Phase. Subjects who are withdrawn from the study also have the option to enroll in a separate LTFU observational study.

4.7.1 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 be withdrawn from the study may do so, preferably by submitting a written request addressed to the site's PI. A 'Study Completion CRF' will be filed for each subject.

4.8 Live Case Presentation

A live case demonstration may be performed for one subject's surgery. Selection of an eligible subject, consent process, conduct of the surgical procedure, and subsequent follow-up visits and monitoring will be performed as defined in the protocol and similarly to subjects who are not participating in the live case demonstration.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Pre-operative Visit

5.1.1.1 Screening

- Potential subject is identified by the treating surgeon (match inclusion/exclusion criteria, surgical candidate)
- Complete informed consent/assent
- Review inclusion/exclusion criteria, complete inclusion/exclusion checklist
- Complete subject screening CRF

5.1.1.2 Pre-operative Medical Record/Radiograph Review

- Name
- Age
- Sex
- Race
- Ethnicity
- Date of birth
- MRN
- Diagnosis
- Clinical and surgical history (including history of pregnancy)
- Radiographic information and reports (including pre-operative coronal/sagittal; spine MRI)
- PFT data (if available)

5.1.1.3 Pre-operative Anesthesia Evaluation and Bloodwork (abstracted from medical record)

- Result of anesthesia evaluation: fitness for surgery, special notes
- Bloodwork results/levels

5.1.1.4 Pre-operative 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
- Clinical photographs

5.1.1.5 Pre-operative Radiographs (abstracted from medical record)

- AP/PA and lateral spine films
- Bone age hand radiograph (performed at physician discretion)
- Bending bolster films

5.1.2 Surgical Intervention and Post-operative Course

5.1.2.1 Intra- and Post-operative Procedures

- Anterior tethering surgery under general anesthesia with spinal cord monitoring
- Intraoperative fluoroscopy (<1 hour)
- AP/PA and lateral standing radiographs of the spine

5.1.2.2 Intraoperative Data (abstracted from medical record)

- Operative efficiency times (i.e. 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 staples, screws, locking caps, and PET cord
    - Type and size of screws 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
- Antibiotic use
- Type and dose of antifibrinolytic
- Time-exposure of fluoroscopic x-ray during procedure

5.1.2.3 Post-surgical Data (abstracted from medical record)

- Chest tube drainage on day #1 - #5, and total collected
- Post-operative day of extubation as well as chest tube removal will be noted
- Post-operative 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 post-operative brace and the number of months utilized will be recorded
- Bloodwork levels and results from the hospital stay will be recorded
- Complications will be recorded: 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-operative drain: type and drainage amounts daily until d/c of drain
- Data abstracted from medical records, radiology reports, and surgical logs
- Post-operative bloodwork

5.1.3 POD 21 Follow up

- Medical and radiographic record review: data abstracted from clinical care exam (medical records, radiology reports, pulmonology tests)
- Standing height
- Weight
- BMI

5.1.4 POD-45 and POD-90 Follow-up

5.1.4.1 Post-Operative Visit

- Medical and radiographic record review: data abstracted from clinical care exam (medical records, radiology reports, pulmonology tests)
- Standing height
- Weight
- BMI
- Trunk flexibility measurements (standardized): **Adam's Forward bending test (degrees) only**

5.1.5 POD-180, POD-365, POD-730 Follow-up

5.1.5.1 Extended Follow-up Visit

- Medical and radiographic record review: data abstracted from clinical care exam (medical records, radiology reports, pulmonology tests)
- 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)
- SRS 30 Questionnaire
- Clinical photographs

5.1.6 Laboratory Evaluations

5.1.6.1 Bloodwork

Pre-operative bloodwork to be performed:

- CBC (Complete Blood Count) with(out) Differential
- CMP (Comprehensive Metabolic Panel) with(out) Albumin
- PT/INR (Prothrombin Time)
- PTT Profile (Partial Thromboplastin Profile)
- Type & Screen

These tests are performed pre- and post-operatively for all patients undergoing surgery, at clinical discretion. This is done as part of the anesthesia team's routine evaluation of the subject, and for tracking safe recovery. Results of these blood tests will be monitored for any abnormal or incidental findings. Abnormal or incidental findings will be documented and communicated to the treating physician(s). The treating physician(s) will determine if these findings would alter the subject's treatment course in any way.

5.1.6.2 Pregnancy Testing: Performed at pre-operative visit only

A blood or urine pregnancy test will be performed for female subjects 11 years of age and older, or any female who has begun menses will be required to complete a blood or urine 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.

5.1.7 Other Evaluations, Measures

Clinical Evaluations/Measurements:

- 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 the 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.
- Clinical Photographs: Photographs will be taken of the subject at specified time points. The photographs will not include facial features, and include the torso from the top of the shoulders to the iliac crests. The patient should stand in a natural standing position for AP, PA, lateral right, and lateral left photos. The subject will perform the Adam's Forward Bending Test, and a photograph will be taken from the view of the examiner (PA). Photos will be taken without shirt or hospital gown. It is permissible for female subjects to wear a top covering that allows for a clear view of the spine and trunk (bra, sports bra, bathing suit top, or similar).

Other Measurements:

- Sanders Bone Age: Attached as Supplement 1
- 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 Anterior Vertebral Tether Device, as described in this IDE application, comprised of the staples, screws, locking caps, and PET cord. 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

This is a safety and feasibility clinical trial. A therapeutic exploratory endpoint for this VBT procedure will be measurement of the Cobb angle. The 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 exploratory therapeutic evaluator of efficacy. 'Success' of the intervention will be defined by a final Cobb angle of less than or maintained at less than 50 degrees, for curves which were less than 50 degrees pre-operatively. For curves which were greater than 50 degrees pre-operatively, a Cobb angle which is less than or maintained at less than 50 degrees is considered a 'success'.

5.4 Chart Review for Withdrawn Subjects

Subjects who are withdrawn from the study during the follow-up phase due to AEs/SAEs will no longer follow the study visit schedule nor participate in study-specific procedures. These subjects have the option to consent and allow for continued monitoring by medical and radiographic record review through the end of the two-year Extended Follow-up Phase. Subjects who are withdrawn from the study also have the option to enroll in a separate LTFU observational study.

6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

The primary endpoint is safety, and will consist of the rate of AEs/SAEs in anterior VBT surgery.

6.2 Secondary Endpoints

The secondary endpoint is feasibility, as determined by the ability to successfully implant the investigational device in study subjects.

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 sex). Categorical data analysis methods such as chi-square will be used for dichotomous variables and 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 the 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's-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 AEs/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 Anterior Vertebral Tether Device composed of the investigational staples, screws, locking caps, and PET cord. Device-related AE incidence will be summarized along with the corresponding exact binomial 95% two-sided confidence intervals.

6.3.3 Efficacy Analysis

This initial clinical study using the Anterior Vertebral Tether Device for pediatric idiopathic scoliosis is focused on safety and feasibility, not efficacy, as primary endpoints. There will be an exploratory therapeutic endpoint, Cobb angle change, based on an intention to treat approach and will include all subjects who have undergone the intervention.

The exploratory therapeutic 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, a 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.

6.3.4 Live Case Demonstration Analysis

Data collected from the subject participating in the live case demonstration will be stratified from the rest of the subjects during analysis. A comparative analysis will be performed to determine whether there are significant differences in risks and outcomes between the live case subject and subjects who were not involved in a live case presentation. If such differences exist, the data from the live case presentation will be excluded from efficacy analyses and independently analyzed. Exclusion of the live case subject from analyses will not impact the power calculations described in Section 6.4.

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 implanted device, referred to as the Anterior Vertebral Tether Device, to explore safety and feasibility of the implant. Based on device implantation in up to 40 subjects, the study will not be sufficiently powered to gain statistical significance. However, this preliminary study will allow some insight into the safety of implantation, as measured by the acceptability of adverse events, as well as feasibility of implantation, as estimated by the proportion of successful implants of the Anterior Vertebral Tether Device. The regulatory status of such an implant requires that the Sponsor obtains an IDE. There is no active comparative group in this limited study. Notably, there is a useful comparator group from review of published data (historical controls) and from the data of the Harms Study Group (CHOP IRB# 06-005052), for which the Sponsor has access. A comparative analysis will be performed combining data from this clinical trial with IRB# 06-005052 to evaluate patient factors and clinical outcomes depending on the intervention received. Data from this clinical trial will not be shared with IRB# 06-005052.

Using data observing pre and post thoracic and lumbar measurements for a small sample of subjects; for the thoracic measurements, a sample size of 40 will have >80% power to detect a difference in means of 17.9, assuming a standard deviation of differences of 6.6, using a paired t-test with a 5% two-sided significance level. For the lumbar measurements, a sample size of 40 will have >80% power to detect a difference in means of 6.5, assuming a standard deviation of differences of 5.38, using a paired t-test with a 5% two-sided significance level. Sample size calculations were performed using NQuery software.

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 AEs/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 greater than 50% of patients after 15 cases

6.6.2 Stopping rules for SAEs that are device-related

Definition of Terms:

- Screw failure – screw, locking caps, 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 radiograph 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, overall Cobb angle worsens compared to the first erect measurement, AND requires re-operation.
- 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 Rules

- Screw/locking cap/staple failure stopping point: 3 of first 5 cases, 5 of first 10, or in greater than 50% of cases 15 and beyond.
- Tether failure stopping point: 3 of first 5 cases, 5 of first 10, or greater than 50% of cases 15 and beyond.
- Implant failure re-operation stopping point: occurs in 3 of first 5, 5 of first 10, or greater than 50% of cases 15 and beyond.

7 STUDY DEVICE

7.1 Description

The device under investigation is the "Anterior Vertebral Tether Device", comprised of components from Globus Medical, Incorporated systems: The *Creo® System* and the *Transition™ Stabilization System or SILC™ Fixation System*. From the *Creo® System* come the staples, screws, and locking caps of the investigational device. From the *Transition™ Stabilization System* or *SILC™ Fixation System* comes the Polyethylene Terephthalate (PET) cord. These four components are part of a 510K-cleared implant system distributed by Globus Medical, Inc. The *Creo®* and *Transition™* Globus systems are classified as Class II under 21 CFR 888.3070, and *SILC™ Fixation System* Globus system is classified as Class II under 21 CFR 888.3010. The devices are manufactured and distributed according to manufacturer guidelines and in compliance with 21 CRF 820.

The entire systems are supplied to CHOP as part of routine surgical treatment. The systems 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 rest of the system will be discarded according to the appropriate CHOP OR policies and procedures.

7.2 Packaging

The device is part of commercially marketed systems 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 and Tracking

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 of the staples, screws, locking caps, and PET cord will be tracked by the study team to comply with FDA standards for investigational device tracking. Those parameters include:

- Manufacturer of device
- Model name of device
- Device Part Number
- Device Lot Number

The device will be received and processed in the usual standard process per hospital standard operating procedures. The medical record and device form, which will contain the parameters stated above, will be the source documents for tracking implanted devices. The process for device handling and tracking will be conducted in accordance with our study device tracking SOP.

7.4 Indications for Use

7.4.1 Intent of the Device:

- The device is intended to normalize the vertebral column of those with pediatric idiopathic scoliosis, by applying tensional force.

7.4.2 Patient population:

- Males and females diagnosed with idiopathic scoliosis (all types - infantile, juvenile, adolescent).
- Spina bifida occulta is permitted.
- 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.

7.4.3 Curve types:

- We will use the Lenke classification system for curve type. The Lenke Classification system is a classification for AIS. For those subjects with AIS, the Lenke types eligible for inclusion are Lenke types 1, 2, and 3. For those subjects with JIS and IIS (idiopathic scoliosis diagnosed before age 10), subjects with curves patterns that match all other criteria to be classified as Lenke types 1, 2, and 3 will be included.

7.4.4 Levels that will be treated:

- Thoracic levels T4-L1 (i.e., most cephalad and caudad levels that may be treated).

7.4.5 Growth and skeletal maturity assessment:

- Chronological age 8-16 years (inclusive)
- Sanders bone age less than or equal to 4.

7.4.6 Range of curve magnitudes that will be treated:

- Thoracic curve greater than or equal to 35 degrees and less than or equal to 60 degrees
- Lumbar curve less than 35 degrees

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 CHOP 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 CHOP 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 <u>Adverse Device Effect</u>. Adverse device effects have special reporting guidelines, as outlined below.**

8.5 Recording plan for AEs/SAEs

<u>Surgery and Post-operative Phase (Day 0 – POD 90):</u>

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.

<u>Extended Follow-up Phase (POD 91-POD 730)</u>:

For this phase, <u>all</u> 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.

<u>Long-term Follow-Up (POD 730 through approximately two years after skeletal maturity):</u>

An observational study involving chart review of medical charts from CHOP and external sources as needed will be undertaken for long-term follow-up. All SAEs identified from the medical records that are considered device related, up to two years after skeletal maturity, will be reported in accordance with FDA requirements. This will be performed under a separate research protocol.

Only the AEs/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

8.6.1 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 and FDA

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 every 6 months for the first 24 months of the study. Then regular intervals, no less than yearly, after the first 24 months of the study.
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. **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	12 month intervals
Progress Report	FDA Form 3419	FDA and reviewing IRB(s)	Regular intervals, no less than every 6 months for the first 24 months of the study. Then regular intervals, no less than yearly, after the first 24 months of the study.
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 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 timelines. 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, dates of service, approximate date at which the subject will need to reconsent upon turning 18, and whether or not the subject has consented for the use of their data for future research studies. 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, including PHI, 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 CHOP'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, signed consent forms, paper forms collected during testing, as well as all other relevant documentation. These will be stored in a locked research office.

2. Data Sharing:

Coded data will be transferred from CHOP to Dr. Sriram Balasubramanian at Drexel University for research collaboration and data analysis via CD/DVD, secure electronic file transfer, and/or on protected Excel spreadsheets sent by secured hospital email. All data transferred will be labeled with the subject's study ID and will not include PHI. Dr. Balasubramanian at Drexel University will not have access to the master list, therefore this data will not be identifiable to them.

A Limited Data Set, including images, will be transferred from CHOP to Globus Medical, Inc. as part of a license agreement executed between the two parties for use in the manufacturer's humanitarian device exemption (HDE) submission. Images will be limited to images of subjects' torsos and will not include video recordings, subject faces, or identifiable features. Data will be sent by secure electronic file transfer and with hardcopy source documents. Hardcopy documents will be redacted to remove identifiers and be transferred via courier or in-person from study team member to an authorized representative of Globus Medical, Inc. Data transferred will

not include PHI, except dates of service, and Globus Medical, Inc. will not have access to the master list to link data back to subjects.

3. Security:

The master sheet will be a password protected Excel file kept in the secure orthopedic research drive at CHOP. 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 CHOP 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 CHOP Research Information Systems to determine the most appropriate recovery strategy. Data and backups are stored in the CHOP 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 CHOP'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.

4. 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 will be destroyed two years after the last marketing application has been approved or two years after all research of the study has been completed, and as approved by the Sponsor.

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 CHOP 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)

- Radiation Exposure (Fluoroscopy and X-ray): This study involves exposure to radiation from intraoperative fluoroscopy and x-rays. The patient will receive a radiation dose, which is necessary for completion of the operation. Radiation can increase the risk of cancer after many years but at a dose much higher than the patient will receive. Because of the low dose of radiation, it is very likely that the patient will see no ill effects.

  Radiation exposure will be tracked during the surgery. This will be recorded as fluoroscopic exposure time recorded in minutes. 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 [49].

- Neurological Injury: There is risk for neurological injury in all surgeries involving spinal correction and device implantation. Intra-operative neuromonitoring (IONM) will be used by the surgical team to monitor for this risk. There are no known adverse neuromonitoring events occurring with this surgery in the literature [21].
- Bleeding: Bleeding is a risk for any surgical procedure. Every reasonable effort will be made by the surgical staff to reduce blood loss. Estimated blood loss during surgery (EBL) will be recorded on CRFs.
- Infection: Infection is a risk for any surgical procedure or hospital stay. All CHOP SOPs regarding sterile procedures and institutional policies on infection prevention will be followed to prevent infection. The patient will be placed on CHOP Orthopedics SOP for pre- and post-operative antibiotic regimen for spine surgery patients.
- Pain: Pain is a risk for a patient during post-operative recovery. CHOP orthopedics pain team will be consulted for pain management in the time following the surgery, to best manage post-operative pain.
- Pneumothorax: 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.
- Bronchopulmonary plug: 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.
- Implant Failure: We will diligently monitor the patient both during and after surgery for signs of implant failure. Some types of implant failure could be:

  - 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, overall Cobb worsens compared to the first erect measurement, AND requires re-operation.
  - 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.
- Overcorrection: It is possible for the device to impart more than the intended correction to the spine curvature. This event will be monitored by consistent follow-up throughout the study, and may require medical or surgical intervention.

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 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. Subjects will be allowed to skip questions which they are not comfortable answering without compromising their participation in the study.
- Study-specific physical exam: The study physical exam uses non-invasive measurement techniques commonly employed in clinical practice.
- Clinical photographs: There is a risk of breach of confidentiality in subject photographs. This risk is minimized by not including the face of the subjects, and by the data protection plan in Section 9.

9.3.2.3 Risks associated with live case demonstration:

- Extended anesthesia exposure: Time under anesthesia may be extended minimally, at most a few minutes, due for example to additional setup procedures, however, this preparation will be done by specialized staff in tandem with the standard surgical preparation to not add extra time under anesthesia.
- Infection risk: There may be added risk of infection with more personnel and additional equipment in the room. However, any additional staff that may be in the operating room will be educated on safe clinical practices when entering and will remain outside of the sterile field during observation. Only the surgeon and other relevant clinicians will be allowed in the sterile field. Any additional equipment used will be covered with sterile cloth and utilized only as necessary during the procedure.
- Surgeon distraction: This risk will be addressed by having a separate surgeon handling commentary of the procedure, allowing the performing investigator and surgical team to continue the surgery as would normally be conducted without distraction.

- Breach of confidentiality: There is a risk of loss of privacy if identifying information is inadvertently disclosed during the surgery. Staff will be aware to not disclose identifying information during the surgical case, unless necessary. If identifying information is disclosed, the videotaped record will be edited to remove those frames. No recording system can completely guard against risks such as a breach caused by an intentional intrusion, inadvertent disclosure of information, or the failures or limitations of equipment used to transmit live or recorded data.

The investigators believe these additional risks associated with the live case demonstration are minimal.

9.3.3 Potential Benefits of Trial Participation

There may be some direct benefits 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 five years post-spinal fusion compared to at two 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 study team in the orthopedic clinic. Potential subjects who may satisfy the inclusion/exclusion criteria will be identified by the clinical 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 inclusion/exclusion 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. Before being presented with the clinical trial, patients that qualify in accordance with the FDA-approved labeling of the HUD, The Tether – Vertebral Body Tethering System, will be offered the approved device first.

In addition, the study recruitment material will be posted on CHOP Orthopaedics department website as an additional source for recruiting potential subjects. A printed packet hand-out will also be available to interested families. These recruitment materials will include information regarding the surgical procedures, risks and follow-up care.

9.5 Informed Consent/Assent and HIPAA Authorization

After the subject has made the decision to have surgery and discussed this decision with their doctor, potential subjects who may satisfy the inclusion/exclusion criteria will be identified by the clinical staff, who will contact a study team member. 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.

For subjects that are withdrawn from the study due to AEs/SAEs, as determined by the investigator, they will undergo consent/assent during their orthopedic visit to decide whether they agree to review of medical and radiographic records following the occurrence of the AE/SAE up to two years post-operatively.

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.