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Signed By	Meaning of Signature	Date/Time (UTC)
van Deursen, Carine	Document Approver	09/20/2018 08:29:50
Matysek, Adrianna	Document Approver	09/20/2018 09:19:16
Limpens, Halina	Document Approver	09/20/2018 09:21:02
Sicurella, Beatrice Carlotta	Document Author	09/20/2018 10:27:32
Cristea, Alexander	Document Approver	09/20/2018 10:31:08
Bachinin, Anton	Document Approver	09/20/2018 10:50:51
Tang, Feng	Document Approver	09/20/2018 12:15:50
Faria, Cristina	Document Approver	09/20/2018 14:05:19

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Author Name: Beatrice C. Sicurella	**Role or Title:** Medical Writer and Clinical Study Manager, Clinical Research Specialist
e-signature	e-signature
Signature	**Signature Date (DD-MMM-YYYY)**

Approver Name: Feng Tang	**Role or Title:** Biostatistician, Sr. Statistics Manager
e-signature	e-signature
Signature	**Signature Date (DD-MMM-YYYY)**

Approver Name: Cristina Faria	**Role or Title:** Clinical Leadership, Clinical Research Manager Spinal and Biologics
e-signature	e-signature
Signature	**Signature Date (DD-MMM-YYYY)**

Approver Name: Adrianna Matysek	**Role or Title:** Clinical Quality/Compliance, Clinical Quality Specialist
e-signature	e-signature
Signature	**Signature Date (DD/MMM/YYYY)**

Approver Name: Anton Bachinin	**Role or Title:** Lead Monitor, Sr. Clinical Research Monitor
e-signature	e-signature
Signature	**Signature Date (DD/MMM/YYYY)**

Approver Name: Halina Limpens	**Role or Title:** Regulatory, Sr. Regulatory Affairs Specialist
e-signature	e-signature
Signature	**Signature Date (DD/MMM/YYYY)**

Approver Name: Alexander Cristea	**Role or Title:** Therapy SME, Principal Medical Affairs Specialist
e-signature	e-signature
Signature	**Signature Date (DD/MMM/YYYY)**

Approver Name: Carine van Deursen	**Role or Title:** Safety Representative, Safety Specialist
e-signature	e-signature
Signature	**Signature Date (DD/MMM/YYYY)**

Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	A Prospective, Multicenter Evaluation of the CD HORIZON® Fenestrated Screw Spinal System with Fenestrated Screw Cement When Used in the Treatment of Spinal Conditions in subjects with Compromised Bone Quality (FNS Study)
Clinical Investigation Plan Identifier	MDT17040SD1703
Study Product Name	• CD HORIZON® Legacy™ Fenestrated Screw Spinal System • CD HORIZON® Solera™ Fenestrated Screw Spinal System • Fenestrated Screw Cement
Sponsor	Medtronic Bakken Research Center BV Endepolsdomein 5 6229 GW Maastricht The Netherlands
Document Version	2.0 / 19 SEP 2018

Confidentiality Statement

1. Investigator Statement

Study product Name	CD HORIZON® Legacy™ Fenestrated Screw Spinal System CD HORIZON® Solera™ Fenestrated Screw Spinal System Fenestrated Screw Cement
Sponsor	Medtronic Bakken Research Center BV
Clinical Investigation Plan Identifier	MDT17040SD1703
Version Number/Date	2.0 / 19 SEP 2018

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with the applicable regulatory guidelines under which the study is being conducted, the ethical principles that have their origin in the Declaration of Helsinki 2013 and the clinical trial agreement.

The study will be conducted in accordance with ISO14155:2011, and any regional or national regulations, as appropriate.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.

Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

Table of Contents

2. Glossary

Term	*Definition*
ADE	Adverse Device Effect
AE	Adverse Event
BMI	Body Mass Index
CIP	Clinical Investigation Plan
DD	Device Deficiency
DXA	Dual-energy X-ray Absorptiometry
eCRF	Electronic Case Report Form
EQ-5D 5L	European Quality of Life-5 Dimensions; 5 Levels
FNS	Fenestrated Screws
IFU	Instructions for Use
ODI	Oswestry Disability Index
PIC	Patient Informed Consent
PMMA	Polymethylmethacrylate
qCT	quantitative Computed Tomography
RC	Research Coordinator
RDC	Remote Data Capture
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
VAS	Visual Analog Scale

3. Synopsis

Title:	A Prospective, Multicenter Evaluation of the CD HORIZON® Fenestrated Screw Spinal System with Fenestrated Screw Cement When Used in the Treatment of Spinal Conditions in Subjects with Compromised Bone Quality (FNS Study)
Clinical Study Type	Post-market
Study Product Name	• CD HORIZON® Legacy™ Fenestrated Screw Spinal System • CD HORIZON® Solera™ Fenestrated Screw Spinal System • Fenestrated Screw Cement
Sponsor	Medtronic Bakken Research Center BV Endepolsdomein 5 6229 GW Maastricht The Netherlands
Indication under investigation	Subjects with compromised bone quality requiring stabilization and/or immobilization of the thoracic and/or lumbar spine for one or more of the following diagnostic indications: • Degenerative Spinal Disease (e.g. degenerative disc disease, spondylolisthesis and/or spinal stenosis) • Deformity (e.g. degenerative deformity)
Investigation purpose	The purpose of this study is to evaluate outcomes in subjects with compromised bone quality diagnosed with one of the conditions described in the indications under investigation. This study is to confirm that the treated spinal segments can be safely and effectively immobilized and/or stabilized with cement-augmented posterior pedicle screw fixation. The study will evaluate clinical benefits and safety of the device.
Product Status	All devices used in this study are commercially available and will be used within the intended approved indication as listed in the Instructions for Use (IFU).
Primary Objective	To demonstrate that Oswestry disability index (ODI) score improved significantly at 12-months post-operatively as compared to baseline for each

	indication (degenerative spinal disease and deformity) in subjects with compromised bone quality, who will receive a surgical procedure requiring posterior stabilization and/or immobilization of one or more spinal segments using CD HORIZON® Fenestrated Screw Spinal System with Fenestrated Screw Cement.
Secondary Objectives	Secondary objectives of this study include the assessment of the following endpoints for each indication (degenerative spinal disease and deformity): • Improvement of ODI at 3- and 24-month visit from baseline. • Improvement of VAS back and leg pain score at 3-, 12- and 24-month visit from baseline. • Improvement of EQ-5D 5L at 3-, 12- and 24-month visit from baseline • Neurological success at 12-month visit. • Intraoperative cement extravasation/leakage. • Device and/or procedure related adverse events through 24 months. • Secondary spinal surgeries at index and/or adjacent level(s), resulting from an AE, up to 24 months after the surgery. • Radiographic confirmation of stabilization of the pedicle screw instrumentation at 12-month visit. • Radiographic fusion at 12-month visit for those subjects where fusion was intended. Secondary objective that is specifically for deformity subjects includes: • Assessment of change in coronal and sagittal spinopelvic parameters from baseline at the 12-month visit.
Study Design	This is a multi-center, single arm, open-label, prospective study that will collect data on subjects with compromised bone quality undergoing thoracolumbar immobilization/stabilization surgery with CD HORIZON® Fenestrated Screw Spinal System, for degenerative spinal disease or deformity. Clinical assessments will be completed at baseline (preoperatively), during surgery, prior to hospital discharge, and postoperatively at 3 months (-1,5/+ 3 months), 12 months (± 3 months), and 24 months (± 6 months). Radiological assessments will be completed at baseline, prior to hospital discharge (for deformity subjects only in those sites where it is standard of care) and

	postoperatively at 12 months. All subjects will be followed through the 24-month visit.
Sample Size	Overall 100 subjects will be included with around 50 subjects (no less than 48 subjects) in each indication group in approximately 10 sites in Europe.
Inclusion/Exclusion Criteria	**Inclusion Criteria:** A subject must meet the following inclusion criteria to participate in this trial: 1. One or more of the following diagnostic indications: • Degenerative Spinal Disease (e.g. degenerative disc disease, spondylolisthesis and/or spinal stenosis) • Deformity (e.g. degenerative deformity) 2. Degenerative Spinal Disease patients only: Patient has been unresponsive to non-operative treatment for at least three months or has progressive symptoms or signs of nerve root/spinal cord compression while undergoing continued non-operative management. 3. Compromised bone quality defined as a hip DXA scan T-score less than or equal to -1.0 or spine quantitative CT (qCT) actual volumetric bone mineral density threshold of ≤ 120 mg/cm^3. 4. Requires a procedure with an instrumented, posterior thoracic and/or lumbar spinal stabilization and/or immobilization. 5. Is scheduled to receive a construct using CD Horizon® Spinal System components with at least one Fenestrated Screw cemented with Fenestrated Screw Cement. 6. At least 22 years old or greater at the time of informed consent. 7. Is able to understand and willing to sign the Patient Informed Consent Form. 8. Is willing and able to undergo the study procedure and perform the follow up visits. **Exclusion criteria:**

	A subject will be excluded from participating in this trial for any of the following reasons: • Has undergone stabilization and/or fusion procedure at the index or adjacent levels. • Will undergo vertebroplasty or kyphoplasty procedure during surgery. • Has been diagnosed with cauda equina syndrome. • Has been previously diagnosed with clinically significant peripheral neuropathy. • Has any degree of permanent neurologic deficit due to the presenting spinal disease (e.g. drop foot or gait deficit). • Has obesity defined by BMI greater than or equal to 35kg/m^2. • Has documented allergy to the materials that will be used in the surgical or any imaging procedure (e.g. titanium alloys, cobalt-chromium-molybdenum alloys, PMMA Fenestrated Screw Cement, contrast medium). • Has overt or active bacterial infection, local or systemic, and/or potential for bacteremia. • Has a non-correctable spontaneous or therapeutic coagulation disorder or history of coagulation disorder associated with bleeding. • Has evolutive cardiac disease (e.g. symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia) nonreactive to medical treatment. • Has any disease (e.g., neuromuscular disease, etc.) that would preclude the potential benefit and/or accurate clinical evaluation of the safety of the spinal implant surgery. • Is pregnant or planning to become pregnant during the study duration. • Is illiterate or considered vulnerable as per the Investigator's assessment (e.g., participants incapable of judgment, or participants under tutelage).

	• Concurrent participation in another clinical study that may add additional safety risks and/or confound study results*. *Subjects in concurrent studies can only be enrolled with permission from Medtronic. Please contact Medtronic's study manager to determine if the subject can be enrolled in the FNS Study.	
Outcomes	Endpoints	Measurements
Primary Endpoint	Improvement of ODI from baseline at 12-month visit.	Oswestry Disability Index (ODI)
Secondary Endpoints	Secondary clinical outcomes including: Improvement of ODI from baseline at 3- and 24-month visit. Improvement of VAS back and leg pain score from baseline at 3-, 12- and 24-month visit. Improvement of EQ-5D 5L from baseline at 3-, 12- and 24-month visit.	 ODI VAS back and leg pain score EQ-5D 5L
	Neurological success at 12-month visit.	Physician Reported
	Intraoperative cement extravasation/leakage.	Physician Reported
	Device and/or procedure related adverse events through 24 months.	Adverse Event Reporting
	Secondary spinal surgeries at index and/or adjacent level(s), resulting from an AE, up to 24 months after the surgery.	Adverse Event Reporting

	Radiographic confirmation of stabilization of the pedicle screw instrumentation at 12-month visit.	Physician assessed radiographic images
	Radiographic Fusion at 12-month visit for those subjects where fusion was intended.	Physician assessed radiographic images
Secondary Endpoints for Deformity subjects	Change in coronal and sagittal spinopelvic parameters from baseline at 12-month visit.	Physician assessed radiographic images
Statistical Methods:	For the primary endpoint improvement of ODI score from baseline at 12-month visit, in addition to the descriptive statistics including mean, standard deviations, minimum and maximum, a paired t-test for normally distributed data or Wilcoxon signed rank test for not normally distributed data will be carried out to test whether the mean improvement from baseline is significantly greater than 0 for each indication subgroup. If P-value is ≤ 0.05, then primary objective is met. Similar method will be used for the secondary clinical outcomes including improvement of ODI from baseline at 3- and 24-month visit, improvement of VAS back and leg pain score from baseline at 3-, 12- and 24-month visit and improvement of EQ-5D 5L from baseline at 3-, 12- and 24-month visit. For the secondary endpoints including neurological success at 12-month visit, intraoperative cement extravasation/leakage, pedicle screw instrumentation stabilization at 12-month visit and fusion success at 12-month visit, simple frequencies will be summarized. As for secondary endpoints including device and/or procedure related adverse events through 24 months and secondary spinal surgeries at index and/or adjacent level(s), resulting from an AE, up to 24 months after the surgery, the event rate will be estimated using time-to-event analysis. All the analyses will be done separately for each indication subgroup. For the deformity group, the secondary endpoints, change in coronal and sagittal spinopelvic parameters from baseline at 12-month visit, will be analyzed using the same method as the one for the primary endpoint.	

4. Introduction

4.1 Background

Posterior stabilization and immobilization of thoracolumbar spinal segments with pedicle screw and rod systems is dependent on the anchor strength of pedicle screws within the vertebrae. One of the determining factors for pedicle screw fixation is the quality of the bone within the vertebral bodies [1, 2]. It's estimated that 50% and 15% of female and male spine subjects respectively, older than 50 years, have osteoporosis [3]. Complications resulting from the use of pedicle screws in compromised bone may include screw loosening, screw pullout and/or complete hardware failure due to the poor fixation strength of the screws within the vertebrae. Therefore, strategies to ensure adequate anchorage of the pedicle screws within the vertebrae are necessary to treat these subjects.

Biomechanical studies have demonstrated that the use of bone cement-augmented pedicle screw fixation results in significantly increased holding power of screws in osteoporotic spine [4, 5]. As a result, clinical techniques have been developed whereby bone cement, such as polymethylmethacrylate (PMMA) is injected into the vertebral bodies, and when cured serves as the screw interface providing adequate pedicle screw fixation.

There are two techniques by which surgeons augment pedicle screw fixation using bone cement. One technique is to create a channel in the pedicle where the pedicle screw will be inserted. Bone cement is first injected into the vertebral body through the channel followed by placement of the pedicle screws [6]. This technique increases the fixation strength of the pedicle screws [7] but is associated with additional risks [8, 9].

The second technique is to use a cannulated pedicle screw that has fenestrations or openings in the distal end of the screw. Fenestrated screws (FNS) are inserted into the vertebral body first, and bone cement is then injected through the screw cannula and extruded through the fenestrations into the cancellous bone of the vertebral body. This method also demonstrated increased fixation strength of the pedicle screws [10] as well as decreased cement leakage [11].

The primary safety risks associated with pedicle screw augmentation are the risks associated with cement extravasation either via the intervertebral vasculature, or perivertebrally through breaches in the cortical shell. Although most cement leakages are asymptomatic [11-15], there are reports of clinically relevant leakages [8, 16]. Two widely accepted procedures that introduce cement into vertebral bodies at considerably higher volumes than FNS are kyphoplasty (KP) and vertebroplasty (VP). In these procedures, cement leakage has been reported from 11.3% [17] to 87.5% [18].

Reports of cement extravasation in PMMA-augmented fenestrated pedicle screw fixation range from 5.7% to 29.3% [13, 14].

The factors associated with the reduced extravasation rate and reduced volume of extravasation per occurrence with FNS is due to the controlled delivery of a lower volume of cement under fluoroscopic imaging that provides immediate feedback and allows precise control of the cement delivery.

There are several clinical reports of FNS use in the literature. Amendola et al. [19], reported on 21 subjects with poor bone quality due to osteoporosis or tumor that underwent posterior stabilization by fenestrated pedicle screws and PMMA augmentation. Pain improvement and long-term clinical outcome were assessed by visual analogue scale (VAS) and SF-36 health survey (SF-36) questionnaire. Complications were evaluated in all cases. VAS-pain scores and SF-36 questionnaires showed a statistically significant reduction in pain and improvement in the quality of life during the 36 months' follow-up period. No screw loosening or screw pullout was observed. In two cases, cement leakage occurred intraoperatively: of these, one subject had transitory nerve root palsy, which improved spontaneously when the excess cement was removed by the surgeon. In three cases, the post-op CT scan revealed a small amount of cement in the canal without clinical relevance. Lubansu et al. [12] described a percutaneous or minimally invasive approach for augmentation of FNS. The safety and effectiveness of this technique was evaluated in 15 elderly osteoporotic subjects (mean T score = -2.7, range = -2.1 to -4.1). Clinical outcomes were assessed using the Visual Analogue Scale (VAS) score and the Oswestry Disability Index (ODI). Both the VAS-pain scores and ODI questionnaires showed a statistically significant improvement up to 13.3 months postoperatively. PMMA asymptomatic extravasations were observed in 5/15 subjects. There were no cases of severe morbidity post-operatively (no death, no myocardial infarction, no pulmonary emboli, or intraoperative hypotension). Two postoperative complications related to the procedure were noted: one S1 screw misplacement associated with nerve radiculitis (no cement injected through this screw), and one subcutaneous infection that was treated with 2 weeks of antibiotic therapy. During the follow-up period, no construct failures, screw fractures, screw pullouts or loss of correction were noted. In another study [14], 37 subjects with degenerative spinal stenosis and osteoporosis (T-score <-2.5) were evaluated after placement of PMMA augmented cannulated pedicle screws. The clinical outcome measurements included the VAS-pain score and the Prolo scale. The postoperative VAS score for low back pain and leg pain (2.30 ± 1.61 and 1.42 ± 0.73) improved significantly ($p = 0.006$, $p = 0.003$) from preoperative VAS scores (7.87 ± 0.95 and 8.82 ± 0.83). The average postoperative Prolo score (7.76 ± 1.74) improved significantly ($p = 0.01$) from the preoperative score (4.22 ± 0.95). There were no screw fractures or construct failures. Pedicle screw loosening was observed in one subject (2.7%). Local extravasations of PMMA into the ventral aspect of the vertebral body were observed in two cases (5.4%). There were no pulmonary emboli or cases of osteomyelitis.

Pinera et al. [13] studied 23 elderly subjects with lumbar degenerative spondylolisthesis with instability, or lumbar stenosis requiring aggressive decompression, that underwent a spinal fusion with PMMA-augmented cannulated pedicle screw instrumentation. All subjects had a history of osteoporotic fractures or had bone mineral density T-scores that indicated osteoporosis (mean T score was -2.4; range -1.8 to -4.1). The results showed that pain and functions improved at 6 months and were maintained over a time. There were no reports of screw pullout or instrumentation failure. There were no cases of adjacent vertebral fractures. Cement leakage was observed in 29.3% of the treated vertebrae; however, no clinical complications secondary to PMMA leakage were reported.

CD HORIZON® Fenestrated Screw Spinal System has been CE-marked since 2011 and received 510(k) clearance in January 2016. Chandra et al. [20] reported on 25 osteoporotic subjects (average T-score -3.0) with up to grade III spondylolisthesis that were treated with the CD HORIZON® Fenestrated Screw Spinal System. The subject group experienced significant improvement in pain (VAS) and disability (ODI) from

pre-op to final post-op evaluation (mean follow-up, 18 months). In this study, there was one event of cement extravasation with no adverse clinical sequelae. There were no reports of screw pull out or instrumentation failure.

Medtronic is proposing this post-market study to evaluate clinical benefits and safety of CD HORIZON® Fenestrated Screw Spinal System with Fenestrated Screw Cement for stabilization and immobilization of spinal segments in subjects with compromised bone quality.

4.2 Purpose

The purpose of the post-market study is to evaluate the clinical benefit and safety of CD HORIZON® Fenestrated Screw Spinal System with Fenestrated Screw Cement when used in subjects with compromised bone quality undergoing a thoracolumbar procedure requiring posterior immobilization and/or stabilization of one or more spinal segments. The data obtained from this study may be used for regulatory purposes worldwide, including supporting a 510(k) application for expanded indications in the US, in addition to possible publications.

5. Objectives and Endpoints

5.1 Objectives

5.1.1 Primary Objective(s)

The primary objective of this post-market study is to demonstrate that Oswestry disability index (ODI) score improved significantly at 12 months post-operatively as compared to baseline for each indication (degenerative spinal disease and deformity) in subjects with compromised bone quality, who will receive a surgical procedure requiring posterior stabilization and/or immobilization of one or more spinal segments using CD HORIZON® Fenestrated Screw Spinal System with Fenestrated Screw Cement.

5.1.2 Secondary Objective(s)

Secondary objectives of this study include the assessment of the following endpoints for each indication (degenerative spinal disease and deformity):

- Improvement of ODI at 3- and 24-month visit from baseline.
- Improvement of VAS back and leg pain score at 3-, 12- and 24-month visit from baseline.
- Improvement of EQ-5D 5L at 3-, 12- and 24-month visit from baseline.
- Neurological success at 12-month visit.
- Intraoperative cement extravasation/leakage.

- Device and/or procedure related adverse events through 24 months.
- Secondary spinal surgeries at index and/or adjacent level(s), resulting from an AE, up to 24 months after the surgery.
- Radiographic confirmation of stabilization of the pedicle screw instrumentation at 12-month visit.
- Radiographic fusion at 12-month visit for those subjects where fusion was intended.

Secondary objective that is specifically for deformity subjects includes:

- Assessment of change in coronal and sagittal spinopelvic parameters from baseline at the 12-month visit.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint is the improvement in ODI at 12 months compared to baseline.

5.2.2 Secondary Endpoints

The secondary endpoints are:

- Improvement of ODI from baseline at 3- and 24-month visit.
- Improvement of VAS back and leg pain score from baseline at 3-, 12- and 24-month visit.
- Improvement of EQ-5D 5L from baseline at 3-, 12- and 24-month visit.
- Neurological success at 12-month visit.
- Intraoperative cement extravasation/leakage.
- Device and/or procedure related adverse events through 24-months.
- Secondary spinal surgeries at index and/or adjacent level(s), resulting from an AE, up to 24 months after the surgery.
- Radiographic evaluation of pedicle screw instrumentation stabilization at 12-month visit.
- Radiographic evaluation of fusion status at 12-month visit for those subjects where fusion was intended.

Secondary endpoint to be assessed specifically for deformity subjects includes:

- Change in coronal and sagittal spinopelvic parameters from baseline at the 12-month visit.

6. Study Design

This is a multi-center, single arm, open-label, prospective study that will collect data on subjects with compromised bone quality undergoing thoracolumbar immobilization/stabilization surgery using CD HORIZON® Fenestrated Screw Spinal System with Fenestrated Screw Cement, for degenerative spinal disease or deformity.

The study will evaluate overall 100 subjects with around 50 subjects (no less than 48 subjects) in each indication subgroup at approximately 10 study sites in Europe. A minimum of 1 subject and a maximum of 25 subjects will be included per site. For each site, no more than approximately 15 patients are allowed to be included per subgroup (degenerative spinal disease, deformity). These limits may be subject to change during the course of the study and will be communicated as appropriate to the Investigators, EC/IRB and regulatory authority, if required.

Commercially available study devices will be used in accordance with the instructions as listed in the IFUs applicable in each country.

Only consented subjects can be enrolled into the study. Every effort will be made to enroll subjects in a consecutive manner. Clinical assessments will be completed at baseline (preoperatively), during the procedure, prior to hospital discharge, and postoperatively at 3 months, 12 months, and 24 months. Radiological assessments will be completed at baseline, prior to hospital discharge (only for deformity subjects if standard of care at the site) and postoperatively at 12 months. All subjects will be followed through the 24-month visit.

6.1 Duration

Enrollment in the study for each subject is defined as the date the subject first signs the informed consent.

Enrolled subjects who do not meet baseline eligibility or who do not undergo the fenestrated screw procedure as defined in this protocol will be exited from the study but can be replaced if enrollment is still open. The completion of the study for each subject is defined as the conclusion of the 24-month visit (Study Exit). Each subject's participation in the study is expected to last approximately 2 years from the date of the procedure. Each subject will be evaluated prior to the procedure (baseline), during the procedure, prior to hospital discharge, 3 months, 12 months, and 24 months post procedure.

The estimated time needed to enroll all subjects is approximately 2 years. The overall study duration, from first subject enrollment to last subject visit, is expected to last approximately 4 years. The completion of the study is defined as the approval of the Final Study Report and closure of all sites. It is anticipated that the total duration of this study will be approximately 4.5 years.

6.2 Rationale

CD HORIZON® Fenestrated Screw Spinal System has been CE-marked since 2011, for the treatment of degenerative disc disease (defined as back pain of discogenic origin with degeneration of the disc confirmed by history and radiographic studies), ankylosing spondylitis, spondylolisthesis, trauma (fracture or dislocation), spinal stenosis, curvatures (i.e., scoliosis, kyphosis or lordosis), tumor, pseudoarthrosis, revision surgery and/or failed previous fusion.

The CD HORIZON® Fenestrated Screw Spinal System with Fenestrated Screw Cement is designed to enhance the fixation strength of instrumentation in vertebrae with compromised bone quality. Currently, in the US, these screws with Fenestrated Screw Cement are 510(k) cleared only for the treatment of advance stage tumor subjects. However, within the US, nearly 50% of the population of subjects requiring spinal immobilization/stabilization procedures for degenerative disc disease, spondylolisthesis, trauma (fracture or dislocation), or spinal stenosis, also have compromised bone quality. Outside of the United States, the CD HORIZON® Fenestrated Screw Spinal System is CE-marked for broader indications and is being used to treat subjects with compromised bone quality. The proposed study design provides an opportunity to collect real-world clinical and radiographic data for CD HORIZON® Fenestrated Screw Spinal System with Fenestrated Screw Cement when used for the treatment of degenerative spinal disease or deformity.

The proposed primary endpoint at 12 months is sufficient to demonstrate improvement in disability (ODI). Furthermore, literature [21, 22] and previous Medtronic sponsored studies have demonstrated that subject reported outcomes at 12 months are consistent with outcomes reported at longer follow-up intervals. To confirm this, we will also be collecting patient reported clinical outcomes at 24 months. In addition, the proposed radiographic evaluation of the pedicle screws at 12 months is sufficient time to reveal any apparent evidence of implant loosening.

To assess long-term safety of the device, subjects will be followed-up for 24 months to collect safety information.

7. Product Description

7.1 General

The figure below shows the CD HORIZON® Legacy™ and Solera™ Fenestrated Screw

Figure 1: CD HORIZON® Legacy™(left) and Solera™(right) Fenestrated Screw

The CD HORIZON® Legacy™ and Solera™ Fenestrated Screw Spinal System consists of a variety of cannulated screws with a series of fenestrations to allow polymethylmethacrylate (PMMA) bone cement (Fenestrated Screw Cement) to be injected into the treated site. The Fenestrated Screw Cement is used to augment screw fixation in subjects with compromised bone quality.

The CD HORIZON® Legacy™ Fenestrated Screws are specifically designed to connect to Ø 5.5mm rods and associated components contained within the CD HORIZON® Spinal System. The CD HORIZON® Solera™ Fenestrated Screws are specifically designed to connect to rods of Ø 4.75, 5.5 and 6.0mm and associated components contained within the CD HORIZON® Spinal System.

The CD HORIZON® Spinal System consists of a variety of rods, hooks, screws, plates, and other connecting components used to build a spinal construct. The entire spinal construct must contain CD Horizon® Spinal System components with at least one Fenestrated Screw cemented with Fenestrated Screw Cement.

Instrumentation is also available to facilitate implantation of these components. Additionally, other commercially available ancillary devices, implants, instrumentation and bone grafts/substitutes can be used during the surgery procedure.

All devices used in this study, shall be used within their intended use as described in the Instructions for Use for which CE mark has been obtained. Labeling of the devices will be in the appropriate local language. It is an investigator's responsibility to only use commercially available devices within intended use in the scope of this study.

The CD Horizon® Legacy™ Fenestrated Screws are fabricated from medical-grade titanium and/or medical grade titanium alloy. The CD HORIZON® Solera™ Fenestrated Screws are fabricated from medical-grade titanium and/or medical grade titanium alloy and/or medical grade cobalt-chromium-molybdenum alloy.

Fenestrated Screw Cement (Reference Number 7480724) is a polymethylmethacrylate (PMMA) that contains approximately 30% barium sulfate.

Nominal Composition of Fenestrated Screw Cement (Reference Number 7480724):
(Actual weight percentages of individual components will vary within accepted ranges)

POWDER (20 g of sterile powder in a packet)	**LIQUID** (9.0 g of sterile liquid in a vial)
Methylmethacrylate-styrene-copolymer 68.0% w/w	Methylmethacrylate (monomer) 99.1% w/w
Barium sulfate 30.0% w/w	N, N-dimethyl-p-toluidine 0.9% w/w
Benzoyl peroxide 2.0% w/w	Hydroquinone 75 ppm

The CD Horizon® Legacy™ and Solera™ Fenestrated Screws and the Fenestrated Screw Cement do not incorporate, as an integral part, a substance or human blood derivative referred to in Section 7.4 of Annex I (93/42/EEC).

For the manufacturing of the CD HORIZON® Legacy™ and Solera™ Fenestrated Screw and the Fenestrated Screw Cement no tissues of animal origin as referred to in Directive 2003/32/EC were used.

7.2 Dosage Form and Route of Administration

The operating surgeon should refer to the Instructions for Use (IFU) for the CD Horizon® Legacy™ and Solera™ Fenestrated Screws and the Fenestrated Screw cement for Warnings, Precautions, and Operative Steps on the usage of the products. The recommended amount of cement to be injected is also specified in the IFU.

7.3 Manufacturer

CD HORIZON® Legacy™ and Solera™ Fenestrated Screw Spinal System:

Medtronic Humacao
PR-909
Humacao 00791
Puerto Rico

Fenestrated Screw Cement:

TECRES S.p.A
Via A. Doria 6
37066 Sommacampagna
Verona - Italy

7.4 Packaging

The CD HORIZON® Fenestrated Screw Spinal System is provided in a set and must be sterilized by the hospital prior to use. The product can be steam-sterilized using process parameters listed in the indication for use.
The Fenestrated Screw Cement is provided sterile and is intended for single use only. The powder and package are sterilized with gamma radiation. The liquid is sterilized using filtration and is contained in a glass vial. The outside of the glass vial is sterilized with ethylene oxide gas. Once the seal on the sterile package has been broken, the product should not be re-sterilized or reused. Labelling is specific to the geography and in accordance with local regulations.

7.5 Intended Population

The CD HORIZON® Fenestrated Screws, when used in conjunction with Fenestrated Screw Cement are intended to provide enhanced pedicular fixation in the treatment of subjects with compromised bone quality for the following indications:

CD HORIZON® Legacy™ Fenestrated Screw Spinal System: degenerative disc disease (defined as back pain of discogenic origin with degeneration of the disc confirmed by history and radiographic studies); ankylosing spondylitis, spondylolisthesis, trauma (i.e. fracture and/or dislocation), spinal stenosis, failed

previous fusion (pseudoarthrosis), deformity (e.g. adult degenerative deformity, scoliosis, kyphosis, lordosis), revision surgery, and/or tumor.

CD HORIZON® Solera™ Fenestrated Screw Spinal System: degenerative disc disease (defined as back pain of discogenic origin with degeneration of the disc confirmed by history and radiographic studies), spondylolisthesis, trauma (i.e. fracture or dislocation), spinal stenosis, curvatures (i.e., scoliosis, kyphosis, or lordosis), tumor, pseudarthrosis, and/or failed previous fusion.

7.6 Product Use

The CD HORIZON® Legacy™ Fenestrated Screw Spinal System, the CD HORIZON® Solera™ Fenestrated Screw Spinal System, and the Fenestrated Screw Cement will be used according to the surgical techniques described in the CD HORIZON® Fenestrated Screw Spinal System Surgical Technique Brochures. The operating surgeon should refer to the respective products' IFU for any corresponding product information prior to using the product.

7.7 Product Training Requirements

The Investigator shall be experienced in the field of application and trained in the use of the study device(s), and qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation. Investigator qualifications will be verified by Curriculum Vitae (CV), and during Site Qualification Visits (SQVs), if applicable.

7.8 Product Receipt and Tracking

This is a post-market study and the CD HORIZON® Legacy™ Fenestrated Screw Spinal System, CD HORIZON® Solera™ Fenestrated Screw Spinal System, and the Fenestrated Screw Cement used during the study are commercially available. Product receipt and tracking is not required as the devices used during the study are purchased through normal commercial channels.

7.9 Product Storage

Products should be stored per the institutions' standard procedures.

7.10 Product Return

Products should be disposed of or returned per the institutions' standard procedures.

7.11 Product Accountability

Product accountability is not required for this post-market study as the devices used during the study are purchased through normal commercial channels and maintained per the institutions' standard procedures.

8. Selection of Subjects

8.1 Study Population

The study population are subjects with compromised bone quality seeking treatment at a participating study center for one or more of the following conditions:

- Degenerative Spinal Disease (e.g. degenerative disc disease, spondylolisthesis and/or spinal stenosis)
- Deformity (e.g. degenerative deformity)

Participating centers will be instructed to consecutively screen all subjects who are planned to undergo a procedure with an instrumented, posterior thoracic and/or lumbar spinal stabilization/immobilization using CD HORIZON® Fenestrated Screw Spinal System with Fenestrated Screw Cement against the eligibility criteria. Every effort will be made to enroll subjects in a consecutive manner.

Overall 100 subjects, with around 50 subjects (no less than 48 subjects) in each indication subgroup, that meet eligibility and provide written informed consent will be enrolled into this study. Subjects will be enrolled in approximately 10 centers in Europe.

The enrollment limit has been defined to be 50 patients per indication (degenerative spinal disease or deformity). Investigators will be requested to stop enrollment for a particular indication when the maximum enrollment (50 patients) for that indication has been reached.

A minimum of 1 subject and a maximum of 25 subjects will be included per site. For each site, no more than approximately 15 patients are allowed to be included per subgroup (degenerative spinal disease, deformity). These limits may be subject to change during the course of the study and will be communicated as appropriate to the Investigators, EC/IRB and regulatory authority, if required.

8.2 Subject Enrollment

Subjects planning to undergo a procedure with an instrumented, posterior thoracic and/or lumbar spinal stabilization/immobilization using CD HORIZON® Fenestrated Screw Spinal System with Fenestrated Screw Cement will be screened for eligibility to participate in the study. Subjects will be considered enrolled in the study once the informed consent form is signed; however, those who do not meet the

baseline inclusion/exclusion criteria or who do not undergo the fenestrated screw procedure as defined in this protocol will be exited from the study but can be replaced if enrollment is still open.

8.3 Inclusion Criteria

A subject must meet the following inclusion criteria to participate in this trial:

1. One or more of the following diagnostic indications:
    - Degenerative Spinal Disease (e.g. degenerative disc disease, spondylolisthesis and/or spinal stenosis)
    - Deformity (e.g. degenerative deformity)
2. Degenerative Spinal Disease patients only: Patient has been unresponsive to non-operative treatment for at least three months or has progressive symptoms or signs of nerve root/spinal cord compression while undergoing continued non-operative management.
3. Compromised bone quality defined as a hip DXA scan T-score less than or equal to -1.0 or spine quantitative CT (qCT) actual volumetric bone mineral density threshold of ≤ 120 mg/cm^3.
4. Requires a procedure with an instrumented, posterior thoracic and/or lumbar spinal stabilization and/or immobilization.
5. Is scheduled to receive a construct using CD Horizon® Spinal System components with at least one Fenestrated Screw cemented with Fenestrated Screw Cement.
6. At least 22 years old or greater at the time of informed consent.
7. Is able to understand and willing to sign the Patient Informed Consent Form.
8. Is willing and able to undergo the study procedure and perform the follow up visits.

8.4 Exclusion Criteria

A subject will be excluded from participating in this trial for any of the following reasons:

1. Has undergone stabilization and/or fusion procedure at the index or adjacent levels.
2. Will undergo vertebroplasty or kyphoplasty procedure during surgery.
3. Has been diagnosed with cauda equina syndrome.
4. Has been previously diagnosed with clinically significant peripheral neuropathy.

5. Has any degree of permanent neurologic deficit due to the presenting spinal disease (e.g. drop foot or gait deficit).
6. Has obesity defined by BMI greater than or equal to 35kg/m^2.
7. Has documented allergy to the materials that will be used in the surgical or any imaging procedure (e.g. titanium alloys, cobalt-chromium-molybdenum alloys, PMMA Fenestrated Screw Cement, contrast medium)
8. Has overt or active bacterial infection, local or systemic, and/or potential for bacteremia.
9. Has a non-correctable spontaneous or therapeutic coagulation disorder or history of coagulation disorder associated with bleeding.
10. Has evolutive cardiac disease (e.g. symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia) nonreactive to medical treatment.
11. Has any disease (e.g., neuromuscular disease, etc.) that would preclude the potential benefit and/or accurate clinical evaluation of the safety of the spinal implant surgery.
12. Is pregnant or planning to become pregnant during the study duration.
13. Is illiterate or considered vulnerable as per the Investigator's assessment (e.g., participants incapable of judgment, or participants under tutelage).
14. Concurrent participation in another clinical study that may add additional safety risks and/or confound study results*.

*Subjects in concurrent studies can only be enrolled with permission from Medtronic. Please contact Medtronic's study manager to determine if the subject can be enrolled in the FNS Study.

9. Study Procedures

9.1 Schedule of Events

The study schedule, procedures, and methods of assessment are defined in detail to enable compliance with the required activities, and to ensure that the resulting data meet the criteria for evaluability. See Table 9-1 for visit schedule. The relevant electronic Case Report Forms (eCRFs) along with the applicable source documentation will be completed for each subject.

Table 9-1: Schedule of Events

	Enrollment / Baseline	Surgery[1]	Prior to discharge	3 months (-1,5 / +3 months)	12 months (±3 months)	24 months (±6 months)
Informed consent	X[2]					
Demographics	X					
Medical History	X					
Hip DXA scan or spine qCT	X[3]					
Surgery Indication	X					
Surgery		X				
Intraoperative cement extravasation/leakage		X				
X-ray or CT scan			(X) [4]		X	(X)[5]

[1] The surgery procedure should occur as soon as possible after baseline but no later than 6 months after the date of acquiring the X-ray, MRI and/or CT-scan images. However, if the surgery cannot be done within 6 months after the date of the images then new images should be obtained.

[2] Patient Informed Consent must be obtained prior to performing any study specific procedure.

[3] Hip DEXA scan or spine qCT can be collected prior to enrollment/baseline visit if this is part of the standard of care and if it is not older than 3 months before the baseline visit. If not standard of care at the site, this is considered a study procedure and Patient Informed Consent must be obtained first.

[4] It is at the Investigator's discretion to do a post-operative CT to assess pulmonary embolism in case there is a possibility for cement extravasation/leakage.

[5] CT-scan or X-rays is required at 12 months follow-up for assessment of fusion (for those subjects where fusion is intended) and confirmation of stabilization of the pedicle screw instrumentation. If no fusion is observed at 1-year follow-up, it will be at the discretion of the Investigator to follow-up if fusion can be observed at 24 months (only if standard of care at the site). In case the patient is symptomatic at 24 months and receives a CT-scan or X-ray, stabilization of pedicle screw instrumentation and fusion status (for those subjects where fusion is intended) will be assessed.

	Enrollment / Baseline	Surgery[1]	Prior to discharge	3 months (-1,5 / +3 months)	12 months (±3 months)	24 months (±6 months)
Spinopelvic alignment[6]	X		(X)[7]		X	(X)[8]
Medication	X		X	X	X	X
Neurological status	X				X	
VAS (back and leg pain)	X			X	X	X
ODI	X			X	X	X
EQ-5D 5L	X			X	X	X
Adverse Events and/or device deficiencies		X	X	X	X	X
Protocol Deviations	X	X	X	X	X	X

9.1.1 Enrollment

All subjects must give their informed consent in accordance with the informed consent regulations per geographic region. At this visit, the following is a list of likely procedures:

- The subject will be presented with information about the clinical study and asked if he/she would like to participate
- The subject will be evaluated for eligibility per the inclusion/exclusion criteria.

If the subject meets the eligibility criteria and agrees to participate in the study, he/she will be asked to sign the patient informed consent (PIC). Once the PIC is signed, a copy of the signed PIC will be provided to the subject.

All subjects must sign the PIC prior to the collection of any study data. A subject is considered enrolled in this study at the time he/she signs the PIC. The subject will be assigned a unique, sequential code linked

[6] Spinopelvic alignment parameters are only required to be assessed for deformity subjects.
[7] Spinopelvic alignment parameters will only be collected prior to discharge in those sites where it is standard of care.
[8] In case the patient is symptomatic at 24 months and receives a standing, frontal and sagittal full spine X-ray (at least C7 + femoral head must be visible), spinopelvic parameters will be assessed.

to their name, alternative subject identification or contact information. The Investigator will maintain a log of all subjects enrolled in the study.

The enrollment limit has been defined to be 50 patients per indication (degenerative spinal disease or deformity). Investigators will be requested to stop enrollment for a particular indication when the maximum enrollment (50 patients) for that indication has been reached. A minimum of 1 subject and a maximum of 25 subjects will be included per site. For each site, no more than approximately 15 patients are allowed to be included per subgroup (degenerative spinal disease, deformity). These limits may be subject to change during the course of the study and will be communicated as appropriate to the Investigators, EC/IRB and regulatory authority, if required.

9.1.2 Baseline

The following information will be collected at the baseline visit:

- Verification of Inclusion/Exclusion criteria
- Demographics
- Medical History
- Hip DXA scan or spine qCT (can be collected prior to baseline visit if this is part of the standard of care and if it is not older than 3 months before the baseline visit)
- Surgery Indication
- Imaging (X-ray, MRI and/or CT-scan) (can be collected prior to baseline visit if it is not older than 6 months before surgery date)
- Spinopelvic alignment parameters (only required for deformity subjects)
- Medication
- Neurological status
- VAS back and leg pain
- ODI
- EQ-5D 5L
- Protocol Deviations

9.1.3 Surgery

The surgery procedure should occur as soon as possible after baseline but no later than 6 months after the date of acquiring the X-ray, MRI and/or CT-scan images. However, if the surgery cannot be done within 6 months after the date of the images then new images should be obtained.

The following information will be collected during surgery:

- Surgery procedure data

- Surgery time
- Blood loss and Transfusion
- Intraoperative cement extravasation/leakage
- Device Models
- Adverse Events and/or device deficiencies
- Protocol Deviations

It is recognized that the situation of a subject might change after enrollment. Due to Investigator's discretion, a subject might not receive at least one Fenestrated Screw cemented with Fenestrated Screw Cement during the procedure. If this situation occurs this shall be documented on a study deviation eCRF, including rationale for change in procedure and the study early termination form will be completed in the eCRF.

9.1.4 Postoperative assessment prior to hospital discharge

The following information will be collected prior to hospital discharge:

- Spinopelvic alignment parameters (only required for deformity subjects in those sites where it is standard of care)
- Medication
- Adverse Events and/or device deficiencies
- Protocol Deviations

It is at the Investigator's discretion to do a post-operative CT to assess pulmonary embolism in case there is a possibility for intraoperative cement extravasation/leakage.

9.1.5 Postoperative assessment at 3 months (-1,5/+3 months), 12 months (±3 months) and 24 months (±6 months)

The following information will be collected at the post-operative visits:

- Medication
- VAS back and leg pain
- ODI
- EQ-5D 5L
- Adverse Events and/or Device Deficiencies
- Protocol deviations

The post-operative assessment at 12 months also includes

- An evaluation of neurological status
- A radiologic evaluation of:
    - Pedicle screw instrumentation stabilization
    - Fusion status for those subjects where fusion is intended (if no fusion is observed at 1-year follow-up, it will be at the discretion of the Investigator to follow-up if fusion can be observed at 24 months (only if standard of care at the site)).
    - Spinopelvic alignment parameters (only required for deformity subjects)

In case the patient is symptomatic at 24 months and receives a CT-scan or X-ray, stabilization of pedicle screw instrumentation and fusion status (for those subjects where fusion is intended) will be assessed.

Every attempt should be made to complete the required onsite clinic visit. However, if a subject is unable to complete an onsite visit at 3 months or 24 months, a remote visit source document worksheet can be completed by the Investigator/RC to obtain the required data elements.

The following data can be collected remotely using the remote visit source document worksheet:

- Medication
- VAS back and leg pain – conducted by phone or via web-based application
- EQ-5D-5L – phone version or via web-based application
- ODI – phone version or via web-based application
- Adverse events and/or device deficiencies

9.2 Subject Screening

Every effort will be made to screen subjects consecutively for treatment and enrollment into the FNS study. Consecutive enrollment per procedure is essential to minimize selection bias.

A subject screening log is provided to the site and should be completed by the site's study staff to maintain a cumulative log of all screened subjects per procedure. Subjects not suitable for the study or refusal to participate are considered screening failures and should also be collected and reported in the subject screening log kept at each site and reported at end of study recruitment. The Investigator will maintain a Subject Identification & Enrollment Log of all subjects enrolled in the clinical investigation, assigning a subject study ID linked to their names. Subject identifier will not leave the hospital.

9.3 Subject Consent

The Investigator or authorized designee must obtain written informed consent before any clinical study related activity takes place.

Prior to entering the study, the Investigator, or his/her designee, will inform all potential subjects about all aspects of the study (e.g. the purpose and nature of the study, procedures, follow-up schedule, and expected duration).
All items addressed in the Patient Information and the Informed Consent Form must be explained. The language used shall be as non-technical as possible and must be understandable to the subject.

The Investigator or designee will discuss the foreseeable risks as well as potential benefits that may result from participating in the study and the available alternative therapies.

The subject must have ample time and opportunity to read and understand the Patient Information and the Informed Consent Form, to inquire about details of the clinical study, and to decide whether to participate in the clinical study. All questions about the clinical study should be answered to the satisfaction of the subject.

Neither the Investigator, nor the investigation site staff shall coerce or unduly influence a subject to participate or to continue to participate in the clinical study. The informed consent process shall not waive or appear to waive the subject's rights. Subjects will be informed by the Investigator or designee that they are free to refuse to participate in the study, and if they choose to participate, that they may withdraw from the study at any time without compromising further medical care. In addition, subjects will be informed that the Investigator may terminate their participation at any time without their consent. Written informed consent will be obtained prior to subject enrollment and before any study-specific procedures are initiated.

Whenever new information becomes available that may be relevant to the subject's confirmed participation in the clinical study, Medtronic will revise the written Patient Information and Informed Consent Form and inform the Investigators. The revised information will be sent to the Investigator for approval or notification by the EC. After approval/notification by the EC, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated. The Investigator should inform the subject in a timely manner whenever new information becomes available that may be relevant to the subject's confirmed participation in the clinical study.

Local practice standards will be used to determine appropriateness of mental capacity to be able to provide general informed consent. If there is any question, the physician staff attending for the subject will have final authority in deciding the subject's capacity to provide their own informed consent.

The Investigator or designee will also determine that the potential subject can read, comprehend and make a decision regarding study participation.

The original, signed and dated ICF must be retained in the subject's study records. The informed consent process must be documented in the source documents and a copy of the ICF will be provided to the subject.

9.4 Assessment of Effectiveness

Subject-reported outcomes will be assessed pre-operatively and at all follow-up visits. Follow-up assessments will be compared to baseline (preoperative) assessments to determine changes in health-related quality of life, pain, and disability following the surgical procedure.

9.4.1 Oswestry Disability Index (ODI)

Disability associated with thoracic/lumbar spine conditions will be assessed using the Oswestry Low Back Pain Disability Questionnaire, which yields the Oswestry Disability Index (ODI), Version 2.1a. [23]. This validated instrument is considered one of the principal condition-specific outcome measures used in the management of spinal disorders.

The questionnaire will be used at baseline (preoperative) and at 3-month, 12-month and 24-month visits (post-operative).

9.4.2 Back and Leg Pain (VAS)

Levels of back pain and leg pain will be measured using the Visual Analogue Scales (VAS) at baseline (preoperative) and postoperative at 3-month, 12-month and 24-month visits. Subjects will be asked to rate the amount of back pain and leg pain they have had in the last week, where 0 is no pain and 10 is the worst pain possible.
A summary of the data will be based on actual measurements or changes in measurements from baseline (preoperative) to postoperative scores.

9.4.3 EQ-5D 5L Questionnaire

The EQ-5D 5L (European Quality of Life-5 Dimensions) self-report questionnaire will be used to assess health-related quality of life status [24] at baseline and postoperative at 3-month, 12-month and 24-month visits. The EQ-5D 5L questionnaire includes five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels, reflecting “no health problems,” “slight health problems,” “moderate health problems,” “severe health problems,” and “extreme health problems.” The EQ-5D 5L will be used for calculating EQ-5D index score. The EQ-5D VAS will also be utilized to document the subject’s self-rated overall health state on a 0 to 100 scale (0 = maximal health-related problems, 100 = minimal health-related problems).

A summary of data from each subject will be based on actual measurements or changes in measurements from baseline (preoperatively) to postoperative scores.

9.4.4 Neurological status

Neurological status will be evaluated at baseline and at the 12-month follow-up visit.

Neurological status is based on four types of measurements (sections): motor, sensory, reflexes, and straight leg raising. Each of the sections is comprised of a number of elements. Following scales will be used to evaluate neurological status: reflexes (0 = Absent or Trace, 1 = Hyper-reflexic, 2 = Normal), sensory function (Light Touch or Pin Prick L1 to S1), motor function (using 0-5 scores 0-5 whereas 0= Total Paralysis, 1 = Palpable or Visible Contraction, 2 = Active Movement, Gravity Eliminated, 3 = Active Movement, Against Gravity, 4 = Active Movement, Against Some Resistance and 5 = Active Movement, Against Full Resistance (full strength) and straight leg raise (positive = patient experiences radiating leg pain below the knee on elevating the leg between 15 and 70 with the knee extended, normal = no pain is experienced on elevating the leg between 15 and 70 with the knee extended).

Overall neurological success will be defined as maintenance or improvement in all sections (motor, sensory, reflex, and straight leg raising) for the time period evaluated. In order for a section to be considered a success, each element in the section must remain the same or improve from the time of the baseline evaluation to the time period evaluated. Therefore, if any one element in any section does not stay the same or improve, then a patient will not be considered a success for neurological status.

9.4.5 Fusion Status (for those subjects where fusion is intended)

The surgeon or hospital radiologist will determine fusion status for those subjects where fusion is intended. Fusion status will be classified as the following: No fusion success, Fusion success, and Unable to determine. The fusion assessment for each subject will be collected at 12 months, preferably by collecting a CT-scan, alternatively fusion may also be collected through X-rays. The criterion for fusion when assessed through a CT-scan is bony bridging and when assessed through X-rays the criteria bony bridging, no motion (<4˚) in Flexion/Extension views, and integrity of the instrumentation (implanted devices). A partial fusion (a fusion not meeting these criteria) should be recorded as “No fusion success”. For multi-level subjects, fusion success will be assessed for each level and overall fusion status for a subject will be defined as achieving fusion at all treated levels. If one level’s fusion status could not be determined while all the levels are success, then the subject level is considered unable to determine.

If no fusion is observed at the 12-month follow-up, it will be at the discretion of the Investigator to follow-up if fusion can be observed at 24 months (only if standard of care at the site).

In case the patient is symptomatic at 24 months and receives a CT-scan or X-ray, fusion status will be assessed.

9.4.6 Stabilization of the pedicle screw instrumentation

The surgeon or hospital radiologist will review radiographs and or CT’s to assess for evidence of instability of the pedicle screw instrumentation at 12 months.

The following are signs of instrumentation instability:

- Screw pullout
- Screw loosening

- Screw toggle

In case the patient is symptomatic at 24 months and receives a CT-scan or X-ray, stabilization of pedicle screw instrumentation will be assessed.

9.4.7 Spinopelvic alignment

Collection of spinopelvic parameters can show us if the patient's spine is balanced or not prior to and after the surgery. Any evolution of parameters after the surgery can indicate a change in spinopelvic alignment or a mechanism of regulation/compensation due to an evolution of the spinal alignment.

The following spinopelvic alignment parameters will be assessed in the deformity patients on standing, frontal and sagittal full spine X-ray (at least C7 + femoral head must be visible):

- Coronal alignment:
    - Distance between C7 plumb line (vertical line from the center of the C7 vertebral body) and the central sacral vertical line (CSVL) (vertical line drawn from the center of the sacrum).
    - Coronal curve type: the curve type is determined on the basis of maximal coronal angle measured according to standard Cobb technique and will be classified as:
        - Curve type T: patients with a thoracic major curve of >30˚ (apical level of T9 or higher)
        - Curve type L: patients with a lumbar or thoracolumbar major curve >30˚ (apical level of T10 or lower)
        - Curve type D: patients with a double major curve, with each curve >30˚.
        - Curve type N: patients with no coronal curve >30˚.

The standard cobb technique to measure coronal angles should be done by drawing a line perpendicular to a second line drawn across the superior endplate of the upper-end (most tilted) vertebra and the inferior endplate of the lowed end vertebra. The angle formed by the intersection of the two perpendicular lines is the Cobb angle, which is the measure of the magnitude of the curve (see Figure 2).

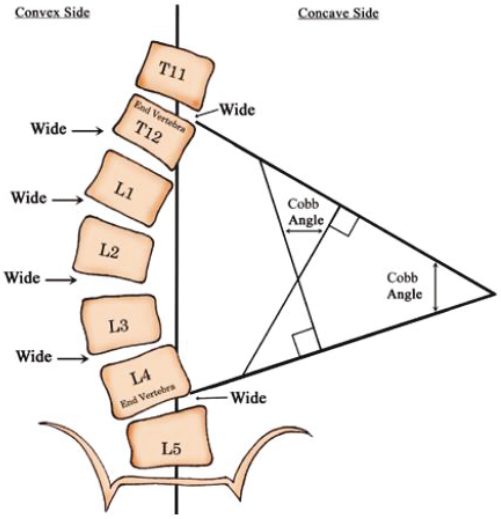

Figure 2: Cobb angle measurement technique.

- Sagittal alignment:
  - Regional parameters:
    - Thoracic Kyphosis (TK): Cobb angle between the superior endplate of T4 and inferior endplate of T12.
    - Thoracolumbar kyphosis (TLK): Cobb angle between the superior endplate of T10 and inferior endplate of L2.
    - Lumbar lordosis (LL): Cobb angle between the superior endplate of L1 and superior endplate of S1.
  - Global parameter: sagittal vertical axis (SVA): distance between a vertical plumb line from the center of the C7 vertebra to the posterior superior corner of the sacrum.
- Sagittal spinopelvic parameters:
  - Pelvic Incidence (PI): angle formed by the intersection of two lines including (1) a perpendicular line that is extended caudal from the middle of the S1 superior endplate and (2) a line that extends from the middle of the S1 superior endplate to the center of the bicoxofemoral axis.
  - Pelvic Tilt (PT): angle formed by the intersection of two lines including (1) a line that extends from the middle of the S1 superior endplate to the center of the bicoxofemoral axis and (2) a vertical line that is extended from the bicoxofemoral axis.
  - Sacral Slope (SS): angle formed by the intersection of two lines including (1) a line that parallels the superior endplate of the sacrum and (2) a horizontal line that is extended from the posterior, superior corner of the sacrum.

The deformity patients will be classified using the Scoliosis Research Society-Schwab Adult Spinal Deformity Classification (see Figure 3) [25].

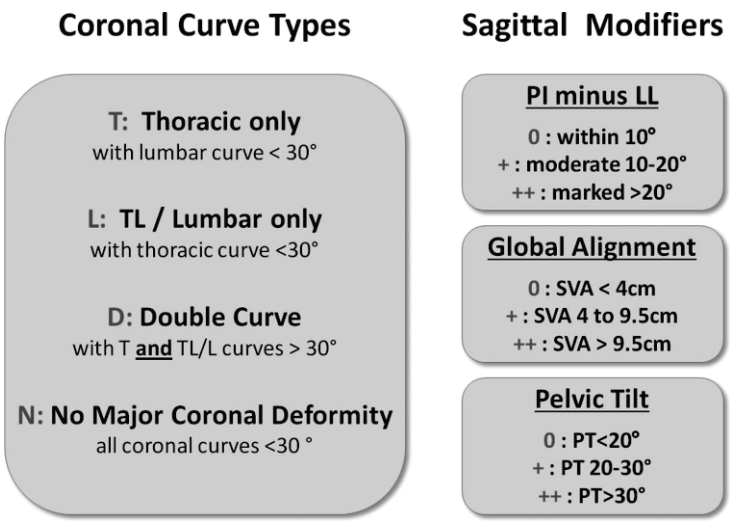

Figure 3: Guide to the SRS-Schwab Adult Spinal Deformity Classification system, including curve type and 3 sagittal modifiers.

Spinopelvic parameters will be assessed in the deformity patients only. The assessment will be done at baseline, prior to hospital discharge (for those sites where this is done as part of the standard of care) and at 12 months. In case the deformity patient is symptomatic at 24 months and receives a standing, frontal and sagittal full spine X-ray (at least C7 + femoral head must be visible), spinopelvic parameters will be assessed.

9.5 Assessment of Safety

Subjects will be assessed for potential adverse events and device deficiencies (as defined in Section 11.2).

9.5.1 Intraoperative cement extravasation/leakage

Subjects will be assessed for intraoperative cement extravasation/leakage. Both symptomatic and asymptomatic cement extravasation/leakage should be reported. In case the cement extravasation is symptomatic to the patient this should be documented in the AE eCRF. In case the cement extravasation is asymptomatic to the patient this should be reported in the DD eCRF. It is at the Investigator's discretion to do a post-operative CT to assess pulmonary embolism in case there is an indication for intraoperative cement extravasation/leakage.

9.5.2 Device and/or procedure related adverse events

Device and/or procedure related adverse events will be collected through 24 months follow-up. These should be documented in the AE eCRF.

9.5.3 Secondary surgery at the index and/or adjacent level(s) throughout the study

When a patient requires additional surgery at the index and/or adjacent level(s), it can be an indicator of insufficient outcomes of the initial surgery. Additional surgeries at the index and/or adjacent level(s) will be collected in the AE eCRF, including cases when the Investigator or study personnel becomes aware of a second surgery at the index and/or adjacent level in another hospital.

Pre-planned secondary surgeries at the index and/or adjacent level(s) should not be reported as adverse events on the AE eCRF but instead a second surgery eCRF should be completed. The pre-planned secondary surgery should be performed within 3 months as of the time of the initial surgery. There should be at least 1 month in between the pre-planned secondary surgery and 3-month (-1,5/+3 months) follow-up visit to reduce any bias on the patient reported outcomes.

9.6 Imaging guidelines

Study subjects are required to undergo imaging procedures at specified time points during the study and these will be obtained per the site's practice. To ensure consistency in the type and quality of all images obtained throughout this study some requirements have been defined:

- Clinical sites must use imaging equipment (DXA, X-ray, (q)CT-scan) that are maintained and calibrated according to the manufacturer's specifications when performing imaging procedures on subjects for this study. Imaging equipment maintenance and calibration will be monitored.
- To reduce the radiation exposure to study subjects, all DXA, X-ray and (q)CT examinations should be realized at the lowest radiation dose that still provides the minimally required image quality.

9.7 Recording Data

The Investigator must ensure accuracy, completeness and timeliness of the data reported in the eCRFs and in all other required reports. Data reported on the eCRFs must be consistent with the source documents, and discrepancies need to be justified in a documented rationale, signed and dated by the Investigator, and filed in the subject medical file or appropriate location.

Patient neurological status can be recorded directly on the eCRF and is considered source data. All other source data entered in the eCRFs should be located in the subject's medical records/source document (electronic or paper), (e.g., hospital records, surgery reports, x-rays, MRIs, CTs, or any other material that contains original information used for data collection including the documentation of AEs

and study source document completed by the Investigator or site staff). Subject completed questionnaires as well as data collected during subject phone calls will be considered as source data.

This study will be conducted using a remote data capture system. The Oracle Clinical Remote Data Capture (RDC) system allows the study centers to enter study data into the sponsor's database over a secure internet connection. Required data will be taken from source documents and directly entered into the study database by authorized site personnel in accordance with applicable regulations.

Every attempt should be made to complete the required onsite clinic visit. However, if the subject is unable to return to the investigational site for their scheduled clinic visit at 3 months and 24 months, the study site can contact the subject and collect the following data remotely using the remote visit source document worksheet:

- Medication
- VAS back and leg pain – conducted by phone or web-based application
- EQ-5D-5L – phone version or web-based application
- ODI – phone version or web-based application
- Adverse events and/or device deficiencies

The Principal Investigator or an individual delegated by the Principal Investigator on the Delegation of Authority Log, is responsible for documenting and entering data for the study on the eCRFs.
Only authorized persons can complete CRFs. CRFs shall be signed by Principal or Sub-Investigators (physicians only) as specified on the Delegation of Authority Log included in the Investigator Site File. The Principal Investigator or delegated Sub-Investigator is required to approve all data on CRFs via electronic signature.

9.8 Deviation Handling

A study deviation is an event where the Investigator or site personnel did not conduct the clinical study according to the Clinical Investigational Plan or Clinical Investigation Agreement. The Investigator is not allowed to deviate from the above-mentioned documents except under emergency circumstances to protect the rights, safety and well-being of human subjects. All deviations shall be documented in the eCRF and explained, regardless the reason for the deviation.

In this post market release study with a prospective design, Protocol Deviations are defined as deviations related to:

- Patient Informed Consent procedure
- Enrolled subject does not meet Inclusion/Exclusion criteria
- Visit not done

- Assessment(s) at the visit not performed
- Visit outside the CIP defined visit window
- Subject did not undergo fenestrated screw procedure as defined in this protocol
- Improper AE / SAE / ADE / SADE / DD reporting
- EC approval not obtained, if required

Medtronic will assess the significance of all deviations and evaluate the need to amend the Clinical Investigation Plan, to early terminate the investigation or site termination in case the deviations only relate to one site, in accordance with Medtronic SOPs.

9.8.1 Request for approval of study deviations

This is a study conducted within the IFU of the used Devices and due to the nature of the Protocol Deviations as defined in the section above pre-approval for study deviations will not be applied in this post market release study.

In any situation during the conduct of this study the Investigator shall exercise his/her judgment to always safeguard the subject's interest independent whether the action to be taken will lead to a Protocol Deviation or not. The Investigator shall report the deviation as soon as possible to Medtronic and the reviewing EC, as required. Medtronic will inform the regulatory authorities, if required.

9.8.2 Reporting requirements for study deviations

The Investigator shall adhere to EC requirements and procedures for reporting study deviations and shall report the deviation as soon as possible to Medtronic. Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, additional training, terminate the study, etc.). Repetitive or serious Investigator compliance issues may result in the need to initiate a corrective action plan, and in some cases, freeze enrollment or ultimately terminate the Investigator's participation in the clinical study. Medtronic will provide investigation site-specific reports to the Investigators on a yearly basis summarizing information on deviations that occurred at the investigational site.

9.8.3 Amendments to the Clinical Investigation Plan

The Investigator will propose any appropriate modification(s) of the Clinical Investigation Plan or investigational device or investigational device use. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

Medtronic will submit any significant amendment to the Clinical Investigation Plan, including a justification for this amendment, to the appropriate regulatory authorities and to the Investigators to obtain approval from their EC and Regulatory Authorities, if applicable. Administrative amendments to

the Clinical Investigation Plan will be submitted to the EC and appropriate regulatory authorities for notification, if applicable.

Furthermore, Investigators shall sign any approved amendment for agreement.

9.9 Subject Withdrawal or Discontinuation

Subjects are free to voluntarily withdraw from the study at any time and for any reason. The Investigator can only withdraw a subject from the study with a valid reason. Withdrawn or exited subjects will be followed under normal medical practice. Examples of reasons for subject discontinuation include, but are not limited to, those listed below:

- Patient Informed Consent procedure not followed
- Subject does not meet all eligibility criteria
- Subject death
- Subject lost to follow-up
- Subject voluntarily withdraws from the study
- Subject did not undergo the fenestrated screw procedure as defined in this protocol

If a subject is withdrawn from the study, the reason for withdrawal (if known) shall be recorded in the eCRF and in the subject's hospital record.

Subjects withdrawn from the study will only be replaced when subjects did not meet baseline eligibility or did not undergo the fenestrated screw procedure as defined in this protocol and if the enrollment is still open.

Compliance to the minimum recommended follow-up schedule is essential to enable the analysis of the results in a scientifically sound and meaningful way. If, for whatever reason, the subject follow-up cannot be scheduled within the time window or occurred outside the time window, it is still essential to schedule a follow-up visit and to document the subject data at a date as close as possible to the calculated follow-up date.

As much as possible, it should be avoided that subjects are lost-to-follow-up and Investigators are urged to do their utmost best to maintain patient's follow-up compliance as per CIP.

9.9.1 Withdrawal of consent:

Subjects may withdraw from the study at any time and for any reason. If a subject withdraws from the study, the reason for withdrawal will be documented, if given by the subject, in the source documents

and in the subject's eCRF. If a subject withdraws consent, they will not be replaced. The follow up of these subjects will be according to the standard of care at the site.

9.9.2 Lost to follow up:

Before considering a subject as lost to follow up, the Investigator should make every attempt to contact the subject (or relevant other persons associated with the subject) to have the subject return for follow-up to determine their clinical status and the occurrence/resolution of AEs, if any.

Before documenting a subject as lost to follow up, the Investigator should document in the eCRF and source documents at least 3 contact attempts with the subject, subject's relatives or other persons associated with the subject. In addition, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights (e.g. if a subject is deceased, the date of death should be completed or if the subject is alive, the date of last contact with subject should be provided).

10. Risks and Benefits

10.1 Potential Risks

In all clinical studies, confidentiality of protected health information (PHI) may be breached due to study-related activities beyond those of routine clinical care. This risk will be minimized by not collecting personally identifying information on case report forms.
The Investigator must continuously monitor, assess and document the risks (Declaration of Helsinki 2013). Medtronic is not aware of any significant problems with this product. In the clinical study, the products will be used in accordance with their labeling; therefore, no risks other than the risks typically associated with a routine device implantation and follow-ups are anticipated. Reference is made to the IFU for a detailed list of all risks and contra-indications associated with the devices. Please specifically note that the CD HORIZON® Legacy™ Fenestrated Screws are contraindicated for pedicular/posterior wall defects and the CD HORIZON® Solera™ Fenestrated Screws are contraindicated for pedicular/posterior wall defects when used with cement.
In addition, subjects are treated according to general clinical practice. No additional risks are associated with participation in this clinical study.

10.1.1 Risk of imaging/Radiation

At baseline, a hip DXA scan or spine qCT-scan will be collected depending on the hospital practice. For some patients/sites the hip DXA scan will be part of their standard of care, while for others this may not be the case. The worldwide average effective dose from natural background radiation is 2.4 mSv/year. An adult hip DXA has been reported to have an effective dose of 0.009 mSV [26]. At baseline and during follow-up, X-ray and/or CT-scan will be collected according to the standard of care so no additional radiation risk is expected. For those countries where the X-ray and/or CT-scan is not standard of care at

the 12-month visit, the patient will be informed about the additional radiation risk and the EC and regulatory body (if applicable) will be notified.

To conclude, the additional radiation risk associated with participation in this clinical study is negligible.

10.2 Potential Benefits

There may be no direct benefits of study participation. However, subject participants may undergo an enhanced level of clinical scrutiny of back health compared to routine clinical care, which may provide some indirect health benefits.

10.3 Risk-Benefit Rationale

Participation in this study will not expose the subject to greater risks than if he/she were receiving the CD HORIZON® Fenestrated Screw Spinal System with Fenestrated Screw Cement outside of the study. There might be other discomforts and risks related to the CD HORIZON® Fenestrated Screw Spinal System with Fenestrated Screw Cement and/or this study that are not foreseen. The risks are minimized by selecting only qualified Investigators experienced in the field of application and trained in the use of the study device(s) and qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation.

11. Adverse Events and Device Deficiencies

All AEs, DDs and deaths, regardless of relatedness to surgical procedure or outcome, should be reported throughout the study in the eCRF and should be made available to the Medtronic study team. If applicable, these AEs and DDs will be reported to other countries where studies are conducted with the same or a similar product. All AEs and DDs will be screened immediately for possible product complaints, to allow compliance with the 48 hours reporting requirement.

11.1 Definitions/Classifications

Medtronic and the Investigator will classify each adverse event according to ISO 14155:2011. Adverse events and device deficiencies are defined as follows

Table 11-1: Definitions

ISO Definitions for Clinical Investigations of Medical Devices for Human Subjects
Adverse Event (AE): *(ISO14155:2011 3.2)* Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device *NOTE 1:* This definition includes events related to the investigational medical device or the comparator. *NOTE 2:* This definition includes events related to the procedures involved. *NOTE 3:* For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse Device Effect (ADE): *(ISO14155:2011 3.1)* Adverse event related to the use of an investigational medical device *NOTE 1:* This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. *NOTE 2:* This definition includes any event resulting from use error or from intentional misuse of the investigational medical device
Device Deficiency (DD): *(ISO 14155:2011 3.15; ISO 14155:2011 3.27; ISO 14155:2011 3.43)* Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Note: Device deficiencies include malfunctions, use errors, and inadequate labeling. • Malfunctions: Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or Clinical Investigational Plan (CIP) • Use Error: Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user Note: Use error includes slips, lapses, and mistakes. Note: An unexpected physiological response of the subject does not in itself constitute a use error.
SERIOUSNESS
Serious Adverse Event (SAE): *(ISO 14155:2011 3.37)* An adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in • a life-threatening illness or injury, or

• a permanent impairment of a body structure or a body function, or • in-patient or prolonged hospitalization, or • medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to foetal distress, foetal death or a congenital abnormality or birth defect. *NOTE:* Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE): *(ISO 14155:2011 3.36)* Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.
Unanticipated Serious Adverse Device Effect (USADE): *(ISO 14155:2011 3.42)* Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report *NOTE:* Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

RELATEDNESS	
Relationship of Adverse Events	The Investigator's assessment of causality must be provided for all adverse events. Adverse events that are related or possibly related to the device, index surgical procedure, or both will be assessed for this study on the following basis: **1. Not related**: relationship to the device or procedures can be excluded when: • The event is not a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has no temporal relationship with the use of the investigational device or the procedures; • the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; • the discontinuation of medical device application or the reduction of the level of activation/exposure when clinically feasible and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;

	• the event involves a body-site or an organ not expected to be affected by the device or procedure; • the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); • the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; • harms to the subject are not clearly due to use error. To establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event. **2. Unlikely**: The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained. **3. Possible**: The relationship with the device is weak but cannot be ruled out completely; alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible. **4. Probable**: The relationship with the use of the device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained. **5. Causal relationship**: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when: • the event is a known side effect of the product category the device • belongs to or of similar devices and procedures; • the event has a temporal relationship with the investigational device • use/application or procedures; • the event involves a body-site or organ that ○ the investigational device or procedures are applied to; the investigational device or procedures have an effect on; the serious event follows a known response pattern to the medical device (if the response pattern is previously known); • the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);

	• other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; • harm to the subject is due to error in use; • the event depends on a false result given by the investigational device used for diagnosis, when applicable; • In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device /procedures and the serious event.
SECONDARY SPINAL SURGICAL PROCEDURES	
Secondary spinal surgical procedures	Secondary spinal surgical procedures will be classified using the following definitions, based on the description provided: • **Revision**: A procedure that adjusts or in any way modifies the original implant configuration at the index level(s). This includes implantation of any product to enhance fusion, such as autogenous or allogenic bone graft, bone graft substitutes, or bone growth stimulators. This also includes replacement of any device component; supplemental placement of a spinal fixation system; or an uninstrumented posterior, posterolateral, or anterior fusion surgical intervention. • **Removal**: A procedure that removes one or more components of the original implant configuration. Possible reasons for removals can be elective (subject preference) or non-elective (surgeon clinical decision). Non-elective removal is the result of an adverse event or treatment failure. This may occur in the case of migrated, bent, broken or infected device components. Whether removal is elective or non-elective, fusion or non-fusion should be noted at the index level(s). • **Reoperation**: Any surgical procedure at the index level that is not classified as a revision or removal. • **Other**: Any additional surgical procedure not classified as a revision, removal or reoperation. **Note**: Although the use of external bone growth stimulators will not be considered a subsequent/secondary surgical procedure, use of external bone growth stimulators to treat the index level(s) will be documented and summarized.

11.2 Reporting of Adverse Events

All adverse events will be considered reportable for this study.

Pain, neurological and function symptoms should be reported as an adverse event when a subject's complaint for any of these symptoms results in an unscheduled visit or when a subject presents with new or worsening pain, neurological and/or function symptoms as compared to the previous visit.

All adverse events will be classified using the following responsibility matrix:

Table 11-2: Event Classification Responsibilities

What is Classified	Who Classifies	Classification Parameters
Relatedness	Investigator and Medtronic	Procedure related Device related
USADE potential	Medtronic	USADE
Seriousness	Investigator and Medtronic	SAE/SADE
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data

All reportable events must be recorded from procedure start onwards in the subject's medical record and on the Adverse Event and/or Device Deficiency eCRF and promptly reported to Medtronic. Procedure start for this study is defined as the time when a patient is prepared for the surgery prior to entry to the operating room theater. EC reporting must be completed in accordance with the policies of the governing EC. Regulatory Authority reporting should be in accordance with applicable local regulations.

It is the responsibility of the Investigator to identify the occurrence of adverse events and device deficiencies and to ensure the required information is accurately documented on the eCRF.
Reports of adverse events and device deficiencies will include the following information, at a minimum:

- Date of event
- Diagnosis or description of the event
- Assessment of the seriousness and relationship to the device and/or index surgical procedure
- Treatment provided
- Outcome and date of resolution

The clinical course of each adverse event must be followed until resolution, subject discontinuation from the study or last study follow up visit, whichever comes first. "Not resolved" adverse events and device deficiencies must be assessed at each protocol required visit, and new or updated information must be documented on the Adverse Event and/or Device Deficiency eCRF and promptly reported to Medtronic and if applicable to the EC. At time of study exit the status of all unresolved Adverse Events should be evaluated and should reflect subject' status at time of study exit.

If necessary, the Investigator may report to the sponsor initially by telephone or email and follow-up with completed eCRFs and, upon request of Medtronic, de-identified source documentation regarding the event (e.g., physician/nurse notes or summaries) should be provided to Medtronic. When printouts of original electronic source documents are obtained, these shall be signed and dated by a member of the Investigator site team with a statement that this is a true reproduction of the original source document. Medtronic study personnel will promptly review all reported adverse events and device deficiencies and if necessary request clarification and/or additional information from the Investigator. If Medtronic disagrees with the Investigator's assessment of the adverse event relationship to the device and/or procedure, Medtronic study personnel will document the disagreement and report or ensure reporting of both opinions to the EC and regulatory authority as necessary. In addition, aggregate safety data will be reviewed and analyzed to identify potential safety issues, signals, and trends at minimum, annually after start of subject enrollment.

11.3 Not reportable events

Examples of events that are not reportable as adverse events for this study are:

- Inability to successfully perform the procedure, unless injury or device deficiency occurs.
- A documented pre-existing condition unless there is a worsening of the nature, severity, duration, or frequency of that condition.
- Pre-planned medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion, cosmetic elective surgery); however, the condition leading to the procedures might be a reportable event if there is a worsening of the nature, severity, duration, or frequency of that condition.

Table 11-3 provides a list of expected surgical events. An expected surgical event will not be considered reportable unless it worsens or is present outside the stated timeframe post-procedure.

Table 11-3: Expected Surgical Adverse Events and Duration

Event Description	Timeframe from the Surgical Procedure
Anesthesia related nausea / vomiting	24 hours
Low-grade fever (<100°F or 37.8°C)	48 hours
Mild to moderate bruising / ecchymosis	7 days
Seroma	72 hours
Sleep problems (insomnia)	72 hours

11.4 Device Deficiencies

A device deficiency (DD) is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling. All device deficiencies must be documented and submitted to Medtronic on the Device Deficiency eCRF. In addition, the Investigator must also determine and document on the eCRF device deficiencies that did not lead to adverse event but could have led to a serious adverse device effect:

- if either suitable action had not been taken,
- if intervention had not been made, or
- if circumstances had been less fortunate
- Refer to Table 14-1 for Investigator reporting timelines for device deficiencies.

11.5 Reporting Adverse Events, Serious Adverse Events, Serious Adverse Device Effects, and Device Deficiencies to Medtronic

Reporting timelines can be found in Table 14-1. The preferred way of transmission of AEs and DDs is the Oracle Clinical (eCRF) system, but in case the eCRF cannot be accessed, the Investigator can send an email to rs.mstsafetyspine@medtronic.com.

The AE/DD worksheet that can be found in the patient binders may be used for completion of available information, preferably signed by Investigators and attached to the email.

The same CIP reporting timelines apply for all types of reporting as if the eCRF would be available.

11.6 Deaths

All subject deaths must be reported to Medtronic and the EC as soon as possible, after learning of a subject's death, regardless of whether or not the death is related to the device system and/or procedure. The Investigator should also attempt to determine, as conclusively as possible, whether such deaths are related to the device system and/or procedure. If the death is evaluated as device and/or procedure related and unanticipated, the event will be reported as a USADE by Medtronic or its designee to the appropriate regulatory agencies.

Any subject death will be reported on the Adverse Event and Study Exit eCRFs. If limited information is known, the Adverse Event eCRF must be completed with available information as soon as possible.

12. Data Review Committees

This study will not use a Clinical Events Committee or Data Monitoring Committee. All devices will be used according to the IFU and patients will be treated according to general clinical practice. Aggregate safety

data will be reviewed and analyzed to identify potential safety issues, signals and trends at minimum, annually after start of subject enrollment.
If a death occurs attributable to the FNS cement, the study will be terminated.

13. Statistical Design and Methods

This is a prospective, single arm and multicenter evaluation of the CD HORIZON® Fenestrated Screw Spinal System with Fenestrated Screw Cement used in the treatment of spinal conditions in subjects with compromised bone quality.

The Statistical Analysis Plan (SAP) will be developed prior to data analysis and will include a comprehensive description of the statistical methods used for the final study report. Any change from the original SAP will be reported in the final study report, along with justification for the change(s).

13.1 Statistical Methods

The primary endpoint of the study is the improvement of ODI at 12-month visit from baseline and the primary objective of the study is to demonstrate that the improvement of ODI at 12-month visit from baseline is significantly greater than 0 for each indication subgroup.

The null hypothesis is H_0: $u_{\_ODI} \leq 0$, and the alternative hypothesis is H_a: $u_{\_ODI} > 0$ where $u_{\_ODI}$ is the mean improvement of ODI score at 12 months from baseline.

A paired t-test for normally distributed data or Wilcoxon signed rank test for not normally distributed data will be carried out to test whether the mean improvement from baseline is significantly greater than 0. If p-value is ≤ 0.05, then primary objective is met. In addition, the descriptive statistics including mean, standard deviations, minimum and maximum will be presented.

For the secondary endpoints including improvement of ODI from baseline at 3- and 24-month visit, improvement of VAS back and leg pain score from baseline at 3-, 12- and 24-month visit and improvement of EQ-5D 5L from baseline at 3-, 12- and 24-month visit, similar methods as the one used for the primary endpoint will be used.

For the secondary endpoints including neurological success at 12-month visit, intraoperative cement extravasation/leakage, pedicle screw instrumentation stabilization at 12-month visit and fusion success at 12-month visit, simple frequencies will be summarized. As for secondary endpoints including Device and/or procedure related adverse events through 24-months and secondary spinal surgeries at index and/or adjacent level(s), resulting from an AE, up to 24 months after the surgery, the event rate will be estimated using time-to-event analysis.

The above analyses will be done separately for each indication subgroup. For the deformity group, the secondary endpoints, change in coronal and sagittal spinopelvic parameters from baseline at 12-month visit, will be analyzed using the same method as the one for the primary endpoint.

13.2 Sample Size

For the primary endpoint, conservatively assuming the true mean improvement from baseline at 12-month visit to be 10 and the standard deviation is 24, the required sample size is 38 using alpha level = 0.05 and 80% power. Again, conservatively assuming 20% attrition rate, the requirement sample size is 48. The study plans to enroll around 50 subjects (no less than 48 subjects) in each indication subgroup.

13.3 Analysis Dataset

All the analysis will be based on the primary dataset which consists of all subjects who are enrolled in this study, undergo the intended surgical procedure and receive the study device. The per-protocol dataset, which excludes from the primary dataset all subjects who violate inclusion/exclusion criteria may also be derived in the case there are a meaningful number of major protocol deviations.

Subjects from all sites will be pooled together. The analysis will be based on the observed data. Missing data will not be imputed.

13.4 Interim Analysis

An interim analysis will be performed when all the subjects in the degenerative spinal disease indication subgroup have reached the 12-month visit. We anticipate that all 12-month clinical outcomes including the primary endpoint will be finalized at the time of interim analysis. Hence the conclusion on the primary objective should remain unchanged when conducting the final analysis.

14. Ethics

14.1 Statement(s) of Compliance

The study will be conducted in accordance with this protocol, ISO14155:2011 and the ethical principles that have their origin in the Declaration of Helsinki 2013, all applicable laws and regulatory requirements of the countries in which the study is conducted, including data protection laws and the clinical trial agreement.

The principles of the Declaration of Helsinki have been implemented in this study by means of the patient informed consent process, EC approval, risk benefit assessment, study training, clinical trial registration, and publication policy. Study Investigators will be required to sign an Investigator Statement stating their intent to adhere to applicable regulations.

The clinical investigation shall not begin at any site until the required approval/favorable opinion from the Ethics Committee (EC) or notification/approval from a regulatory authority have been obtained, if appropriate.

Any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

14.2 Principal Investigator Obligation

Each site will have a Principal Investigator (PI). The PI has overall responsibility for the day-to-day conduct of the trial at the site and for the integrity of the trial data generated by their site. Specifically, the PI is responsible for the following:

- Protecting the rights, safety, and welfare of the subjects in their care
- Obtaining written informed consent of all subjects prior to any trial-related procedures, and only after Ethics Committee and regulatory approval (if applicable) of the trial
- Obtaining and maintaining Ethics Committee approval
- Conducting the investigation in accordance with the signed agreement, clinical investigation plan, applicable laws and regulations, and any conditions of approval imposed by an Ethics Committee or regulatory authority
- Providing accurate financial disclosure to the sponsor, including any relevant changes during the course of the trial and for 1 year after the completion of the trial.
- Reporting adverse events and device deficiencies in accordance with the CIP and according to country regulations
- Approving all case report forms (or authorizing a Sub-Investigator to do so); approval of the case report form indicates the data represented are accurate and have been reviewed.
- Maintaining accurate, complete, and current records, including:
    - All correspondence with another Investigator, the sponsor, the monitor, the Ethics Committee (including required reports), or regulatory agency
    - Records of each consented subject's case history signed and dated informed consent(s), exposure to the device, eCRFs, and source documents
    - The CIP, and documentation of dates of and reasons for each protocol deviation
    - Any records required by a regulatory agency
- Ensuring that clinical records are clearly marked to indicate that the subject is enrolled in the study.
- Allowing time with the trial monitor and Sponsor trial staff members during Sponsor site visits
- Informing the sponsor if any action is taken by an Ethics Committee or regulatory authority

Failure to perform the Investigator obligations or to complete corrective and preventive actions identified during monitoring or auditing activities may result in Principal Investigator or site personnel disqualification, and/or lead to suspension or termination of the study at the site.

14.3 Reporting requirements

Table 14-1 includes minimum reporting requirements for Investigators participating in studies in Europe. Medtronic study personnel will immediately report Adverse Events and Device Deficiencies, related to CE marked devices used during the study, to Medtronic's Complaint Handling Unit who will ensure prompt review, and appropriate reporting.

Table 14-1: Reporting requirements

Serious Adverse Events (SAEs)	
Investigator submit to:	
Medtronic	Immediately after the Investigator first learns of the event or of new information in relation with an already reported event (within 3 calendar days).
EC	Reporting timeframe as per local EC per local requirement.
Sponsor submit to:	
EC	Reporting timeframe as per local EC per local requirement.
Regulatory Authorities	Reporting timeframe as per local requirement.
Serious Adverse Device Effects (SADEs)	
Investigator submit to:	
Medtronic	Immediately after the Investigator first learns of the event or of new information in relation with an already reported event (within 3 calendar days).
EC	Reporting timeframe as per local EC per local requirement.
Sponsor submit to:	
EC	Reporting timeframe as per local EC per local requirement.
Regulatory Authorities	Reporting timeframe as per local requirement.

Unanticipated Serious Adverse Device Effects (USADEs)	
Investigator submit to:	
Medtronic	Immediately after the Investigator first learns of the event or of new information in relation with an already reported event (within 3 calendar days).
EC	Reporting timeframe as per local EC per local requirement.
Sponsor submit to:	
Investigators	Notification as soon as possible and not later than 10 working days after the sponsor first learns of the effect.
EC	Reporting timeframe as per local EC per local requirement.
Regulatory Authorities	Reporting timeframe as per local requirement.
All Other Adverse Events	
Investigator submit to:	
Medtronic	Submit within 20 calendar days after the Investigator first learns of the event.
EC	Reporting timeframe as per local EC per local requirement.
Device Deficiencies (DD) with SADE potentials	
Investigator submit to:	
Medtronic	Immediately after the Investigator first learns of the deficiency or of new information in relation with an already reported deficiency (within 3 calendar days).
EC	Reporting timeframe as per local EC requirement.
Sponsor submit to:	
EC	Reporting timeframe as per local EC requirement.
Regulatory Authorities	Reporting timeframe as per local requirement.
All other Device Deficiencies	
Investigator submit to:	
Medtronic	Submit within 20 calendar days after the Investigator first learns of the deficiency.

EC	Reporting timeframe as per local requirement.
Withdrawal of EC Approval	
Investigator submit to:	
Medtronic	Report a withdrawal of the reviewing EC approval **within 5 days** of Investigator notification.
Interim Reports and Final Report	
Investigator submit to:	
EC	Study reports must be submitted as required by EC per local requirement.
Sponsor submit to:	
Regulatory Authorities	Study reports must be submitted as required by applicable local regulation.

14.4 Oversight of Study Personnel

The Principal Investigator may delegate study-related tasks to appropriate trained and qualified personnel to ensure alignment between contractual obligations and delegated study responsibilities.

The delegation of study-related tasks will be documented on the Delegation of Authority Log and the Principal Investigator will provide ongoing oversight of all delegated study-related tasks.

The Principal Investigator will ensure training is provided, completed and documented for all staff performing delegated study-specific tasks.

At a minimum, the training will consist of the following items:

- Clinical Investigation Plan (CIP)
- Informed consent process (covered by CIP training)
- Data collection tools
- Regulations

Study center personnel participating in the clinical study will be trained in study activities relevant to their role. Training must be completed and documented prior to that individual conducting any study related activities.

Investigator and/or study coordinator meeting(s) or telephone conference call(s) may be held to discuss the Clinical Investigation Plan (CIP), training, study results, etc. Continued training may occur through interim meetings or telephone conference calls to discuss relevant study issues.

14.5 Medtronic Representative Role

Medtronic representatives may provide support as required for the study under the direct supervision of the principal Investigator as described below. The Principal Investigator or a person designated on the Delegation of Authority Log must be present to collect source documentation, record the study activities, and to be responsive to the subject's needs during an activity performed by a Medtronic representative.

Medtronic personnel may:

- Provide technical support during the procedure and follow-up visits
- This support may include the training of site personnel on the use of the Medtronic equipment or CIP-related procedures and data collection
- Clarify device behavior, operation, or diagnostic output as requested by the Principal Investigator or other health care professional
- Assist with the collection of technical data during the procedure (technical worksheets)

Medtronic personnel may not:

- Practice medicine, provide medical diagnoses or make decisions related to subject treatment/care
- Express opinions about the product/feature under study
- Assist the subject by direct physical contact except as required by the specific protocol-related task to be conducted
- Discuss a subject's condition or medical treatment with the subject or a member of the subjects' family
- Provide the subject with any form/questionnaires related to the product(s) under investigation
- Enter data on eCRFs, except on the Medtronic Use Only Field

15. Study Administration

15.1 Site activation

During the activation process (prior to subject enrollment), Medtronic will train site personnel on the Clinical Investigation Plan, relevant standards and regulations, informed consent process, and on data collection and reporting tools. If new members join the investigation site team afterwards, they will receive training on the applicable clinical study requirements relevant to their role before contributing to the clinical study.

Prior to performing study related activities, all local regulatory requirements shall be fulfilled, including, but not limited to the following:

- Ethics Committee approval (and voting list, as required by local law) of the current version of the CIP and Patient Informed Consent.
- Regulatory authority approval or notification (as required per local law)
- Fully executed Clinical Trial Agreement (CTA)
- Financial Disclosure
- Curriculum Vitae of Investigators and key members of the investigation site team (as required by local law)
- Documentation of delegated tasks
- Documentation of study training

Medtronic will provide each study center with documentation of investigation site/Investigator readiness; this letter must be received prior to subject enrollment.

15.2 Monitoring

Monitoring visits will be conducted at the start, during and at the closure of the clinical study in accordance with Medtronic SOPs and the monitoring plan. The sponsor will adhere to the monitoring plan which contains the strategy for frequency of monitoring visits and source data verification to be performed for this study. Medtronic is responsible for ensuring the proper conduct of this study in terms of adherence to applicable regulations, protocol compliance, and the validity and accuracy of the study data entered on eCRFs. The Principal Investigator and site personnel will provide the Medtronic monitor(s) with complete access to primary source data (e.g., paper and electronic hospital/clinical charts, appointment books, laboratory records) that support the data on the eCRFs as well as other documentation supporting the conduct of the study. The monitor will perform source data verification and routine reviews of study-related regulatory documents during scheduled monitoring visits and work to secure compliance should any deficiencies be observed. Monitoring frequency may be increased if there are changes in study center personnel (to allow for training and additional sponsor oversight), a protocol amendment/safety issue that significantly affects study procedures or design, a documented or suspected lack of study compliance or Investigator oversight, or an issue with recruitment or enrollment.

15.3 Data Management

Medtronic personnel will perform routine edit and consistency checks for items such as missing data or inconsistent data. Identified data inconsistencies will be resolved by use of data discrepancies; Investigators and site personnel will review data discrepancies and respond to the discrepancies in a timely manner. The resolved discrepancy will become a part of the eCRF record for the subject.

The Oracle Clinical Remote Data Capture (RDC) system which is 21CFR§11 Part E compliant controls user access and ensures data integrity. This system is a fully validated system. The RDC system maintains an audit trail of entries, changes or corrections in eCRFs. User access will be granted to each individual based on his or her delegation of authority and completion of required training. If a person only authorized to complete eCRFs makes changes to an already signed eCRF, the system will require the Principal Investigator, or authorized Sub-Investigator, to re-sign the eCRF.

The Principal Investigator, or designated Sub-Investigator, is responsible for the data submitted and must review all data for accuracy and provide his/her approval of the eCRF and sign each form with an electronic signature.

15.4 Direct Access to Source Data/Documents

The Investigator(s)/institution(s) will permit study-related monitoring, audits, EC review, and regulatory inspection(s), providing direct access to source data/documents.

Medtronic or third-party auditors representing Medtronic may perform Quality Assurance audits to verify the performance of the monitoring process and study conduct, and to ensure compliance with applicable regulations. Representatives for regulatory bodies such as the FDA may also perform site inspections related to this clinical study. The Principal Investigator, site personnel, and institution will provide auditors with direct access to primary source data and all study-related documentation.

Medtronic will investigate, and report suspected cases of fraud or misconduct as appropriate.

15.5 Confidentiality

Subject confidentiality will be maintained throughout the clinical study to the extent permitted by law. That is, every attempt will be made to remove subject identifiers from clinical study documents. For this purpose, a unique subject identification code (site number and subject number) will be assigned and used to allow identification of all data reported for each subject. This will also ensure that the information can be tracked back to the source data.
The sponsor, Medtronic, will collect this key-coded data and monitor study records. Third parties e.g. auditors, ECs, Governmental regulatory authorities may also have access to the study records. Participating patients will not be identified by name in any published reports about this study.

15.6 Liability

Medtronic Bakken Research Center BV is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the EC, and/or the governing regulatory authority (if applicable).

15.7 CIP Amendments

Protocol amendments may be initiated by Medtronic to address changes to the conduct of the study.

Protocol amendments must be approved by Medtronic and submitted to the ECs and the governing regulatory authority (if required); protocol amendment approval and approval of any associated changes to the informed consent document must be obtained prior to implementation of the amendment except:

- When necessary to eliminate an immediate/or apparent immediate hazard to participating subjects
- When the change involves purely administrative or logistical aspects of the study

15.8 Record Retention

The Investigator or the medical institution where the study was conducted must retain the Investigator Site File, patient medical files and CRFs in accordance with local law and regulations for a minimum period of 5 years (or longer if local laws require) after study completion. The Investigator or the medical institution where the study was conducted should take measures to prevent accidental or early destruction of the clinical study related materials.

Medtronic will retain the study records according to Medtronic policy.

15.9 Publication and Use of Information

Medtronic intends to publish the results from the FNS study in a timely manner as data become available. These publication activities may include abstracts, presentations/posters to scientific meetings, and manuscripts.

Investigators who gathered data for this study (i.e., enrolled subjects and complied with the protocol) may be asked to write or contribute to the writing of abstracts and manuscripts based on the results of this study. Principal Investigators who meet the study-specific criteria above will be considered for abstract/manuscript authorship if they meet the International Committee of Medical Journal Editors,

Ethical Considerations in the Conduct and Reporting of Research criteria available via the following link: http://www.icmje.org. Specifically, authorship credit should be based on the following and should meet all criteria listed below:

- Substantial contributions to conception or design; or the acquisition, analysis and interpretation of data for the work;
- Drafting the article or revising it critically for important intellectual content;
- Final approval of the version to be published; and

- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Medtronic employees who meet the International Committee of Medical Journal Editors criteria for authorship will have the right to authorship.

All contributors who do not meet the criteria for authorship are to be listed in an acknowledgments section according to the guidelines of the applicable scientific journal. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair that provided only general support.

Before publication of any study-related data, the following guidelines will apply:

- Investigators are obligated to provide Medtronic with an opportunity to review any publication developed from data derived from this study.
- Medtronic will not financially compensate health care professionals (HCPs) or health care organizations (HCOs) for writing or editing activities on scientific publications related to research sponsored by Medtronic.

15.10 Suspension or Early Termination

Medtronic reserves the right to suspend or terminate the study at any time. Reasons may include, but are not limited to, the following:

- Insufficient enrollment to complete the study within the expected timeframe
- Identification of unacceptable safety profile; suspicion of an unacceptable risk will result in a suspension, confirmation of an unacceptable risk will result in termination
- If a death occurs attributable to the FNS cement, the study will be terminated.
- Product performance/product supply issues
- EC or governing regulatory authority (if applicable) suspension and/or termination of the study

Medtronic reserves the right to suspend or terminate the study at an individual site. Reasons may include, but are not limited to, the following:

- Noncompliance with the protocol
- Serious or repeated deviations at the site
- Failure to implement required corrective and preventive actions
- Insufficient enrollment to complete the study within the expected timeframe

- Loss of appropriately trained site personnel

Investigators are required to notify the EC of study suspension/termination. Subjects will be notified by the Investigator of suspension/termination due to unacceptable risk or of termination due to any other cause.

If, for any reason, Medtronic suspends or prematurely terminates the investigation at an individual investigation site, Medtronic shall inform the responsible regulatory authority as appropriate and ensure that the EC is notified, either by the Principal Investigator or by Medtronic. If the suspension or premature termination was in the interest of safety, Medtronic shall inform all other Principal Investigators and investigational sites. The Principal Investigator or authorized designee shall promptly inform the enrolled subjects at his/her investigation site, if appropriate.

16. References

1. Wittenberg, R.H., et al., *Importance of bone mineral density in instrumented spine fusions.* Spine (Phila Pa 1976), 1991. **16**(6): p. 647-52.
2. Halvorson, T.L., et al., *Effects of bone mineral density on pedicle screw fixation.* Spine (Phila Pa 1976), 1994. **19**(21): p. 2415-20.
3. Chin, D.K., et al., *Prevalence of osteoporosis in patients requiring spine surgery: incidence and significance of osteoporosis in spine disease.* Osteoporos Int, 2007. **18**(9): p. 1219-24.
4. Becker, S., et al., *Assessment of different screw augmentation techniques and screw designs in osteoporotic spines.* Eur Spine J, 2008. **17**(11): p. 1462-9.
5. Pare, P.E., et al., *Biomechanical evaluation of a novel fenestrated pedicle screw augmented with bone cement in osteoporotic spines.* Spine (Phila Pa 1976), 2011. **36**(18): p. E1210-4.
6. Chang, M.C., C.L. Liu, and T.H. Chen, *Polymethylmethacrylate augmentation of pedicle screw for osteoporotic spinal surgery: a novel technique.* Spine (Phila Pa 1976), 2008. **33**(10): p. E317-24.
7. Sawakami, K., et al., *Polymethylmethacrylate augmentation of pedicle screws increases the initial fixation in osteoporotic spine patients.* J Spinal Disord Tech, 2012. **25**(2): p. E28-35.
8. Janssen, I., et al., *Risk of cement leakage and pulmonary embolism by bone cement-augmented pedicle screw fixation of the thoracolumbar spine.* Spine J, 2017.
9. Akinola, B., et al., *Pulmonary cement embolism during cement augmentation of pedicle screw fixation: a case report.* J Orthop Surg (Hong Kong), 2010. **18**(3): p. 364-6.
10. Dai, F., et al., *Surgical treatment of the osteoporotic spine with bone cement-injectable cannulated pedicle screw fixation: technical description and preliminary application in 43 patients.* Clinics (Sao Paulo), 2015. **70**(2): p. 114-9.

11. Hu, M.H., et al., *Polymethylmethacrylate augmentation of the pedicle screw: the cement distribution in the vertebral body.* Eur Spine J, 2011. **20**(8): p. 1281-8.

12. Lubansu, A., et al., *Minimally invasive spinal arthrodesis in osteoporotic population using a cannulated and fenestrated augmented screw: technical description and clinical experience.* Minim Invasive Surg, 2012. **2012**: p. 507826.

13. Pinera, A.R., et al., *Instrumented lumbar arthrodesis in elderly patients: prospective study using cannulated cemented pedicle screw instrumentation.* Eur Spine J, 2011. **20 Suppl 3**: p. 408-14.

14. Moon, B.J., et al., *Polymethylmethacrylate-augmented screw fixation for stabilization of the osteoporotic spine : a three-year follow-up of 37 patients.* J Korean Neurosurg Soc, 2009. **46**(4): p. 305-11.

15. Mueller, J.U., et al., *Cement leakage in pedicle screw augmentation: a prospective analysis of 98 patients and 474 augmented pedicle screws.* J Neurosurg Spine, 2016. **25**(1): p. 103-9.

16. Girardo, M., et al., *Surgical treatment of osteoporotic thoraco-lumbar compressive fractures: the use of pedicle screw with augmentation PMMA.* Eur Spine J, 2017.

17. Guan, H., et al., *Early or delayed operation, which is more optimal for kyphoplasty? A retrospective study on cement leakage during kyphoplasty.* Injury, 2012. **43**(10): p. 1698-703.

18. Lee, I.J., et al., *CT evaluation of local leakage of bone cement after percutaneous kyphoplasty and vertebroplasty.* Acta Radiol, 2010. **51**(6): p. 649-54.

19. Amendola, L., et al., *Fenestrated pedicle screws for cement-augmented purchase in patients with bone softening: a review of 21 cases.* J Orthop Traumatol, 2011. **12**(4): p. 193-9.

20. Chandra, V.V., et al., *Segmental polymethylmethacrylate-augmented fenestrated pedicle screw fixation for lumbar spondylolisthesis in patients with osteoporosis - A case series and review of literature.* Neurol India, 2017. **65**(1): p. 89-95.

21. Triebel, J., et al., *Women do not fare worse than men after lumbar fusion surgery - Two-year follow-up results from 4,780 prospectively collected patients in the Swedish National Spine Register with lumbar degenerative disc disease and chronic low back pain.* Spine J, 2017. **17**(5):p. 656-662.

22. Dimar, J.R., et al., *Clinical and radiographic analysis of an optimized rhBMP-2 formulation as an autograft replacement in posterolateral lumbar spine arthrodesis.* J Bone Joint Surg Am, 2009.**91**(6):p. 1377-1386.

23. Fairbank, J.C. and P.B. Pynsent, *The Oswestry Disability Index.* Spine (Phila Pa 1976), 2000. **25**(22): p. 2940-52; discussion 2952.

24. Kind, P., *The EuroQol instrument: an index of health-related quality of life*, in *Quality of Life and Pharmacoeconomics in Clinical Trials*. 1996. p. 191-201.

25. Schwab F., *Scoliosis Research Society - Schwab Adult Spinal Deformity Classification.* Spine (Phila Pa 1976), 2012. **37**(12): p. 1077-82.

26. Damilakis J., *Radiation exposure in X-ray-based imaging techniques used in osteoporosis.* Eur Radiol, 2010. **20**(11):p.2707-2714.

17. Appendices

17.1 Sponsor contact information

Detailed sponsor contact information not outlined in the Clinical Investigational Plan will be provided under a separate cover.

17.2 Participating Investigators and Investigation Sites

At the time of completion of the FNS study Clinical Investigation Plan, site selection is not yet complete. Therefore, a complete list of names, addresses, and professional positions of the clinical Investigators and clinical investigation sites will be distributed under a separate cover when available.

18. Version History

Version	Summary of Changes	Author(s)/Title
1.0, 1 AUG 2018	• Initial release	Ellen Konings, Clinical Study Manager
2.0, 19 SEP 2018	**3. SYNOPSYS** • Page 8 (page 8 in CIP v1.0): The sentence "*one of the following indications*" has been replaced with "*one or more of the following diagnostic indications*". • Page 8 and 10, (page 8 and 10 in CIP v1.0): *scoliosis*, *kyphosis* and *lordosis* have been removed from the examples of deformity indications. • Page 10 (page 10 in CIP v1.0): The sentence "*one of the following*	Beatrice C. Sicurella, Clinical Study Manager

	diagnostic indications" has been replaced with "*one or more of the following diagnostic indications*". • Page 11 (page 11 in CIP v1.0): the sentence "*Has documented allergy to the instrumentation materials that will be used for the procedure (e.g. titanium alloys, cobalt-chromium-molybdenum alloys and PMMA Fenestrated Screw Cement)"* has been changed to "*Has documented allergy to the materials that will be used in the surgical or any imaging procedure (e.g. titanium alloys, cobalt-chromium-molybdenum alloys, PMMA Fenestrated Screw Cement, contrast medium).* **7.0 PRODUCT DESCRIPTION** • Page 20 (page 20 in CIP version 1.0): "*polymethymethacrylate"* has been corrected to "*polymethylmethacrylate".* **8.0 SELECTION OF SUBJECTS** • Page 23 and 24 (page 23 and 24 in CIP v1.0): *scoliosis*, *kyphosis* and *lordosis* have been removed from the examples of deformity indications. • Page 23 (page 23 in CIP version 1.0): The sentence "*one of the following conditions*" has been replaced with	

	"*one or more of the following conditions*". • Page 25 (page 25 in CIP v1.0): the sentence "*Has documented allergy to the instrumentation materials that will be used for the procedure (e.g. titanium alloys, cobalt-chromium-molybdenum alloys and PMMA Fenestrated Screw Cement)"* has been changed to "*Has documented allergy to the materials that will be used in the surgical or any imaging procedure (e.g. titanium alloys, cobalt-chromium-molybdenum alloys, PMMA Fenestrated Screw Cement, contrast medium).*	