(Published in JPOSNA Oct 2019)

Pediatric Device Regulation: The Case of Anterior Vertebral Body Tethering

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and the SRS/POSNA Combined Committee for Pediatric Medical Devices

SRS
Scoliosis Research Society

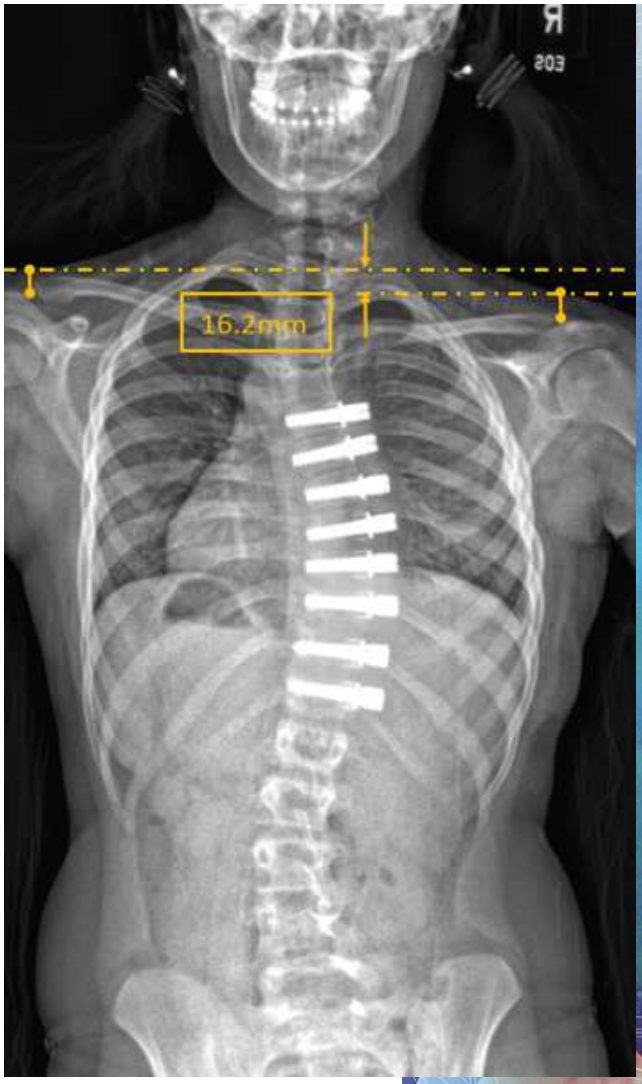
POSNA
PEDIATRIC ORTHOPAEDIC SOCIETY OF NORTH AMERICA

PEDIATRIC SPINE STUDY GROUP

NewYork-Presbyterian

COLUMBIA | COLUMBIA UNIVERSITY DEPARTMENT OF ORTHOPEDIC SURGERY

- ***Royalties:*** **Zimmer-Biomet *****
- ***Consultant:*** **Stryker, Zimmer-Biomet**
- ***Research Support:*** **PSSG, SRS,POSNA; OREF**
- ***BOD*****: POSNA, PSSG; SP3**

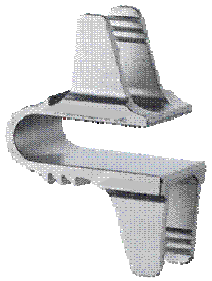


The (Massive) Task Of the FDA

to balance safety and innovation by regulating availability of medical devices (drugs, radiation, cosmetics, food etc)

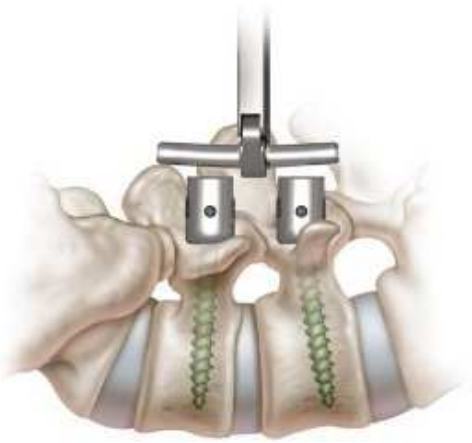
- All products released after Medical Device Amendment (1976) default to “class III devices” – highest risk level
- Requires PreMarket Approval (PMA) scientifically demonstrating **safety and effectiveness**.
- Many years/ >$20,000,000

Disc Replacement and Interspinous Spacer for Nonfusion



510 K Process

- If product is deemed “substantially equivalent” to a lower risk (Class 1 or 2) device, the FDA will grant “510 K clearance”



- Generally relies on use prior to 1976

Dynamics of *Pediatric* Device Innovation: Fundamentally Different Than That in Adults

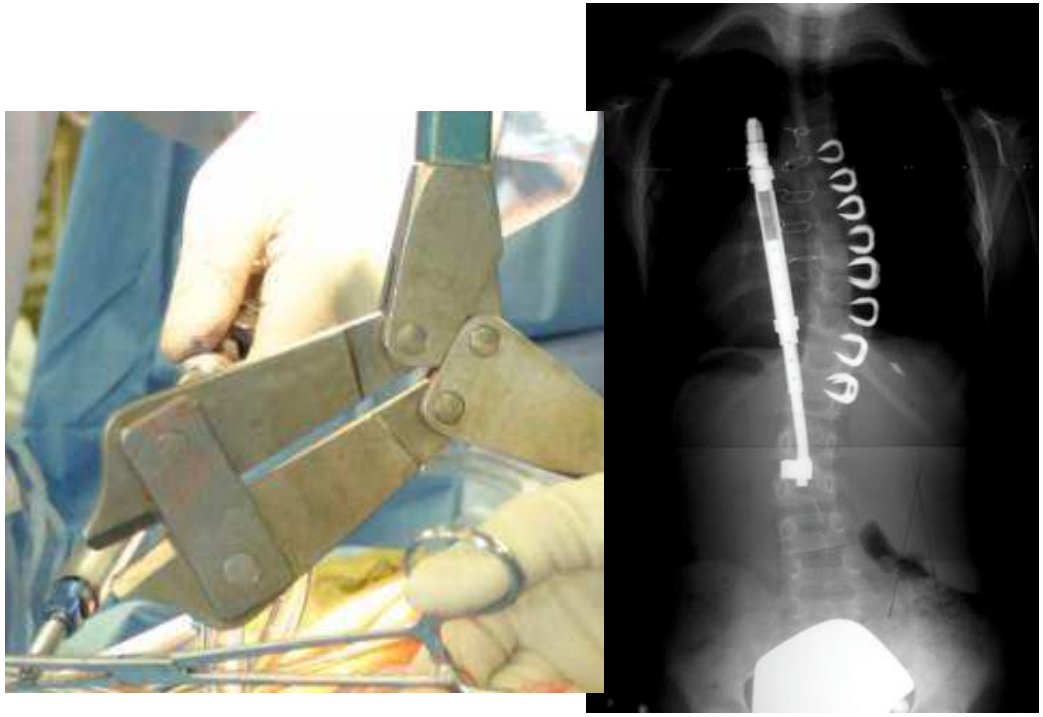
- Markets are small
- Financial incentives weak
- Incremental improvements = moving target
- Liability concerns
- Device life cycle short and patents not as strong

- Methodological challenge to pre-market trials and post market surveillance
  - Size, outcomes

→ **Unmet need for novel, *child specific*, medical devices**

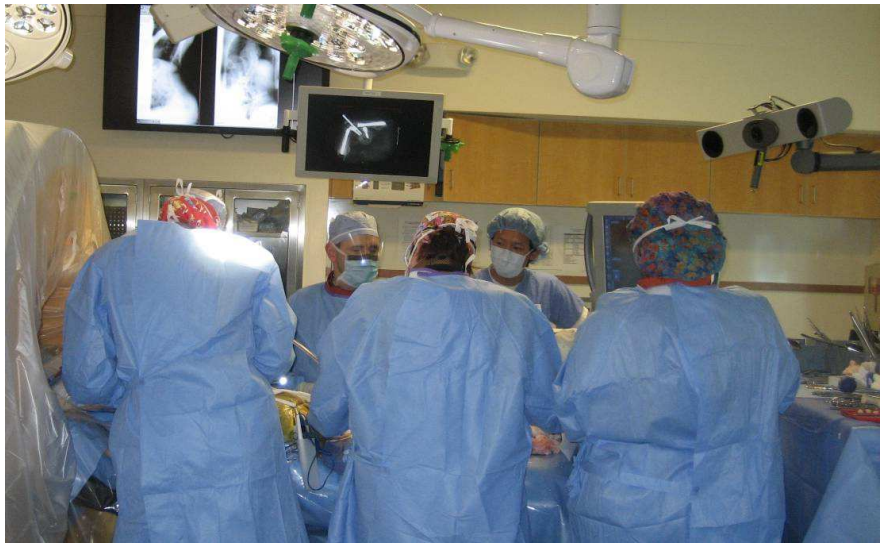
How does a clinician treat a child when an ideal implant is not available?

- Use adult device
  - e.g. spine instrumentation and trauma care
- Modify adult device
  - e.g. cut screws and plates in OR
- Use implants designed for other purposes
  - e.g. foot staples in spine



Physician-Directed Use

- Not ideal
- Implants not subject to testing
- Research and education difficult
- Innovation stagnates

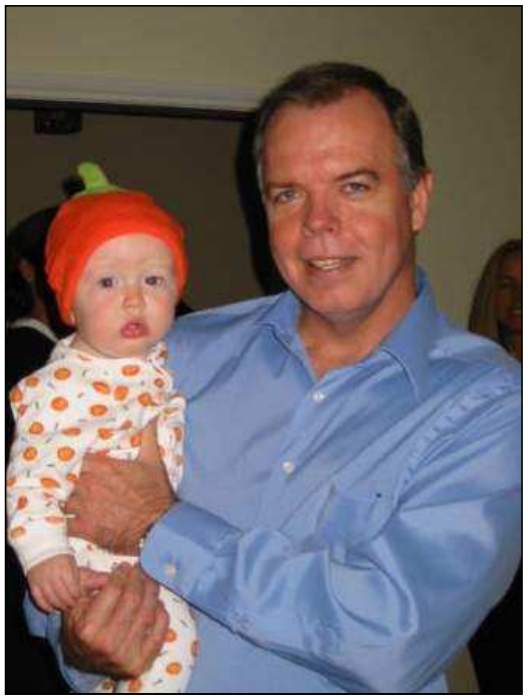


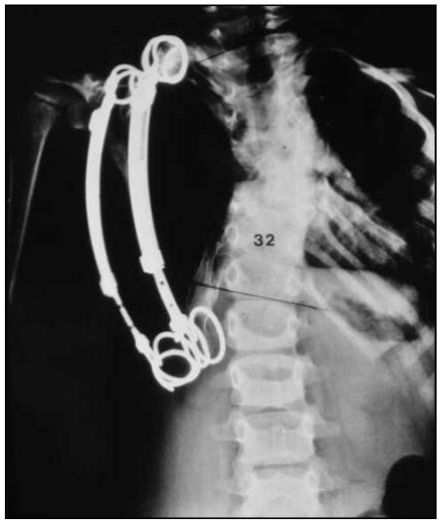
Nevertheless, we have an ethical obligation to do the best that we can given limits. FDA does not regulate clinical use, only marketing

HDE – Humanitarian Device Exemption

- Novel technology for use in “orphan population” (<8,000/yr per year)

- Must demonstrate reasonable assurance of **safety and probable benefit** (lower bar than ***effectiveness***)





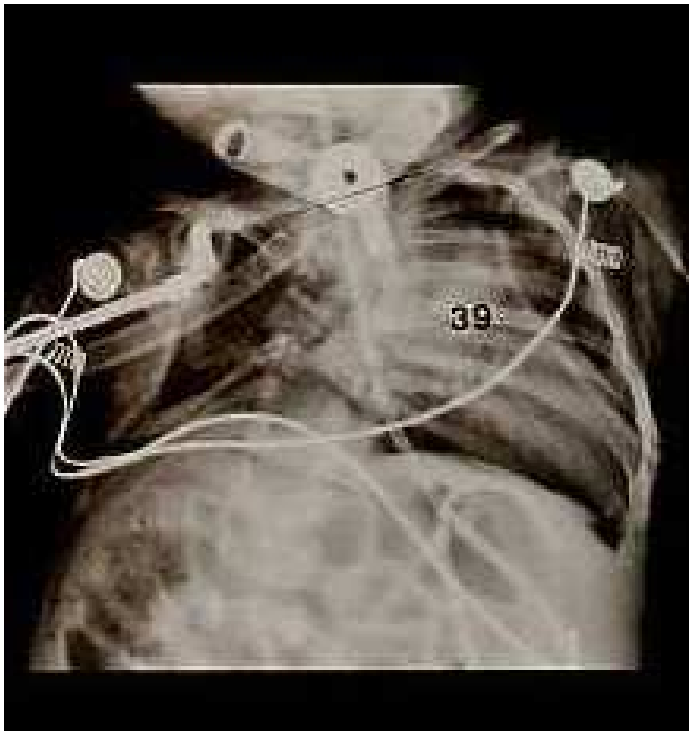
Pediatric Clinical Trials Workshop
October 29, 2009

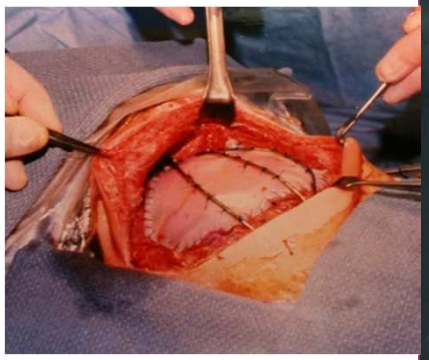
Unmet Need

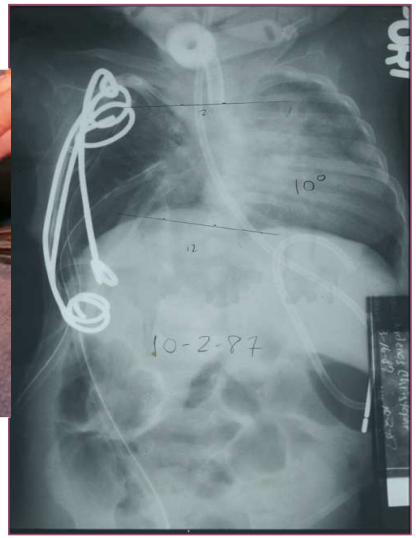
Lessons lear

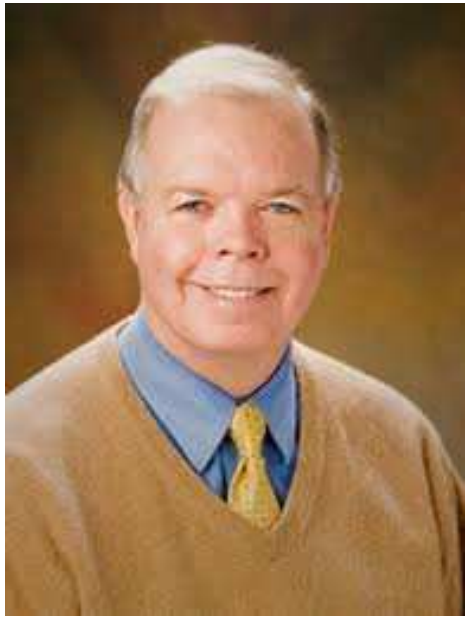
Division of O

Bob Campbell, and the story of the VEPTR HDE

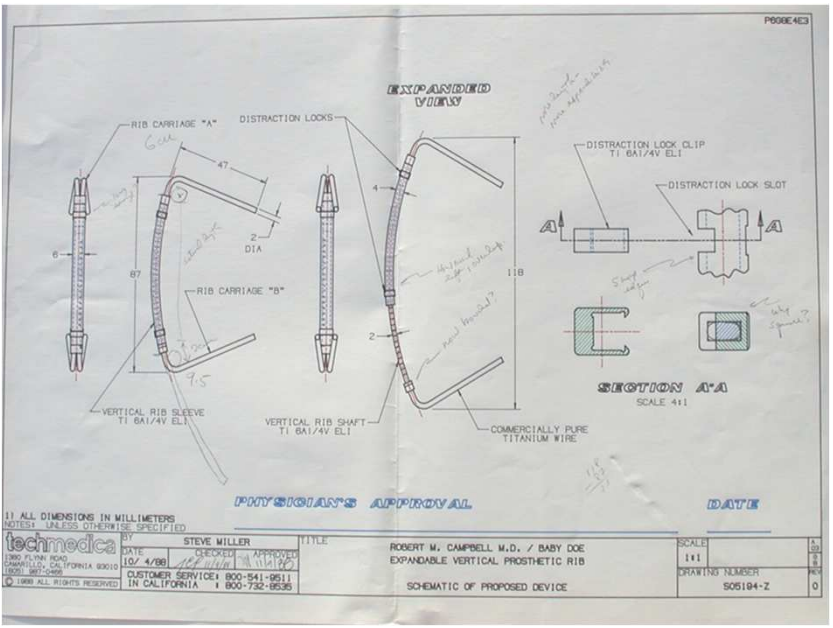


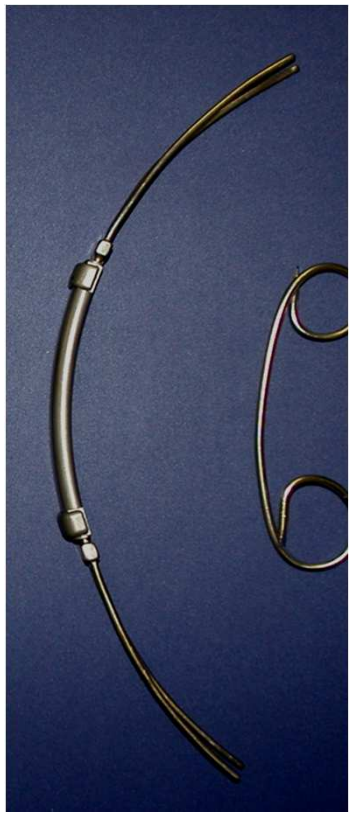


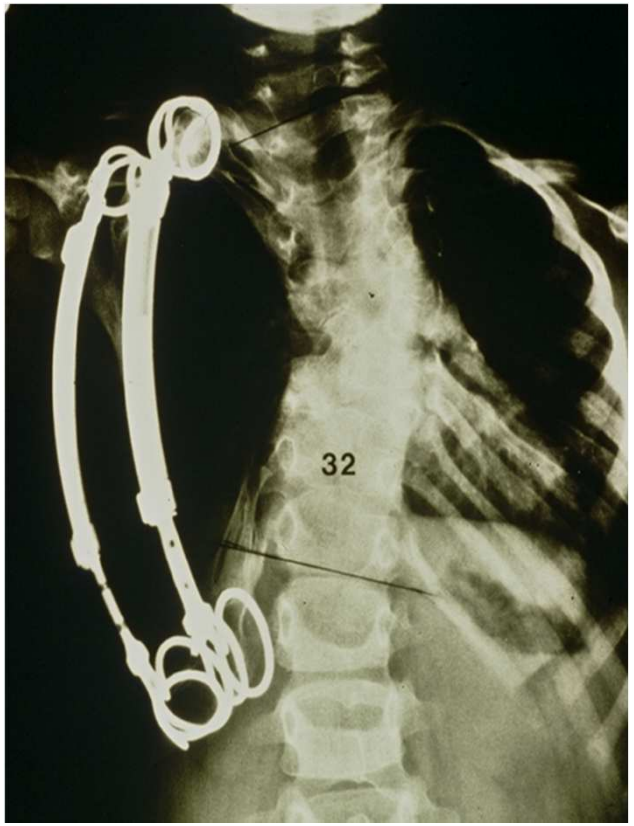




9 months from napkin to patient: custom device







May 9th, 1989
The Press Conference

Photo by Joan Glenn Snow

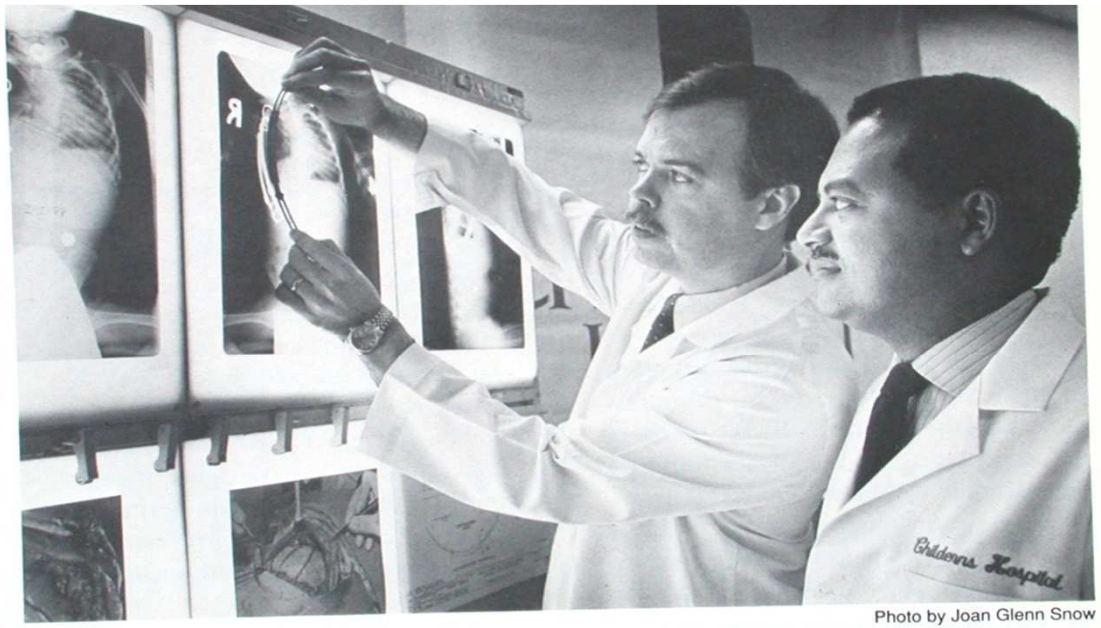


Photo by Joan Glenn Snow

Dr. Robert Campbell, (left) pediatric orthopaedic surgeon, and Dr. Melvin Smith, pediatric thoracic surgeon, review the position of a titanium rib over an X-ray of Christopher Cardenas.

VEPTR FDA Approved, August 24, 2004, Humanitarian Device Exemption

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Director of Regulatory and Clinical Affairs
Synthes (USA)
1230 Wilson Drive
West Chester, Pennsylvania 19380

AUG 24 2004

17 years!

Re: H030009
Vertical Expandable Prosthetic Titanium Rib (VEPTR)
Filed: December 23, 2003
Amended: January 29, January 30, February 17, March 23, June 14, June 28, June 30, July 30, 2004
Product Code: MDI

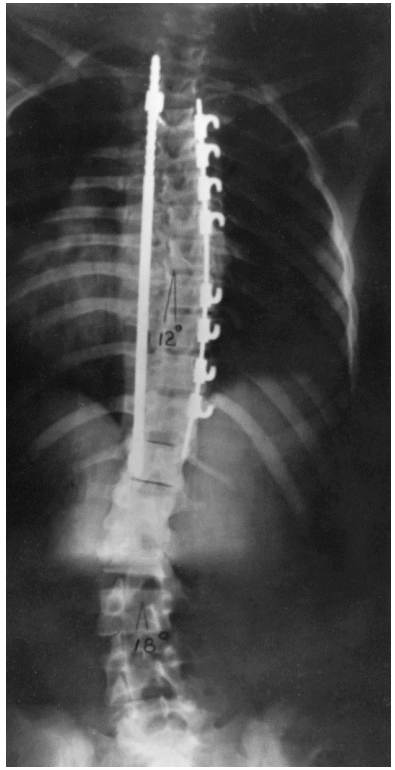
" This device is indicated for the treatment of Thoracic Insufficiency Syndrome (TIS) in skeletally immature patients."

Growing Spine 2013-2019 : Rapidly Evolving Regulatory Landscape Harrington Rods

510 K

09/11/2013

- Harrington pre-amendment determination for non-fusion
  - Harrington Rod System
  - Non-fusion treatment of scoliosis in T1 – S1 using either compression or distraction forces in patients < 10 years of age
  - Did not identify specific points of attachment

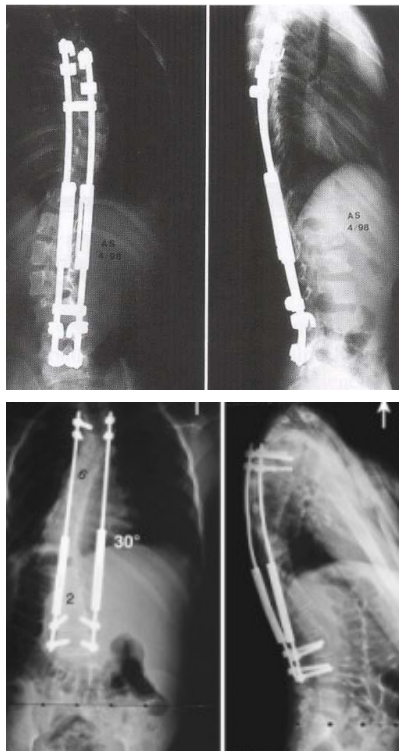


Growing Spine 2013-2019 : Rapidly Evolving Regulatory Landscape Growing Rods

510 K

02/25/2014

- Growing Rod 510(k)s (K133904, K141509)
  - Non-fusion correction of severe, progressive, life-threatening early-onset spinal deformities associated with TIS, including early-onset scoliosis in patients < 10 years

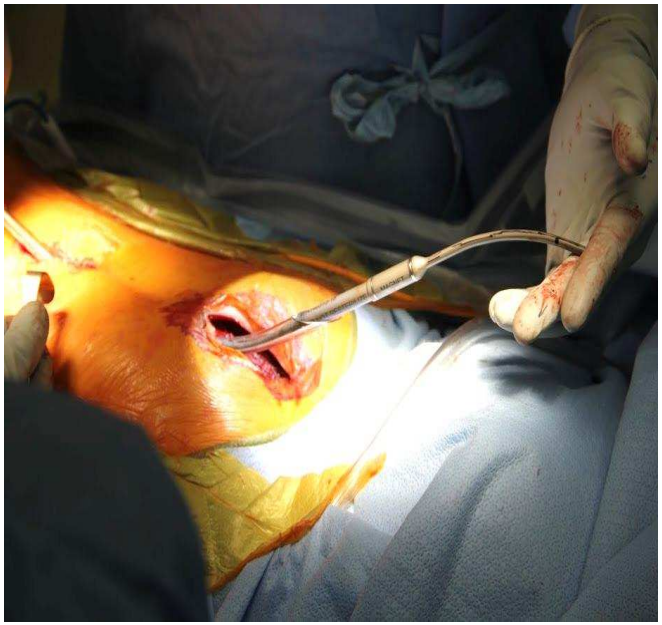


Growing Spine 2013-2019 :
Rapidly Evolving Regulatory Landscape
MAGEC RODS

510 K

02/27/2014

- MAGEC (K140178)
  - Non-fusion treatment of TIS in patients < 10 years

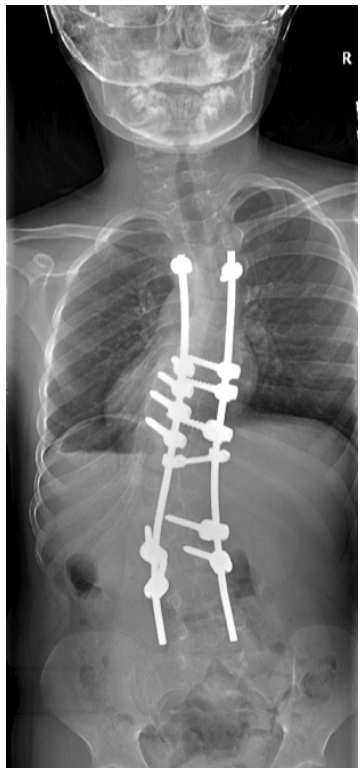


Growing Spine 2013-2019 : Rapidly Evolving Regulatory Landscape Shilla Rod

510 K

07/17/2014

- SHILLA (K140750)
  - Non-fusion correction of severe, progressive, life-threatening early onset deformities, including early-onset scoliosis, associated with or at risk of TIS in patients < 10 years



Growing Spine 2013-2019 : Rapidly Evolving Regulatory Landscape Pediatric Pedicle Screws

510 K

03/13/2014

- Expanded pediatric indications of pedicle screw and rod fixation for fusion
  - Progressive spinal deformities (i.e. scoliosis, kyphosis, or lordosis)
  - Including idiopathic scoliosis, neuromuscular scoliosis, congenital scoliosis

US: FDA Approval (HDE) - August 2019
ApiFix HDE

FDAnews Device Daily Bulletin
Medical Devices / Submissions and Approvals

ApiFix Earns FDA Approval for Scoliosis Device

Aug. 29, 2019

A A

The FDA granted ApiFix a humanitarian device exemption for its MID-C (minimally invasive deformity correction) device for treating progressive adolescent idiopathic scoliosis.

The device treats the most common type of scoliosis with no identifiable cause, which affects two to three percent of children between the ages of ten and 21.

MID-C allows surgeons to perform a procedure that gives permanent curve correction

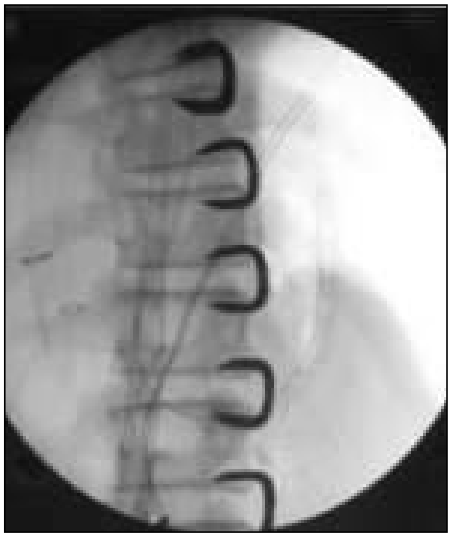
	US
Type of Spinal Deformity	AIS
Curve Classification	Lenke 1, Lenke 5
Curve Magnitude	45° - 60° (40° curve lower limit FDA pending)
Skeletal Maturity	Risser 0 - 5
Sagittal Profile	Kyphosis measured from T5-T12 < 55°
Curve Flexibility	Reduce to ≤30° on supine lateral bending x-rays

Early Experience with Spinal Growth Modulation in Humans (2000) Off Label Use

- 80% success in curves < 35deg”

An Innovative Technique of Vertebral Body Stapling for the Treatment of Patients With Adolescent Idiopathic Scoliosis: A Feasibility, Safety, and Utility Study

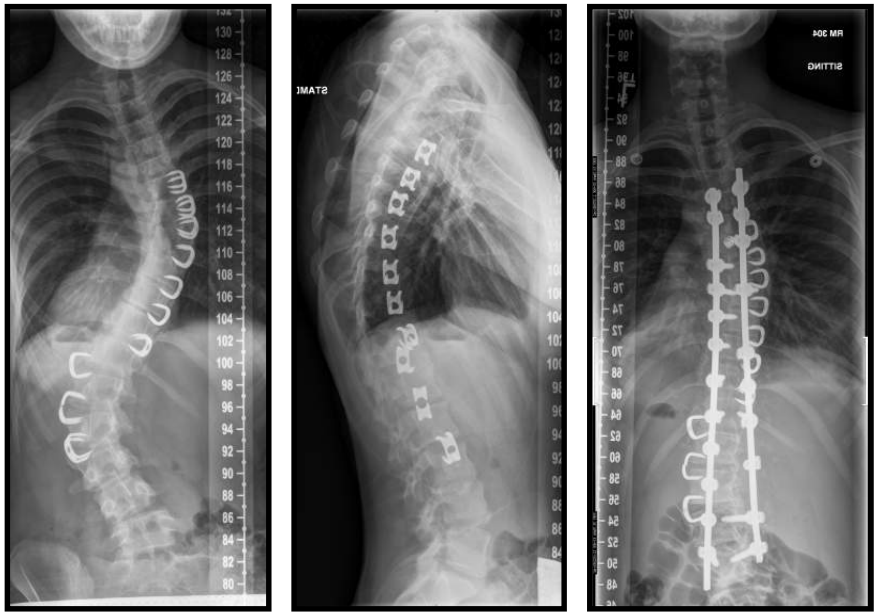
Randal R. Betz, MD,* John Kim, MD,† Linda P. D'Andrea, MD,* M. J. Mulcahey, MS,* Rohinton K. Balsara, MD,‡ and David H. Clements, MD§



Betz et al, *Spine* 2003

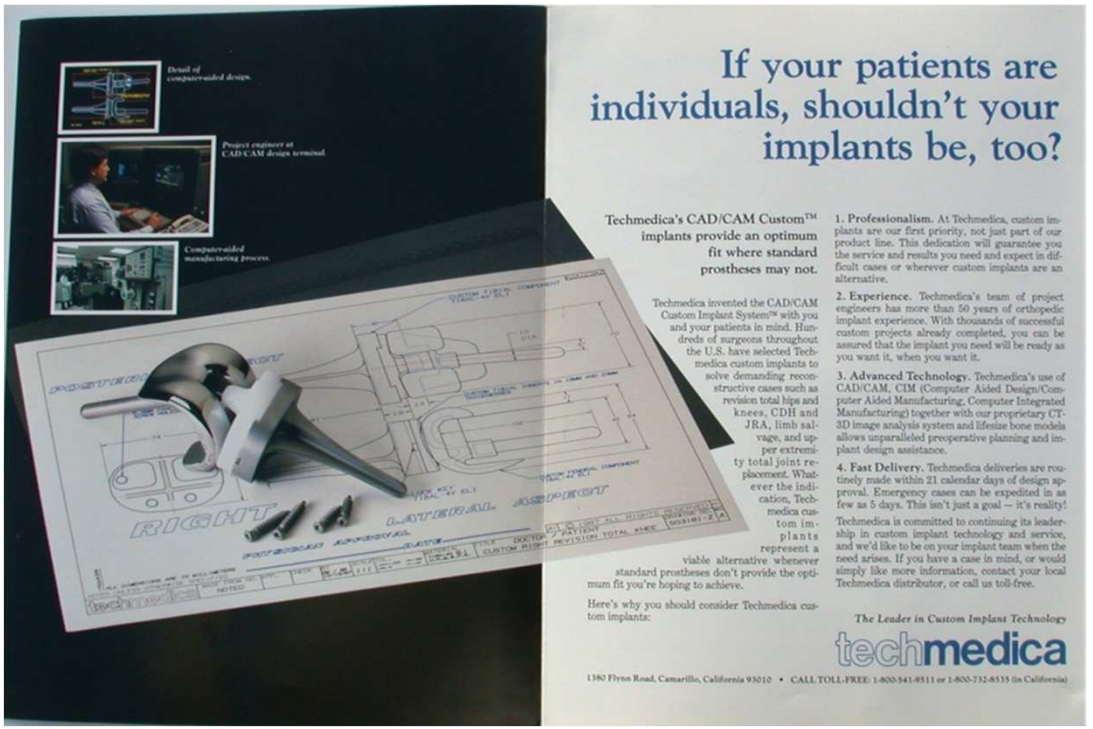
Vertebral Stapling has been Abandoned
Trupia, Vitale et al; JSD 2019

- Min 5 year outcomes of curves < 35 deg
- Minority showed growth modulation over time
- 50% curves progressed over time
- 40% PSIF



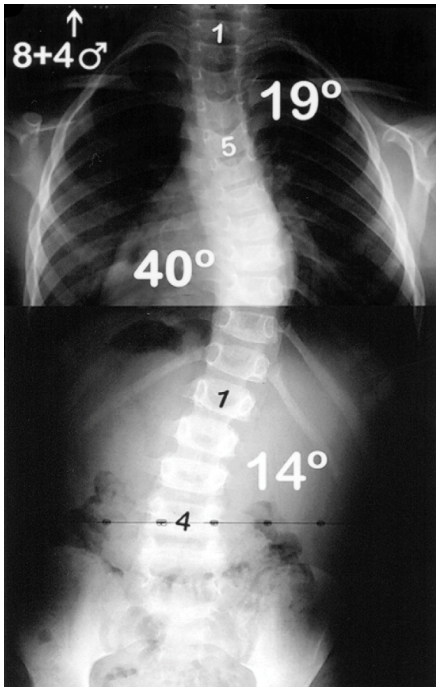
Alternative Approaches to IDE, 510k, or HDE

- **Compassionate Use**
  - Contact FDA CDRH in advance of surgery to plea case
- **Custom Device**
  - No more than 5 “units” per year

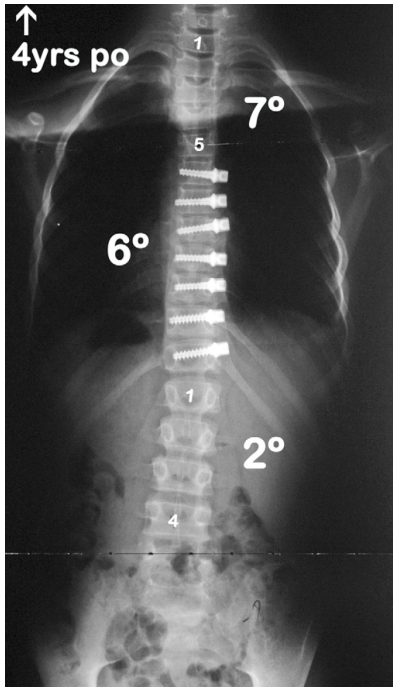


2010 - Crawford and Lenke publish the first human use of AVBT as custom device

- 8.5-year-old JIS patient
- Pre-Op Major Curve : 40º
- 4 Year Post-Op Major Curve: 6º
- Patient grew 33.1 cm during follow up
- No complications



Pre-Op



4 years Post-Op

2014 - Samdani et al. publish first AVBT cohort experience

- 11 patients with thoracic idiopathic scoliosis
  - Mean age of 12.3 years

At 2 years follow up:

- Thoracic Cobb Angle Correction: 44.2° to 13.5°
- Compensatory Curve Correction: 25.1° to 7.2°
- Scoliometer Improvement: 12.4° to 6.9°

- No major complications
  - 2 revision surgeries

TABLE 1. Perioperative Data

Surgical procedure		
Vertebral body tethering	8 (73%)	
Tethering + lumbar stapling	3 (27%)	
	Mean	**Median**
Levels tethered	7.8 ± 0.9	8
Operative time (min) tethering only	348 ± 44	352
Operative time (min) tethering + VBS	512 ± 69	476
EBL (mL) tethering only	205 ± 161	113
EBL (mL) tethering + VBS	483 ± 404*	250

**One patient in the tether + VBS group had a segmental bleed with a total EBL of 950 mL.*

EBL indicates estimated blood loss; VBS, vertebral body stapling.

2015 - Samdani et al. expand upon their initial study to include 32 patients with min. 1 year follow-up

- Mean age: 12 years

- Mean Sanders score: 3.2

At most recent follow up:

- Thoracic Curve Correction: 42.8° to 17.9°
- Compensatory Lumbar Curve Correction: 25.2° to 12.6°.

- 1 bronchoscopy secondary to prolonged atelectasis, 3 overcorrections without revision surgery
  - No other major complications were observed.

2017 – Boudissa et al. recreate Samdani et al. study with positive results

- 6 patients with mean age of 11.2 years

At 1 year follow up:

- Thoracic Cobb Correction: 45° to 38°
- Lumbar Cobb Correction: 33° to 25°

- No complications and no progression to fusion

These early human trials demonstrated the potential efficacy and safety of AVBT for the treatment of EOS, but were limited by small sample sizes and short follow-up timelines.

2017 - Newton et al. expand follow-up time to a minimum of 2 years

- Retrospective case series
  - 17 patients
  - 2-4 years follow up
  - Mean age: 11 years

At most recent follow up:

- Thoracic Curve Correction: 52° to 27°

- 7 revision surgeries
  - 4 tether removals for overcorrection, 1 addition of a lumbar tether, 1 tether replacement due to breakage, and 1 PSIF

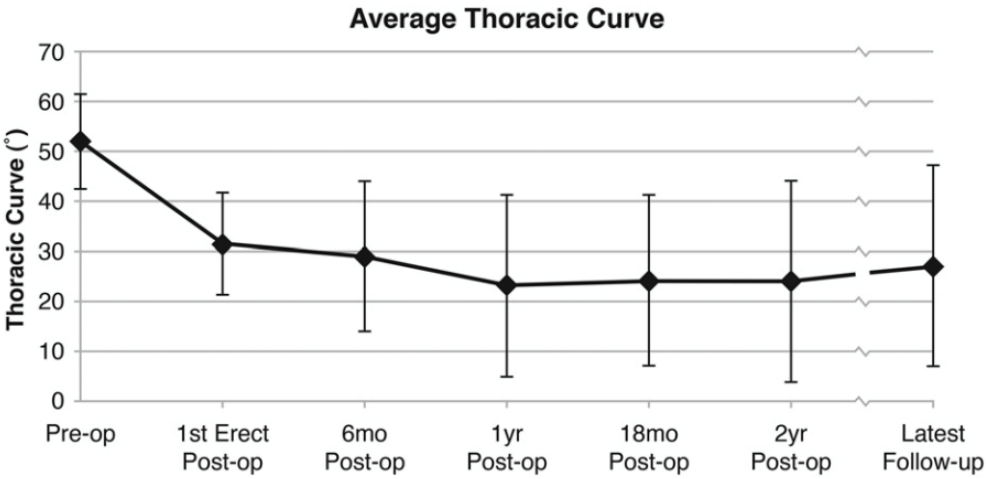


Fig. 1
The average thoracic curve magnitude over time. The I bars represent the standard deviation.

Conference Presentations on AVBT Outcomes (SRS 2018)

Authors	N	Mean Age (Years)	Follow-Up‡	Complications & Revisions	Mean Preoperative Major Curve	Mean Postoperative Major Curve	Percent Correction
Turcot O, Roy-Beaudry M, et al.	23	11.8	2 years	Not reported	53°	27°	49%
Yilgor C, Cebeci B, et al.	19	12.5	Mean 1.5 years	1 screw loosen 2 atelectasis 3 tether release	RG*: 45° SG*: 44°	RG: 11° SG: 19°	RG: 75% SG: 57%

‡ All listed Follow-Up values are time to Postoperative Major Curve measurement
* RG – Rapid Growing, Sanders ≤4; SG – Steady Growing, Steady 5-7

Conference Presentations on AVBT Outcomes (SRS 2019)

Authors	N	Mean Age (Years)	Follow-Up‡	Complications & Revisions	Mean Preoperative Major Curve	Mean Postoperative Major Curve	Percent Correction
Alanay A, Yucekul A, et al.	14	12.3	Mean 2.4 years	1 atelectasis 1 pulmonary effusion 2 overcorrection	45°	10°	78%
Braun and Croitoru	47	14	Mean 3.1 years	3 overcorrection 5 tether rupture 2 pleural effusion	48°	19°	60%
Pehlivanoglu T, Ofluoglu E, et al.	24	11.4	Mean 2 years	No major complications	48°	10°	79%
Samdani A, Pahys J, et al.	53	12.5	Mean 4.0 years	5 revisions	40°	16°	60%

‡ All listed Follow-Up values are time to Postoperative Major Curve measurement

Conference Presentations on AVBT Outcomes (POSNA 2019)

Authors	N	Mean Age (Years)	Follow-Up‡	Complications & Revisions	Mean Preoperative Major Curve	Mean Postoperative Major Curve	Percent Correction
Hoernschemeyer D, Worley J, et al.	31	12.7	2 years	4 overcorrection 2 progression	Lenke 1A: 47° Lenke 1B: 48° LT^: 54°	1A: 20° 1B: 22° LT: 27°	1A: 57% 1B: 54% LT: 50%
Miyanji F, Pawelek J, et al.	57	12.7	Mean 2.4 years	5 reoperations 1 tether rupture 7 minor†	51°	23°	53%

‡ All listed Follow-Up values are time to Postoperative Major Curve measurement
^ LT – Long Thoracic curve
† 2 patients with persistent pain, 1 superficial infection, and 4 patients with respiratory related complications

Results Summary

5 Published

outcomes papers in

67

patients

8 Unpublished

conference abstracts in

>200

patients

2019 FDA Reviewers' Course

Experience with a Sponsor-Investigator IDE

Patrick J. Cahill, MD

Noelle Larson, MD did same

Protocol Development: ~100h

Conducting the Study: ~2h/week + episodic reporting

CHOP Ortho staff time (~1 FTE)

Anthony Capraro
James Gordon
Catherine Qiu

Children's Hospital of Philadelphia
Division of Orthopaedics

Perelman School of Medicine
University of Pennsylvania

FDA NEWS RELEASE

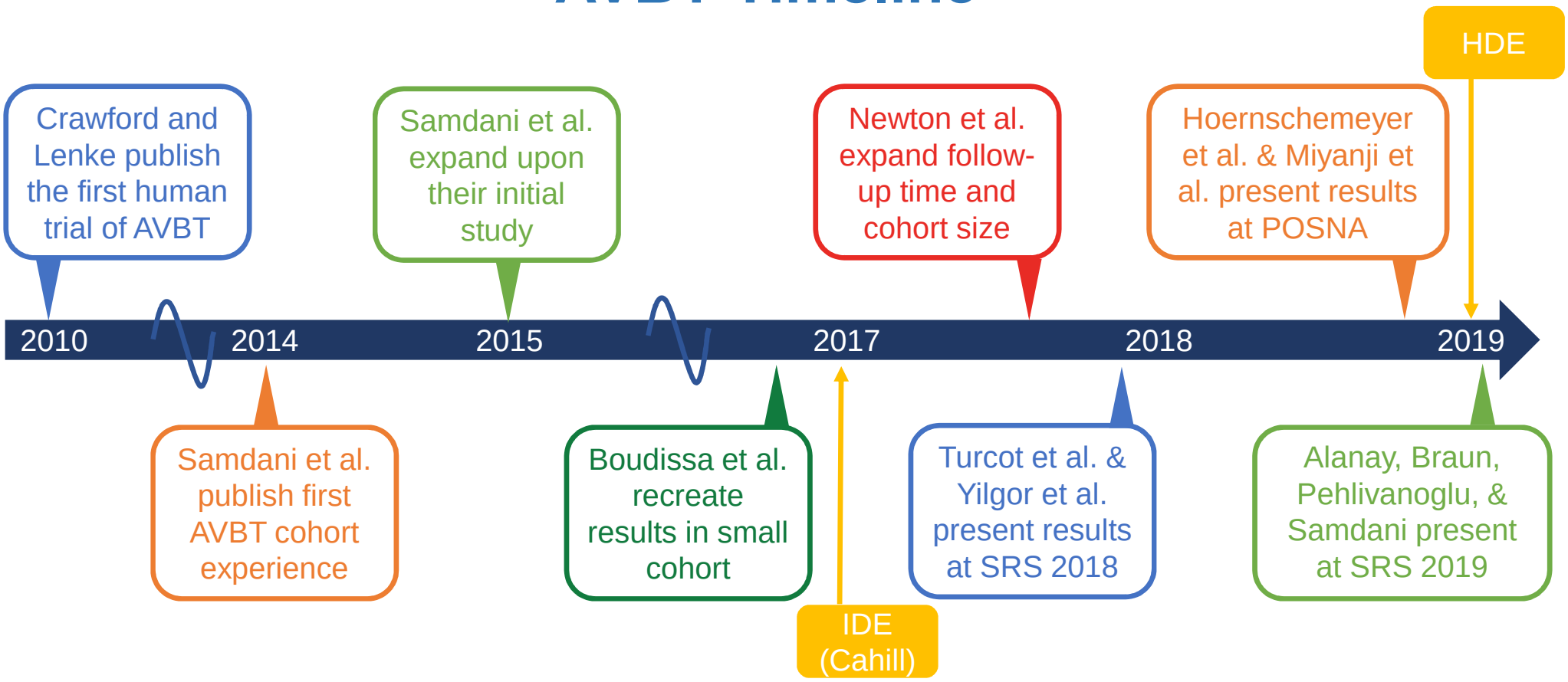
FDA approves first of its kind device to treat pediatric patients with progressive idiopathic scoliosis

August 2019 – ZBS granted HDE approval for Tether

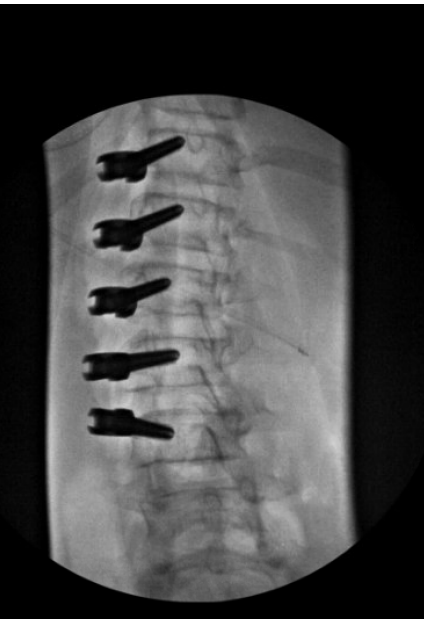
For Immediate Release: August 16, 2019

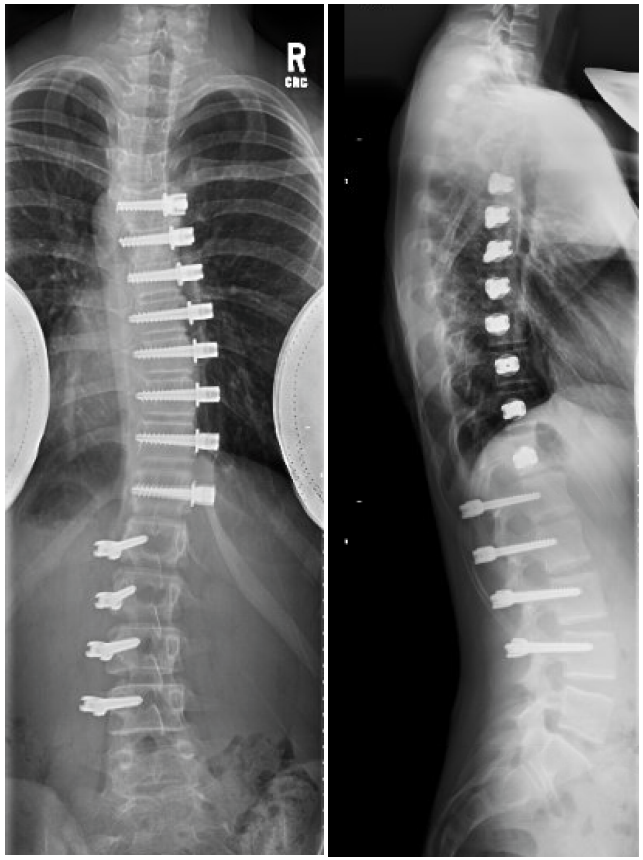
The U.S. Food and Drug Administration today approved the first spinal tether device intended to be used in children and adolescents to correct the most common form of scoliosis, called idiopathic scoliosis, that has not responded to conservative treatment

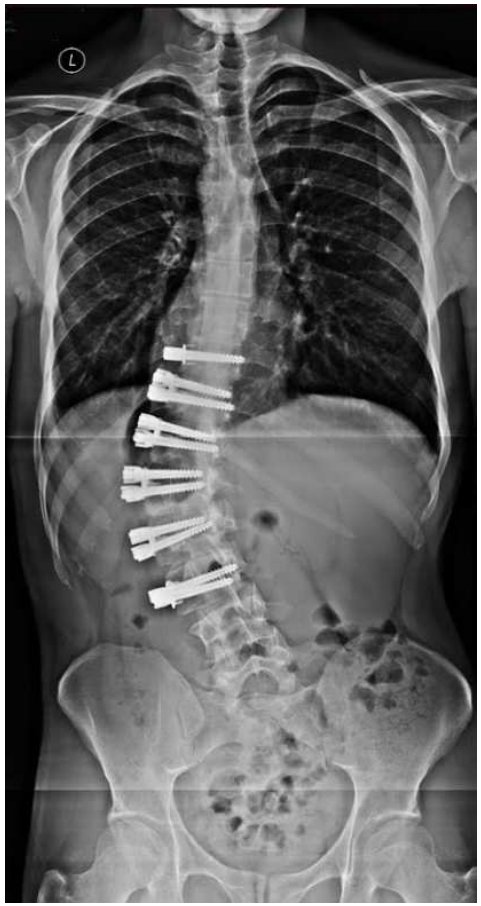
AVBT Timeline



Pushing Indications…?
Caveat Emptor…







Conclusions

FDA has been appropriately responsive to the evolution of options for the care of children with juvenile scoliosis

To date, nearly all patients with anterior vertebral body tethering (AVBT) have been treated in off-label use

- Recent AVBT approval via the HDE mechanism will enable timely **evolution of innovation and appropriate use** for the treatment of early onset scoliosis.

Thank You!

Michael G. Vitale MD MPH

mgv1@columbia.edu

www.pediatricscoliosissurgery.com

www.safetyinspinesurgery.com

AMAZING THINGS ARE HAPPENING HERE for Kids

NewYork-Presbyterian

COLUMBIA | COLUMBIA UNIVERSITY DEPARTMENT OF ORTHOPEDIC SURGERY

Purpose

To review the unique dynamics inherent in the timely regulatory approval and innovation of pediatric medical devices using anterior vertebral body tethering (AVBT) as a case study

Summary of Published Results on AVBT Outcomes

Authors	Year	N	Mean Age (Years)	Follow-Up‡	Complications & Revisions	Mean Preoperative Major Curve	Mean Postoperative Major Curve	Percent Correction
Crawford CH, Lenke LG	2010	1	8.5	4 years	None	40°	6°	85%
Samdani AF, Ames RJ, et al.	2014	11	12.3	2 years	2 revision for overcorrection	44°	14°	69%
Samdani AF, Ames RJ, et al.	2015	32	12	Mean 1.2 years	3 overcorrection* 1 atelectasis	43°	18°	58%
Boudissa M, Eid A, et al.	2017	6	11.2	1 year	None	45°	38°	16%
Newton PO, Kluck DG, et al.	2018	17	11	Mean 2.5 years	7 revision 4 progression† 2 atelectasis	52°	27°	48%

‡ All listed Follow-Up values are time to Postoperative Major Curve measurement
* No revision surgeries were performed at publication
† 1 of 4 posterior spinal fusions performed at publication

Shoulder Balance Following AVBT

- **81 Patients** with Idiopathic Scoliosis
- Shoulder Imbalance = |Shoulder Height| >2cm
- Preoperatively
  - 21 Patients (27.2%) with shoulder imbalance
- Most Recent Follow Up **(>20 months**)
  - 11 (13.6%) of patients with shoulder imbalance
- Comparable to previous studies on selective thoracic fusion.