



CLINICAL STUDY PROTOCOL

Protocol Title: The INSPIRE Study: InVivo Study of Probable Benefit of the *Neuro-Spinal Scaffold™* for Safety and Neurologic Recovery in Subjects with Complete Thoracic AIS A Spinal Cord Injury

Investigational Product Name: *Neuro-Spinal Scaffold™*

Protocol Number: InVivo-100-101

Protocol Date/Version: 29 June 2017, v12.1

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PROTOCOL APPROVAL

Protocol Number:	InVivo-100-101
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**Principal Investigator's
Statement and Signature:**

I, the undersigned, have read protocol InVivo-100-101 (including all appendices). I agree to conduct the clinical study as described and in compliance with International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements. I agree to inform all who assist me in the conduct of this study of their responsibilities and obligations.

Signature of Principal Investigator

Date

Name of Principal Investigator (printed)

Investigative Site Name, Address and Telephone Number:

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1 PROTOCOL SYNOPSIS

Protocol Title:	The INSPIRE Study: InVivo Study of Probable Benefit of the <i>Neuro-Spinal Scaffold™</i> for Safety and Neurologic Recovery in Subjects with Complete Thoracic AIS A Spinal Cord Injury
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Study Phase:	Pivotal
Study Design:	Open-label, non-randomized, single-arm, multicenter
Study Duration:	10 years from date of Scaffold implantation <u>Primary Endpoint:</u> 6-months post-Scaffold implantation <u>Long-term Follow-up Period:</u> 6-months through 10 years post-Scaffold implantation (in-clinic visits through 24-months; annual telephone follow-up years 3 to 10 post-Scaffold implantation)
Study Objectives:	Primary Objective: To evaluate whether the Scaffold is safe and demonstrates probable benefit for the treatment of complete T2-T12 spinal cord injury. Regulatory Objective: This is a Humanitarian Device Exemption (HDE) Probable Benefit study to demonstrate safety and probable benefit in support of future studies and an HDE application with subsequent approval.
Investigational Product:	The investigational product (" <i>Neuro-Spinal Scaffold™</i> " or "Scaffold") is a porous bioresorbable polymer scaffold comprising a synthetic biomaterial, poly(lactic-co-glycolic acid)-b-poly(L-lysine) (PLGA-PLL). The Scaffold is cylindrical in shape and comes in 2 sizes, 2 mm diameter by 10 mm length and 3 mm diameter by 10 mm length. The Scaffold is designed for optimal fit in the intraspinal lesion cavity and can be trimmed if necessary to a specific length. Based upon pre-clinical testing, the Scaffold is expected to be resorbed from the site of implant within 4 to 8 weeks.

- Intended Use:** The Scaffold is intended for use in patients age 16 – 70 years diagnosed with a T2 - T12 neurological level of injury functionally complete (AIS A) spinal cord injury, for whom open spine surgery (e.g., laminectomy, spine stabilization) which allows access to the dura of the injured spinal cord is recommended as an option. The Scaffold is intended to be implanted in a cavity at the epicenter of the spinal cord contusion during open spine surgery. The Scaffold is intended to act as a physical substrate for cell growth, appositional healing, and tissue remodeling, and preserve the structural integrity of the cord. The Scaffold is intended for use in recent (≤ 7 days) spinal cord injuries that do not involve penetrating injury to the cord or complete severing of the cord.
- Number of Subjects:** Up to 36 subjects to ensure 20 subjects in the Primary Endpoint Analysis Set (defined as subjects with a successful Scaffold implantation, no major protocol deviations, and a complete 6-month Primary Endpoint Follow-up Visit)
- Number of Sites:** Up to 40 sites in the United States, Canada, and the European Union
- Inclusion Criteria:**
1. AIS A classification of traumatic spinal cord injury at T2 – T12 neurological level of injury confirmed by a qualified medical professional
 2. Recent injury (must receive Scaffold within 7 days from injury)
 3. Non-penetrating SCI (contusion injury) that is no less than approximately 4 mm in diameter by MRI
 1. Requires open spine surgery allowing access to the injured spinal cord (subjects requiring either posterior surgical approach or posterior plus anterior approach will be eligible)
 2. Informed consent obtained
 3. 16–70 years of age, inclusive
 4. Hemodynamically stable and deemed a suitable candidate for surgery
- Exclusion Criteria:**
1. Terminally ill subjects not likely to be able to participate in follow-up
 2. Incomplete spinal cord injury (AIS B, C, D, and E injuries)
 3. Subjects with more than one discrete spinal cord injury (contusion) will be excluded.
 4. No discrete cavity (existing or created by irrigation/myelotomy) in the contused spinal cord in which a Scaffold can be placed
 5. Evidence of clear and significant Somatosensory Evoked Potentials (SSEP) transmission through the injury site before Scaffold implantation (based on the judgment of the Investigator)
 6. Subjects with clinically significant pre-existing neurological comorbidities that are unrelated to the contusion being treated (e.g. MS, ALS, significant prior peripheral nerve dysfunction, residual problems

- related to previous spine-related neurological pathologies) will be excluded only if it is felt that these preexisting morbidities will increase risk, affect safety monitoring, or confound study results
7. Spinal cord injury associated with significant traumatic brain injury or coma that, in the opinion of the Investigator, would preclude adequate assessment of spinal cord function, brain injury that could be associated on its own with sensory or motor deficits, or subjects with any other reason that results in an unreliable ISNCSCI exam
 8. Subjects with clinically significant pre-existing respiratory disease not related to the contusion being treated (e.g., COPD)
 9. Subjects requiring long-term ongoing mechanical ventilation
 10. Subjects with documented immune deficiency disorders, including a known diagnosis of HIV infection/AIDS
 11. Recent (according to DSM IV or DSM V criteria) history of abuse of narcotics or other significant substance abuse
 12. Significant injury complications where, in the view of the Investigator, participation in the study could further complicate subject care, limit study follow-up, or confound interpretation of safety or efficacy data.
 13. A female who is:
 - Pregnant, or planning to become pregnant within the next 12-months; or
 - Breastfeeding; or
 - A woman of child-bearing potential (defined as post menarche and biologically capable of becoming pregnant [i.e., not surgically sterile]) who is engaged in active heterosexual relations and is not willing to use a barrier or hormonal form of birth control for 12-months following Scaffold implantation (e.g., oral, injected, or implanted contraceptives)
 14. A male who is engaged in active heterosexual relations and is not willing to use birth control for 3-months following Scaffold implantation including sperm donation or banking
 15. Current or impending incarceration
 16. Complete spinal cord transection
 17. Subjects with spinal cord injuries directly due to gunshot, knife, or other penetrating wounds.
 18. Known hypersensitivity to PLGA or PLL (e.g., hypersensitivity to absorbable sutures containing PLGA)
 19. History of severe mental illness (according to DSM IV or V)
 20. Evidence of pre-trauma active local or systemic infection
 21. Participation in another interventional clinical trial for six months after Scaffold implantation
 22. BMI over 39
 23. Having a medical condition (e.g., cardiovascular disease, life threatening injuries), or receiving medical treatment, or having any other reason that, in the judgment of the Investigator, precludes successful participation and

follow-up for at least six months or confounds collection or interpretation of study safety, feasibility, or efficacy data

Study Assessments:

Screening Assessments:

Subjects with recent (≤ 7 days) T2 –T12 neurological level of injury (NLI) spinal cord injury (SCI) will be screened for participation. After informed consent is obtained, neurological status will be assessed according to the International Standards for Neurological Classifications of SCI (ISNCSCI) as developed by the American Spinal Injury Association (ASIA). The 5-grade ASIA Impairment Scale (AIS) will be used to determine the completeness of a subject's injury. The ISNCSCI examination includes sensory and motor examinations. A rectal examination will be used to assess deep anal pressure sensation and voluntary anal contraction. Any variables that may affect the ability to obtain a reliable ISNCSCI exam should be eliminated (e.g., temporarily eliminating medication that would interfere with a valid ISNCSCI exam for ventilated subjects). Only AIS A subjects will continue with screening assessments.

A magnetic resonance imaging (MRI) study without contrast will be performed to measure and characterize the contusion and to identify the contusion location. The contusion dimensions (length and anteroposterior diameter) will be estimated. The screening MRI will also be used to assess the presence or absence of a cavity, parenchymal sparing, atrophic changes of the cord, and areas of edema and hemorrhage.

Other baseline assessments to be performed at the screening visit will include subject demographics, general medical/medication history, neurological examination, physical examination, vital signs, Vital Capacity (VC) for subjects who are not ventilator dependent, and baseline clinical laboratory tests. For subjects ages 16 and 17, baseline skeletal maturity will be assessed using an accepted measure (e.g. bone age as determined by hand and wrist x-ray or Risser stage as determined by iliac crest x-ray) prior to hospital discharge, but assessment is not required prior to open spine surgery/Scaffold implant. X-rays obtained during the preoperative period may be used for this assessment.

If clinical assessments are conducted during post-injury care and before informed consent is obtained, they may be used for the study once informed consent is obtained.

Scaffold Implant Assessments:

At any time within the 8 hours prior to surgery, a confirmatory ISNCSCI exam will be performed to ensure the subject has a reliable ISNCSCI exam and is an AIS A classification. Any variables that may affect the ability to obtain a reliable ISNCSCI exam should be eliminated (e.g., temporarily eliminating medication that would interfere with a valid ISNCSCI exam for ventilated subjects). The Scaffold implantation will occur at the time of open spine surgery, ideally within 24-hours from the time of injury but no longer than 7 days from the time of injury. Electrophysiological studies (somatosensory evoked potential) will be performed intra-operatively to determine if there is a clear and significant signal (based on the judgment of the Investigator) through the contusion, which would exclude a subject from proceeding to

Scaffold implantation. In addition, for T2 and T3 neurological level injuries, intraoperative neuromonitoring will be conducted during the investigational portion of the open spine surgery. Ventilator parameters and duration will be documented beginning pre-operatively and through the postoperative ventilation time. If changes in ventilator parameters are necessitated by a worsening of pulmonary function, the Investigator will assess if the worsening is due to the Scaffold implant procedure.

Preoperative, intraoperative, and postoperative vital signs will be monitored during surgery, including heart rate, systolic and diastolic blood pressure, mean arterial pressure (MAP), oxygenation and ventilation rate. Source documentation (e.g., anesthesia flow sheets) will be collected, and significant changes will be documented and noted as safety events if appropriate.

Upon visualization of the dura, an intraoperative ultrasound will be performed to evaluate and confirm the contusion size, presence or absence of a cavity, and location of the contusion, as initially assessed by the preoperative MRI. After a durotomy is performed or an existing dural tear is extended where needed to expose the contusion site, the contused cord will be irrigated with isotonic saline to wash away any superficial hemorrhagic material or devitalized tissue. If necessary, an arachnoid/pial incision will be made over the contusion allowing direct access to the injured parenchyma. The surgeon will collect a sample of the spontaneous exudate or debris if present, and submit to pathology for routine examination/testing, for example Hematoxylin and Eosin (H&E) staining for histology. After the epicenter of the contusion cavity has been identified/reached (e.g., by myelotomy), the contusion is further irrigated with isotonic saline for the purposes of debridement as necessary to remove additional areas of hemorrhage and necrotic tissue within the cavity. The Scaffold is wetted and trimmed, if necessary, on one end only to obtain the desired length needed to fit the cavity and to avoid undue tension on the spinal cord surrounding the contusion site. The Scaffold is then gently implanted into the epicenter of the intraspinal contusion cavity. A second intraoperative ultrasound, with photograph, should be performed to confirm placement of the Scaffold in the spinal cord.

Following surgery, the subject will be monitored in a manner consistent with standard post-anesthesia care.

Ventilator duration and parameters will be documented for all subjects beginning pre-operatively and through the postoperative ventilator support time. For changes in ventilator parameters that indicate a worsening of pulmonary function, including changes from partial to full mechanical ventilation or a longer-than-expected time to be weaned from ventilation, the Investigator will assess if the worsening is due to the Scaffold or the Scaffold implant procedure.

**Follow-up
Assessments:**

Follow-up assessments will occur post-Scaffold implantation at 24-hours, 48-hours, 72-hours, 1-week, at hospital discharge, 1-month, 2-months, and 3-months. Follow-up assessments consist of:

- All Follow-up Visits

- Resting vital signs
- Routine clinical safety laboratory tests
- Neurological exam
- Vital Capacity (VC) for subjects who are not ventilator dependent at 24-hours, 48-hours, 72-hours, 1-week, and hospital discharge
- Safety event monitoring including potential complications related to the procedure to implant the Scaffold and Scaffold-related complications
- Hospital Discharge through 3-month Follow-up Visit
 - ISNCSCI exam
 - Neurological examinations to include hip abduction/adduction and great toe flexion/extension
 - Rehabilitation Therapy Log
 - Pain assessment
 - Spinal Cord Independence Measure (SCIM III)
 - Ferrans and Powers Quality of Life Index — Spinal Cord Injury (QLI-SCI III)
 - Beck Depression Inventory (BDI-II)
- 1-month Follow-up through 3-month Follow-up Visits
 - Bowel and bladder function assessments
 - Sexual function assessment
- MRI without contrast at 72-hour and 3-month Follow-up Visits
- Physical examination at Hospital Discharge

**Primary Endpoint
Analysis
Assessments:**

The Primary Endpoint Analysis is at the 6-month Primary Endpoint Follow-up Visit post-Scaffold implantation. Assessments at this visit include:

- Resting vital signs
- Routine clinical safety laboratory tests
- Neurological examinations (including hip abduction/adduction and great toe flexion/extension)
- ISNCSCI exam
- MRI without contrast
- Physical examination
- Bowel and bladder function assessments
- Sexual Function Assessment
- Rehabilitation Therapy Log

**Long-term
Follow-up
Assessments:**

- Pain assessment
- Spinal Cord Independence Measure (SCIM III)
- Ferrans and Powers Quality of Life Index — Spinal Cord Injury (QLI-SCI III)
- Beck Depression Inventory (BDI-II)
- Safety event monitoring including potential complications related to the procedure to implant the Scaffold and Scaffold-related complications

The Long-term Follow-up period begins after the 6-month Primary Endpoint Follow-up Visit and has in-clinic visits at 12-months and 24-months post-Scaffold implantation and yearly follow-up visits via telephone through 10 years post-Scaffold implantation.

In-clinic Long-term Follow-up assessments include:

- Neurological examinations including hip abduction/adduction and great toe flexion/extension, ISNCSCI exam, MRI without contrast, physical exam, routine clinical safety laboratory tests, resting vital signs and safety event monitoring including potential complications related to the procedure to implant the Scaffold and Scaffold-related complications (12- and 24-month Long-term Follow-up Visits)
- Rehabilitation Therapy Log, pain assessment, bowel and bladder function assessments, Sexual Function Assessment, SCIM III, QLI-SCI III, and BDI-II (12-month Follow-up Visit only)

After the last in-clinic Long-term Follow-up visit at 24-months post-implantation of the Scaffold, the subjects will be contacted via telephone on the annual anniversary of the date of the Scaffold implantation through the 10-year anniversary of the Scaffold implant. The site staff will conduct a general health assessment, which will collect subject-reported information on their health throughout the past year, including information on any Serious Safety Events.

Safety Endpoints:

1. General safety assessments
 - a. Incidence of all safety events (Adverse Events/Adverse Device Effects) of any kind/seriousness
 - b. Incidence of all serious safety events (Serious Adverse Events/Serious Adverse Device Effects)
 - c. Incidence of unanticipated ADEs (Unanticipated Adverse Device Effects)
2. Incidence of the following safety events of interest for assessment of the potential risk associated with the use of Scaffold
 - a. Scaffold migration or malposition
 - b. Untoward physiologic reaction to PLGA-PLL materials
 - c. Scaffold-related loss of motor or sensory neurologic function
 - d. Increased inflammatory response

- e. Persistent cerebrospinal fluid leak
 - f. Damage to adjacent structures post Scaffold implant
 - g. Re-operation or removal of the Scaffold
 - h. Hemorrhage into or around the spinal cord causing neurologic deficit or possible need for further surgery
 - i. Surgical infection
 - j. Increased anesthesia time
 - k. Adhesion between the spinal cord and dura
 - l. Postoperative symptomatic or asymptomatic intraspinal cyst or syrinx
 - m. Post-Scaffold implant on-ventilator time for subjects with sensory deterioration of 2 or more dermatomes determined by either ISNCSCI pinprick or light touch exam as compared to subjects without sensory deterioration of 2 or more dermatomes.
3. Incidence of the following safety events for assessment of the potential risk associated with neurosurgical procedures
- a. Soft tissue wound infection or dehiscence
 - b. Surgical injury to the cord
 - c. Cerebrospinal fluid (CSF) leakage
 - d. Progressive neurological deterioration beyond that normally expected
 - e. Bacterial meningitis
 - f. Cord abscess
 - g. Failure to alter the natural course of healing from a spinal cord injury
4. Incidence of the following safety events for assessment of the most common general risks of surgery and spinal surgery:
- a. Adverse reactions to the anesthetic
 - b. Postoperative pneumonia
 - c. Blood clots in the legs or elsewhere (deep vein thrombosis) that may travel to the lungs (pulmonary embolus)
 - d. Infection at the site of surgery
 - e. Blood loss during surgery requiring a transfusion
 - f. Injury to the nerves or spinal cord resulting in pain or further paralysis
 - g. Instrumentation breaking, dislodging, or irritating the surrounding tissues
 - h. Pain from the surgery itself
5. Findings of clinical laboratory tests, including routine blood chemistry and hematology tests
6. Findings from vital signs measurements
7. New onset or worsening of depression by BDI-II

Efficacy Endpoints:

Primary Efficacy Endpoint

Improvement in AIS grade of one or more levels

Secondary Efficacy Endpoints

1. Changes in NLI, sensory scores, motor scores
2. Changes in spinal cord anatomy

Exploratory Endpoints

3. Changes in bowel function, bladder function, sexual function
4. Changes in pain
5. Changes in SCIM III
6. Changes in QLI-SCI III

Statistical Analysis:

General Considerations:

The primary analyses (safety and efficacy) will employ data up to and including the 6-month Primary Endpoint Follow-up Visit. Additional Long-term Follow-up analyses will be performed for data obtained after the 6-month Primary Endpoint Follow-up Visit.

The results will be presented primarily via data tabulation and listed by subject ID and time course because this is an HDE Probable Benefit study with a small sample size. Group descriptive statistics and cumulative statistics will be utilized if appropriate. Data from subjects enrolled prior to the conversion of the study from a pilot study to the INSPIRE pivotal probable benefit study, and data from subjects < 22 years old (i.e., pediatric population) will be clearly identified in the data tabulations.

Analysis Populations:

The **Safety Set** includes all enrolled subjects (i.e., subjects who have signed an Informed Consent Form) that passed the screening assessments. The Safety Set will serve as the analysis set for demographic and safety endpoints.

The **All Treated Analysis Set** includes all subjects who have a successful Scaffold implant. The All Treated Analysis Set will serve as the analysis set for all efficacy endpoints.

The **Primary Endpoint Analysis Set** includes all subjects who have a successful Scaffold implant, no major protocol deviations, and who have completed the 6-month Primary Endpoint Follow-up Visit. The Primary Endpoint Analysis Set will serve as the analysis set for the primary efficacy endpoint.

Primary Endpoint Analysis:

The primary efficacy analysis is the proportion of subjects who demonstrate an improvement of at least one grade on AIS assessment at the 6-month

Primary Endpoint Follow-up Visit. If the proportion of subjects who demonstrate an improvement of at least 1 grade on AIS assessment at the 6-month Primary Endpoint Follow-up Visit is at or above 25%, the study will be deemed a success using this preset Objective Performance Criterion (OPC) of $\geq 25\%$ as a measure of success. The Primary Endpoint Analysis set will be used for this analysis. In addition, the above analysis will be performed on the All Treated Analysis Set as a confirmatory analysis.

2 INTRODUCTION

Each year, hospitals in the United States receive over 15,000 new cases of spinal cord injuries (SCI), and more than 282,000 people in the nation are currently living with SCI [1–4]. Annual global incidence rate is estimated to be 22 per million population, which adds to the total of nearly 2.5 million current survivors [5]. Moreover, researchers across all recent studies of SCI incidence have noted increasing trends in both the percentage of tetraplegics and percentage of complete lesions [6].

Initial spinal cord injury is most often caused by blunt mechanical injury, which may result from contusion or compression [5]. While this primary injury results in contusion of the cord, the secondary injury mechanisms following the initial trauma exacerbate the damage. Substantial necrosis immediately follows primary injury, and the effects are compounded by continuous neuronal and oligodendroglial apoptosis [7]. Throughout the secondary injury, substantial loss of myelin has also been noted [8]. These secondary injury mechanisms expand the severity of the primary injury, and current options for treatment fail to effectively repair or mitigate these destructive processes. Treatment standards for this sort of injury have experienced little improvement in recent years.

In the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), a spinal cord injury classification of AIS A is considered to be complete—no motor or sensory function is preserved in the sacral segments (S4-S5) [9]. This is the most severe and disabling type of spinal cord injury as it entails a complete loss of motor and sensory function below the level of injury.

InVivo Therapeutics Corporation has developed an investigational *Neuro-Spinal Scaffold™* or “Scaffold” for the treatment of SCI to address this unmet medical need. A prospective, open label, multicenter, non-randomized, single arm study of this investigational product is being conducted to assess its overall safety and probable benefit. Because this is the first in-human clinical trial to be conducted with the investigational Scaffold, participation is limited to subjects suffering from complete (AIS A) functional spinal cord injury at the time of presentation. The Scaffold is intended for use only in subjects presenting with recent (≤ 7 days since injury) spinal cord injuries that do not involve penetrating injury to the cord or complete severing of the cord. With the exception of Scaffold implantation, subjects are treated according to standard of care at a qualified trauma center, have comprehensive post-injury rehabilitation as described in Section 7.3, and are followed on-study for a period of 10 years after the implant.

3 INVESTIGATIONAL PRODUCT DESCRIPTION

3.1 Scaffold

The Scaffold is being investigated as an innovative modality to enhance functional neurologic recovery of an irreversibly injured spinal cord when used as an adjunct treatment along with standard of care. The cylindrical-shaped Scaffold is a porous bioresorbable polymer comprising poly(lactic-co-glycolic acid)-b-poly-(L-lysine) (PLGA-PLL), a synthetic biomaterial. Secondary processes of spinal cord injury (including ischemia, anoxia, free-radical formation, and excitotoxicity) promote glial scarring and impede axonal regrowth through myelin-associated inhibitors, both of which contribute to paralysis and other devastating effects observed post-SCI. However, past studies [10] have demonstrated that preservation of merely 10% of spinal tissue bears significant benefit for functional recovery.

The Scaffold is designed to provide structural support to injured spinal tissue, and to provide a supportive matrix for endogenous healing/repair processes following implantation within a spinal cord contusion thereby preserving more of the spinal tissue and increasing the chances for functional recovery. The Scaffold is designed for use in the most common SCI, a contusion injury. The Scaffold is fragile and should be handled during preparation with the sized matched Cupped Forceps. The Scaffold is wetted and can be trimmed to the size needed to fit the intraspinal contusion cavity if necessary. The Scaffold is placed into the epicenter of the contusion cavity, and degrades inside the body over a time-course that is intended to favor functional recovery. Details regarding the preparation of the Scaffold and surgical procedure are outlined in Instructions for Use (Appendix E).

The Scaffold is intended to serve as an extracellular matrix aiming to provide support to surrounding spared tissue after injury, minimize expansion of areas of necrosis, and support endogenous healing/repair processes following injury, and harbors the promise of sparing of white matter, increasing neural sprouting, and diminishing post-traumatic cyst formation.

3.2 Summary of Prior Investigations

In vivo testing of the Scaffold utilized hemisection models in rats and nonhuman primates, and contusion models in rats and pigs. In unilateral hemisection injury models, sections of one side of spinal cord are surgically cut or removed. The other side remains intact, resulting in preserved function on the uninjured side, and improved morbidity due to recovery of bladder and bowel function. Unilateral hemisection injuries in rats and nonhuman primates were used to evaluate the Scaffold due to the improved morbidity, and the ability to place the Scaffold into the void created by the sectioned/removed tissue. Nonhuman primates were used because the high degree of similarity to human spinal cord anatomy is important for

translating experimental SCI treatments to humans. Contusion injury models rely on the rapid delivery of a blunt force to the spinal cord, and are more representative of the majority of human SCIs. However, due to the degree of functional loss and the increased need for daily veterinary care (such as bladder expression), especially for non-human primates, contusion injury models were used to evaluate the safety and effectiveness of the Scaffold in rats, and surgical feasibility in acutely-injured pigs.

The first nonclinical evaluation of the Scaffold was in rats with thoracic T9-T10 spinal cord lateral hemisection [11]. The results of this study demonstrate that implantation of Scaffolds at the site of SCI promotes functional recovery, mitigates tissue loss and cyst formation, and contributes to an environment capable of supporting axon regeneration.

The Scaffold was then evaluated in a non-human primate hemisection model of SCI. After performing a pilot study to test the T9–T10 hemisection and Scaffold implantation surgery in African green monkeys [12], two subsequent studies were performed in the African green monkey hemisection model to evaluate the safety and efficacy of the Scaffold. Results from these two studies were combined for analysis [13]. The Scaffold was well tolerated, and clinical chemistry and hematology values from Scaffold-implanted monkeys, as well as body and organ weights at sacrifice, were similar to nonimplanted controls. Kinematics analysis at 12 weeks post-lesion revealed that Scaffold-implanted monkeys with complete hemisection lesions showed significantly improved functional recovery compared with control monkeys with similar lesions. Histological assessment demonstrated that Scaffold-implanted monkeys displayed a large layer of morphologically distinct remodeled tissue in the region of the hemisection, more than twice the volume seen in control monkeys. Furthermore, immunolabeling revealed that the remodeled tissue in Scaffold-implanted monkeys was positive for both non-phosphorylated neurofilament H (a major cytoskeletal protein in neurons), GAP-43 (indicating the presence of sprouting neurites), and myelin basic protein (indicating the presence of myelin-producing cells), indicating that the remodeled tissue represents a permissive environment for the survival and growth of axons.

Because most human SCIs are non-penetrating contusion injuries, the Scaffold was next evaluated in the rat contusion injury model in which scaffolds were surgically implanted 24–72-hours after injury (two internal studies and an outsourced study). In these studies, Scaffold implantation was not associated with any change in latency to respond to a noxious stimulus (no allodynia) or a decrease in body weight. No differences were observed in clinical pathology between Scaffold and surgical control groups, although a minimal- to-mild foreign body inflammatory reaction was associated with animals receiving Scaffold. Also, in these studies, Scaffold implantation was not associated with a significant improvement in functional recovery. However, Scaffold implantation (24–72-hours after injury) was shown to promote beneficial tissue remodeling at the injury epicenter when evaluated by histology and immunolabeling. By 3-months

after contusion injury, rats in the non-implanted, contusion-only control group developed large cavities surrounded by a thin rim of spared white matter. In contrast, in rats treated with Scaffold implantation, cavity volume decreased by 86%, and spared white matter width increased by 44%. Although Scaffolds were resorbed by 12 weeks after implantation, the amount of remodeled tissue at the implantation site in the lesion epicenter increased by 111%. Remodeled tissue in Scaffold-implanted rats contained abundant laminin and sprouting axons. Moreover, Scaffold implantation appeared to support the infiltration of Schwann cells capable of (re)myelinating bare axons. Schwann cell myelination was extensive within the preserved penumbra white matter and myelination was also detected throughout the injury epicenter within the Scaffold-remodeled tissue.

Cavitation and the feasibility of Scaffold implantation at early time points after contusion injury were evaluated in the Gottingen pig, which has a spinal cord similar in size and structure to the human spinal cord. At 4, 6, and 24-hours following spinal cord contusion injury, intraoperative ultrasound was used to identify the extent of the injury at the epicenter, the dura was opened, and (when possible), midline pialotomy and myelotomy were performed. In each pig, a large volume of necro-hemorrhagic fluid and debris rapidly effluxed from the injury site, releasing built-up pressure and resulting in a substantial cavity in the center of the spinal cord. Following gentle irrigation and aspiration to debride the wound, Scaffolds were placed easily into the resulting cavity. The surgical procedure also reduced intraparenchymal pressures below pre-surgery levels. These findings demonstrate the feasibility of Scaffold implantation within the acutely contused spinal cord in a clinically-relevant large animal model of SCI.

Taken together, results from non-clinical studies in two rat spinal cord injury models, the African green monkey unilateral hemisection injury model, and the Gottingen pig contusion injury model demonstrate that the Scaffold can be safely implanted in the acutely-injured spinal cord. The process of Scaffold implantation provides the dual benefit of debridement of necrotic tissue, which removes a nidus of inflammation, and normalization of elevated intraparenchymal pressure, which restores local vascular perfusion. The Scaffold contains positively-charged functional groups, which promote cellular infiltration and adhesion, and high interconnected porosity, which provides space for fluid flow, waste removal, and nutrient exchange. This enables the Scaffold to work in concert with endogenous healing mechanisms, serving as a structural support and providing an adhesive substrate for the survival and growth of endogenous cells. Once implanted at the wound epicenter, the Scaffold may provide therapeutic benefit through the following mechanisms: (1) promotion of drainage by preventing compartmentalization, (2) preservation of white matter and reduction of cyst formation via appositional healing by primary intent, (3) neural regeneration through the formation of neuropermissive remodeled tissue, and (4) remyelination of

segmentally demyelinated white matter axons by Schwann cells. These actions of the Scaffold may improve the probability of subsequent recovery of function after acute spinal cord injury.

3.3 Potential Risks of the Scaffold and Procedure to Implant the Scaffold

As with any surgical procedure, there are general risks and procedure-specific risks. Risks associated with general surgery include:

1. Allergic reactions (including reaction to IV antibiotic, local anesthetic, sedative, dressing materials, wound care products, etc.)
2. Anaphylactic shock
3. Anesthesia risks
4. Angina
5. Bleeding (requiring or not requiring transfusion)
6. Blood clots
7. Cellulitis
8. Dermatitis
9. Convulsions
10. Death
11. Erythema
12. Edema
13. Failure to heal (bone fusion or wound)
14. Fever
15. Hypotension
16. Hypertension
17. Hypoglycemia
18. Infection, Incision
19. Infection, Sepsis
20. Laboratory values, abnormal
21. Mental Status, altered/confused
22. Myocardial Infarction
23. Non-improvement
24. Stress Ulcer
25. Pneumonia
26. Hematuria
27. Pulmonary Embolus
28. Deep Venous Thrombosis

29. Rash, Generalized Skin
30. Renal Failure/Insufficiency
31. Stroke
32. Thrombocytopenia/thrombosis induced by heparin
33. Incision site complications
34. Instrumentation breaking, dislodging or irritating the surrounding tissues
35. Pain from the surgery itself

In addition, complications associated with the neurosurgical and spinal procedures may include:

1. Infection, Myelitis
2. Loss of bladder, bowel, or sexual function
3. Muscle weakness
4. Nerve Injury
5. Osteomyelitis/Diskitis
6. Pain (back or legs)
7. Spinal cord edema
8. Syrinx formation/ Syringomyelia
9. Transient Ischemic Attack (TIA)
10. Paralysis
11. Surgical injury to the cord
12. Cerebrospinal fluid (CSF) leakage, which could result in positional headaches, an increase in the risk of infection, and wound complications
13. Progressive neurological deterioration beyond that normally expected
14. Bacterial meningitis
15. Cord abscess
16. Failure to alter the natural course of healing from a spinal cord injury
17. Intradural surgery risks, including intradural hemorrhage within the neuraxis (with or without excess CSF egress); neurologic deficit as a consequence of spinal cord manipulation and myelotomy with consequent deterioration; dorsal column dysfunction, which manifests with loss of proprioception (loss of joint sensation), sensory loss, bowel and bladder dysfunction, and paralysis; and intradural infection.
18. Autonomic dysreflexia and spasticity
19. Dural graft replacement
20. Increased risk with administration of steroids

In addition, potential risks associated with the specific use of the Scaffold may include:

1. Scaffold migration or malposition
2. Untoward physiologic reaction to PLGA-PLL materials
3. Scaffold-related loss of motor or sensory neurologic function
4. Increased inflammatory response
5. Persistent cerebrospinal fluid leak
6. Damage to adjacent structures post Scaffold implant
7. Re-operation or removal of the Scaffold
8. Hemorrhage into or around the spinal cord causing neurologic deficit or possible need for further surgery
9. Surgical infection
10. Increased anesthesia time
11. Adhesion between the spinal cord and dura
12. Postoperative symptomatic or asymptomatic intraspinal cyst or syrinx
13. In the acute period after injury, there may be some transient loss of residual function below the level of spinal cord injury that could be damaged by the Scaffold

The implantation procedure presents no additional or greater risks than those of a standard myelotomy procedure such as that performed in resection of spinal cord tumors. In addition, unlike tumor patients, this study will enroll subjects classified as AIS A at presentation who have no motor or sensory function at or below the level of injury. Thus, the risk of additional injury at or below the initial contusion site is low. However, the potential for the level of dysfunction to ascend to higher levels in the spinal cord is unknown as is the effect of the Scaffold on the small percentage of subjects who recover function after initially being classified as AIS A.

3.4 Potential Benefits of the Scaffold

The AIS A patient is destined to a lifetime with significant motor and sensory impairment that may include the inability to breathe, urinate, feed, or bathe without assistance. In addition, the immobility this injury creates is associated with a significant co-morbidity profile including frequent infections, pneumonia, and spasticity. As a result, even modest benefits from the Scaffold have the potential to improve the function and lives of this patient population. In addition, if the Data Safety Monitoring Board (DSMB) determines that there is substantial and unexpected benefit from the Scaffold, the study data will be analyzed and submitted to FDA for review and recommendation of next steps.

Potential benefits of the Scaffold include:

1. Improvement of AIS grade with related motor and sensory function recovery
2. Improvement in motor or sensory function at any level
3. Decreased incidence of repeat hospitalizations related to SCI complications
4. Decreased pain

4 STUDY OBJECTIVES AND INTENDED USE

Primary Objective: To evaluate whether the Scaffold is safe and demonstrates probable benefit for the treatment of complete T2–T12 spinal cord injury.

Regulatory Objective: This is a Humanitarian Device Exemption (HDE) Probable Benefit study to demonstrate safety and probable benefit of the Scaffold in support of future studies and an HDE application with subsequent approval.

Intended Use: The Scaffold is intended for use in patients age 16–70 years diagnosed with a T2–T12 NLI functionally complete (AIS A) SCI for whom open spine surgery, (e.g., laminectomy, spine stabilization) which allows access to the dura of the injured spinal cord, is recommended as an option. The Scaffold is intended to be implanted in a cavity at the epicenter of the spinal cord contusion during open spine surgery. The Scaffold is intended to act as a physical substrate for cell growth, appositional healing, and tissue remodeling, and to preserve the structural integrity of the cord. The Scaffold is intended for use in recent (≤ 7 days) spinal cord injuries that do not involve penetrating injury to the cord or complete severing of the cord.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design

This is an HDE probable benefit, open-label, non-randomized, single-arm, multicenter study to evaluate the safety and probable benefit of the poly(lactic-co-glycolic acid)-b-poly(L-lysine) Scaffold (“Scaffold”) in subjects with thoracic AIS A traumatic spinal cord injury at neurological level of injury of T2–T12.

5.2 Study Centers

The study will be conducted at up to 40 sites in the U.S, Canada and the European Union by qualified Investigators who have been trained on the surgical Scaffold implant procedure in order to obtain 20

subjects in the Primary Endpoint Analysis Set, defined as all subjects with a successful Scaffold implant, no major protocol deviations (Section 9.4.3), and a complete 6-month Primary Endpoint Follow-up Visit. After receiving the Scaffold and following discharge, subjects will participate in a comprehensive rehabilitation program (Section 7.3). For the first 24-months after implantation of the Scaffold, Follow-up and Long-term Follow-up assessments will be conducted at either the study site or the rehabilitation center depending on the preference of the Investigator and subject, and provided appropriate Institutional Review Board (IRB)/Research Ethics Committee (REC)/Research Ethics Board (REB) approvals are in place. The Long-term Follow-up annual visits for years 3 through 10 will be conducted over the telephone.

5.3 Study Purpose and Rationale for Study Design and Control Groups

This study is a HDE probable benefit study of the Scaffold for treatment of acute SCI. The purpose is to demonstrate the safety and probable benefit of the Scaffold to treat functionally complete spinal cord injury.

The European Multicenter Study about Spinal Cord Injury (EMSCI) database was used to set the benchmark for the Objective Performance Criterion (OPC) in this HDE Probable Benefit study. This large database of almost 2,600 subjects is being updated continuously. A recent paper including almost 400 subjects with thoracic (T2–T12) complete (AIS A) SCI (same population evaluated in this study) [14] carefully delineated the ISNCSCI-based neurologic outcomes over 48 weeks for subjects segmented by three thoracic level groupings (T2–T5, T6–T9, T10–T12) as well as outcomes for the entire thoracic group. This paper clearly demonstrates that outcomes are poorer for higher level injuries. The subjects in this HDE Probable Benefit study will have similar demographics and mechanisms of injury as in the EMSCI database.

Although standard of care in rehabilitation has changed significantly over the past several decades with introduction of new experimental devices such as exoskeletons, nothing has been demonstrated to improve neurologic outcome in patients with thoracic complete SCI. As evidence of the lack of effect of rehabilitation modernization with respect to AIS category changes, the results are similar for the U.S. Model Systems, EMSCI, and Sygen databases. Published data from the EMSCI, U.S. Model Systems, and Sygen databases found approximately 13%–16% of subjects (thoracic AIS A) spontaneously improved AIS grade by one or more level at six or more months post-injury [14–16]. The neurologic outcomes published from these databases are very consistent, establishing community norms for spontaneous neurologic recovery after SCI. As level of injury is the one criterion which does appear to influence neurologic outcome, assuming a similar distribution of location of injury as these larger databases, establishing a study success goal or OPC of at least 25% of subjects demonstrating an improved AIS grade by one or more level at the 6-month Primary Endpoint Follow-up Visit post-Scaffold implantation is a rigorous efficacy requirement in this population. Thus, the current study will be deemed a success if at least 25% of subjects demonstrate

an improved AIS grade by one or more levels at 6-month Primary Endpoint Follow-up Visit post-Scaffold implantation (the final visit for the Primary Endpoint).

6 STUDY POPULATION

6.1 Inclusion Criteria

Subjects must meet all of the following to be considered eligible:

1. AIS A classification of traumatic spinal cord injury at T2–T12 neurological level of injury confirmed by a qualified medical professional
2. Recent injury (must receive Scaffold within 7 days from injury)
3. Non-penetrating SCI (contusion injury) that is no less than approximately 4 mm in diameter by MRI
4. Requires open spine surgery allowing access to the injured spinal cord (subjects requiring either posterior surgical approach or posterior plus anterior approach will be eligible)
5. Informed consent obtained
6. 16–70 years of age, inclusive
7. Hemodynamically stable and deemed a suitable candidate for surgery

6.2 Exclusion Criteria

Subjects who meet any of the following will be excluded:

1. Terminally ill subjects not likely to be able to participate in follow-up
2. Incomplete spinal cord injury (AIS B, C, D, and E injuries)
3. Subjects with more than one discrete spinal cord injury (contusion) will be excluded.
4. No discrete cavity (existing or created by irrigation/myelotomy) in the contused spinal cord in which a Scaffold can be placed
5. Evidence of clear and significant Somatosensory Evoked Potentials (SSEP) transmission through the injury site before Scaffold implantation (based on the judgment of the Investigator)

6. Subjects with clinically significant pre-existing neurological comorbidities that are unrelated to the contusion being treated (e.g., MS, ALS, significant prior peripheral nerve dysfunction, residual problems related to previous spine-related neurological pathologies) will be excluded only if it is felt that these preexisting morbidities will increase risk, affect safety monitoring, or confound study results
7. Spinal cord injury associated with significant traumatic brain injury or coma that, in the opinion of the Investigator, would preclude adequate assessment of spinal cord function, brain injury that could be associated on its own with sensory or motor deficits, or subjects with any other reason that results in an unreliable ISNCSCI exam
8. Subjects with clinically significant pre-existing respiratory disease not related to the contusion being treated (e.g., COPD)
9. Subjects requiring Long-term ongoing mechanical ventilation
10. Subjects with documented immune deficiency disorders, including a known diagnosis of HIV infection/AIDS
11. Recent (according to DSM IV or DSM V criteria) history of abuse of narcotics or other significant substance abuse
12. Significant injury complications where, in the view of the Investigator, participation in the study could further complicate subject care, limit study follow-up, or confound interpretation of safety or efficacy data.
13. A female who is:
 - Pregnant, or planning to become pregnant within the next 12-months; or
 - Breastfeeding; or
 - A woman of child-bearing potential (defined as post menarche and biologically capable of becoming pregnant [i.e., not surgically sterile]) who is engaged in active heterosexual relations and is not willing to use a barrier or hormonal form of birth control for 12-months following Scaffold implantation (e.g., oral, injected, or implanted contraceptives)
14. A male who is engaged in active heterosexual relations and is not willing to use birth control for 3-months following Scaffold implantation including sperm donation or banking
15. Current or impending incarceration
16. Complete spinal cord transection

17. Subjects with spinal cord injuries directly due to gunshot, knife, or other penetrating wounds.
18. Known hypersensitivity to PLGA or PLL (e.g., hypersensitivity to absorbable sutures containing PLGA)
19. History of severe mental illness (according to DSM IV or V)
20. Evidence of pre-trauma active local or systemic infection
21. Participation in another interventional clinical trial for six months after Scaffold implantation
22. BMI over 39
23. Having a medical condition (e.g., cardiovascular disease, life threatening injuries), or receiving medical treatment, or having any other reason that, in the judgment of the Investigator, precludes successful participation and follow-up for at least six months or confounds collection or interpretation of study safety, feasibility, or efficacy data

6.3 Duration of the Study

The screening period is a maximum of 7 days between the time of injury and the time of Scaffold implantation. Subjects will be followed for a total of ten years after Scaffold implantation. The Primary Endpoint Follow-up period is the first 6-months post-Scaffold implantation and requires frequent in-clinic study visits at the study center. The Long-term Follow-up is after the 6-Month Primary Endpoint Follow-up visit through 10 years, with 12-month and 24-month Long-term Follow-up visits at the study centers, and the remaining annual Long-term Follow-up visits are conducted over the telephone. If during the Follow-up or Long-term Follow-up periods the subject reports a neurologic deterioration consisting of loss of bowel or bladder function or complete loss of motor function at any joint that had at least 2+ movement at the prior examination, the subject will be asked to return to the clinic for a follow-up evaluation.

6.4 Screen Failures

A screen failure is a subject from whom informed consent is obtained, but for whom Scaffold implantation was not attempted because it was determined (after informed consent was obtained and up to the time of open spine surgery) that the subject did not meet all of the eligibility criteria. The number of screen failures will be reported and included in the approved subject limit of 36 subjects, but such subjects will not be included in the efficacy analyses. Screen failures may be re-screened at any time if there is reason to believe that the reason for initial screen failure has been corrected. Screen failures will be replaced to ensure 20 subjects in the Primary Endpoint Analysis Set.

6.5 Discontinuation of Subjects

Subjects for whom the Scaffold implant is attempted but not successful (identified as a subject enrolled but not treated), and in whom a durotomy is not performed, will be withdrawn from the study, but will be followed until their date of discharge for safety purposes. These enrolled but not treated subjects will be withdrawn from the study on the date of discharge and will not be followed post discharge. The date that the subject is withdrawn and the primary reason for discontinuation will be recorded on the subject's Study Completion eCRF. In addition, the DSMB and regulatory authorities will be notified within 10 days of the occurrence of a subject enrolled but not treated.

Subjects for whom the Scaffold implant is attempted but not successful, and in whom a durotomy is performed (identified as a subject enrolled with procedure but not treated), will continue in the study for safety purposes only through the Primary Endpoint Follow-up period (6-months post-Scaffold implant). After discharge, only safety data including resting vitals, clinical labs and safety events will be collected for subjects who are enrolled with procedure but not treated. At the 6-month Primary Endpoint Follow-up Visit, the subject enrolled with procedure but not treated will be withdrawn from the study. The date that the subject is withdrawn and the primary reason for discontinuation will be recorded on the subject's Study Completion eCRF. The DSMB and regulatory authorities will be notified within 10 days of the occurrence of a subject enrolled with procedure but not treated.

Subjects may withdraw from the study after Scaffold implantation for any reason. If the subject withdraws from the study for any reason other than withdrawing consent before the 6-month Primary Endpoint Follow-up Visit, the site should make every effort to conduct a final study visit which includes all Visit 11 (6-month Primary Endpoint Follow-up Visit) protocol-required assessments (see Section 7.9.6). If the subject withdraws from the study for any reason other than withdrawing consent after the 6-month Primary Endpoint Follow-up Visit and before the final in-clinic 24-month Long-term Follow-up Visit, the site should make every effort to conduct a final study visit that includes all Visit 13 (24-month Long-term Follow-up Visit) protocol-required assessments (see Section 7.9.7). The date that the subject is withdrawn and the primary reason for discontinuation will be recorded on the subject's Study Completion eCRF.

Two attempts by telephone and one by letter will be made to contact a subject who has missed a scheduled visit. If a subject does not respond after the telephone and letter contacts, the subject will be designated as "lost to follow-up." The date that the subject is "lost to follow-up" will be documented on the subject's Study Completion eCRF.

All subjects who withdraw from the study or are "lost to follow-up" prior to their 6-month Primary Endpoint Follow-up Visit will be replaced to ensure 20 subjects in the Primary Endpoint Analysis Set.

7 STUDY PROCEDURES, SCAFFOLD IMPLANTATION, STUDY EVALUATIONS, AND STOPPING RULES

7.1 Screening

The Sponsor will provide an Informed Consent Form (ICF) template to each site for review, incorporation of local requirements, and approval by the Institutional Review Board (IRB)/Research Ethics Committee (REC) / Research Ethics Board (REB).

Prior to any study-specific procedures, the subjects will be invited to participate and written informed consent will be obtained by the Investigator. If clinical assessments are conducted during post-injury care and before informed consent is obtained, they may be used for the study once informed consent is obtained. After informed consent, the subject is enrolled into the INSPIRE study.

The Investigator conducts procedures specific to the study protocol that are needed to evaluate the subject's eligibility for Scaffold implantation, which include a review of demographics, medical and surgical history, prior and concomitant medications, interventions and procedures, physical examination, neurological examination, resting vital signs, Vital Capacity (VC) for subjects who are not ventilator dependent, clinical laboratory tests including serum pregnancy test, blood alcohol and urine drug toxicology, and blood type and coagulation test, and ESR/CRP.

Neurological status will be assessed by the Investigator or a designated trained medical professional according to the International Standards for Neurological Classification of SCI (ISNCSCI) as developed by ASIA. The five-grade ASIA Impairment Scale (AIS) will be used to determine the completeness of a subject's injury. The ISNCSCI examinations will also include sensory and motor examinations. Sensory function will be tested bilaterally by pinprick (sharp) and light touch sensation. Any variables that may affect the ability to obtain a reliable ISNCSCI exam should be eliminated (e.g., temporarily eliminating medication that would interfere with a valid ISNCSCI exam for ventilated subjects).

The motor examination will include a bilateral assessment (manual muscle testing score of 0–5 per muscle group) of 10 myotomes. In addition, a rectal examination will be used to assess deep anal pressure sensation and voluntary anal contraction to determine the completeness of the injury. In accordance with the ASIA Impairment Scale, the injury is considered complete (AIS A) when there is no motor and sensory function in the lowest sacral segments. The results from these tests will be used to establish baseline neurological

scores, to confirm reliable AIS A status within the 8 hours prior to open spine surgery, and to assess the subject's AIS classification at follow-up examinations.

Further, magnetic resonance imaging (MRI) studies without contrast will be performed prior to the open spine surgery to characterize the contusion, estimate the contusion dimensions (length and anteroposterior diameter), and identify the contusion location. The MRI will also be used to assess the presence or absence of a cavity, parenchymal sparing, atrophic changes of the cord, and areas of edema and hemorrhage.

Subjects who are 16–17 years of age may be less skeletally mature than subjects 18 years and older. To enable assessment of the degree to which skeletal maturity at the time of open spine surgery may affect Long-term outcome, a baseline measure of skeletal maturity will be obtained before hospital discharge, but is not required prior to open spine surgery/Scaffold implant. An accepted measure of skeletal maturity must be employed such as bone age as determined by hand and wrist x-ray or Risser stage as determined by iliac crest x-ray (Section 7.7.13). X-rays obtained during the preoperative period may be used for this assessment.

Immediately prior to open spine surgery and after eligibility is confirmed, a subject may proceed to open spine surgery and Scaffold implantation.

7.2 Surgery Procedure Summary

The Scaffold is implanted at the time of open spine surgery, ideally within 24-hours from the time of injury but no longer than 7 days from the time of injury. Sites/OR staff should bring all available Scaffolds and sterilized Cupped Forceps to the Scaffold implant procedure. All procedures to prepare the Scaffold will be performed by an Investigator or site staff trained on the Scaffold preparation procedure. All neurosurgical procedures to implant the Scaffold will be performed by an Investigator trained on the Scaffold implantation procedure. Details regarding the preparation and implantation of the Scaffold are also outlined in the Appendix E - Instructions for Use.

Within the 8 hours prior to the open spine surgery, the Investigator or a designated trained medical professional will repeat the ISNCSCI exam to confirm that the subject is reliably classified as AIS A.

After the induction of satisfactory general anesthesia, the subject will be carefully maneuvered to a prone position and placed on a spinal frame. Subject handling and positioning should be accomplished according to accepted principles of spine stabilization and transport. The skin corresponding to the area of incision will be prepared as indicated according to standard of care. Prophylactic antibiotics will be administered perioperatively as per institutional practice for open spine surgery. All relevant information regarding the preoperative preparation will be recorded on the surgical source document. In addition, preoperative, intraoperative, and postoperative vital signs will be monitored, including heart rate, systolic and diastolic

blood pressure, mean arterial pressure (MAP), oxygenation and ventilation rate. Source documentation (e.g., anesthesia flow sheets) will be collected, and significant changes will be documented and noted as safety events if appropriate.

Once the subject has been prepared and draped for surgery, open spine surgery — which may include bony decompression, reduction, and/or stabilization — will be carried out according to best practices applicable for the level and contusion. All relevant information regarding the open spine surgery will be recorded on the surgical source document.

Before proceeding to the Scaffold implant procedure, the Investigator will ensure the subject continues to meet all eligibility criteria. An SSEP assessment (tibial or sciatic) must be conducted prior to opening the dura to determine if there is clear and significant evidence of signal transmission through the injury site based on the judgment of the Investigator. If a clear signal is present indicating transmission through the injury site, the subject does not qualify for the Scaffold implant. The subject should be withdrawn from the study and is categorized as “enrolled but not treated.” See Section 6.5 Discontinuation of Subjects for details.

In addition, for subjects with a T2 or T3 neurological level of injury, bilateral intraoperative median and ulnar nerve SSEP monitoring will be performed as an added safety precaution for the investigational procedure from durotomy through Scaffold placement and dural closure. The objective of this monitoring is to identify potential loss of neurologic function of the hand at the C8 and T1 neurologic levels. The median nerve signals may be used as a control for the C8 and T1 levels as the median nerve also includes contribution from C7. An adequate baseline should be obtained per institutional protocol to ensure interpretable recordings from both median and ulnar SSEPs prior to beginning the investigational procedure (i.e. the durotomy). Should the SSEP recordings indicate potential loss of function, appropriate steps should be taken per institutional guidelines such as adjustment of anesthesia, operating procedure, etc. The Investigator should determine whether the Scaffold can be placed safely if this deterioration occurs prior to Scaffold placement. The Investigator may also utilize additional modes of intraoperative neuromonitoring, such as MEPs, if the risk of upper extremity movement is outweighed by the potential benefit. If the surgical procedure includes anterior cord manipulation, stronger consideration should be given to use of MEPs of the abductor pollicis brevis (C8, T1).

Changes in ventilator parameters due to worsening of pulmonary function will be documented during the investigational portion of the open spine surgery (durotomy, myelotomy, Scaffold implant, dural closure). If changes in ventilator parameters are necessitated by a worsening of pulmonary function, the Investigator will document the ventilator setting changes and assess if the worsening is due to the Scaffold implant procedure.

Upon visualization of the dura, an intraoperative ultrasound will be performed to evaluate and confirm the contusion size, presence or absence of a cavity, and location of the contusion. The ultrasound probe will be introduced into the wound superficially and not in direct contact with the dorsal dura after flooding the operative site with isotonic saline. Ultrasound recordings or a photo of the image of the spinal cord contusion or cavity where the Scaffold will be implanted should be included in the source documents. The Sponsor will provide individually packaged Scaffolds in two sizes. Based upon the cavity size (as determined by MRI, intraoperative ultrasound, and visual inspection), the Investigator will select the appropriate diameter Scaffold. The Investigator should use the size-matched Cupped Forceps for all handling of the Scaffold during preparation, wetting, and trimming, as the Cupped Forceps are specifically sized and designed to grasp the fragile Scaffold in a way that will ensure the Scaffold is not damaged. Note that using the wrong size Cupped Forceps or using the Cupped Forceps incorrectly to handle the Scaffold could cause Scaffold damage or breakage. After wetting the Scaffold per the Instructions for Use (Appendix E), the Investigator will trim the length of the Scaffold on one end only if necessary to ensure the Scaffold will fit lengthwise into the cavity without causing undue tissue tension or bulging.

If necessary (i.e., subject does not have a dural tear as a result of the injury that allows access to the injury epicenter), a durotomy will be performed, or an existing dural tear extended where needed, and the contused cord will be carefully irrigated with isotonic saline to wash away any superficial hemorrhagic material or devitalized tissue. After durotomy and irrigation, some SCI lesions (contusion-type or “closed”) have an intact pial surface and the lesion cavity is not visible. Other SCI lesions (compound-type or “open”) have a disrupted pia with spinal cord tissue laceration and/or maceration, and the lesion cavity is exposed.

For closed lesions, an arachnoid/pial incision will be made over the contusion allowing direct access to the injured parenchyma. A myelotomy will be performed to access the epicenter of the contusion. For open lesions, pial incision/myelotomy is not necessary to gain access to the lesion epicenter cavity. The surgeon will capture a sample of the spontaneous exudate or debris, if present, and submit to pathology for routine examination/testing, for example H&E staining for histology. Note that irrigated tissue fragments and cells may best be collected in a test tube for subsequent preparation of a cell pellet by centrifugation. Once the lesion cavity is exposed, it is further gently irrigated for the purposes of debridement as necessary with isotonic saline to remove additional areas of hemorrhage and necrotic tissue, and to create or further define a cavity for Scaffold implantation.

Local hemostasis is secured using standard of care neurosurgical methods that are routinely used for human spinal cord surgery and that were also utilized and validated for Scaffold implantation in the preclinical nonhuman animal studies. Because the spinal cord blood supply only involves capillary and small arteriolar vessels, clip or suture ligation is not indicated for procedures on the spinal cord. Rather, current surgical

standard of care involves control of capillary bleeding using temporary topical application of bovine thrombin, or using hemostatic collagen sponges (e.g., Gelfoam™) and gentle cotton pledget tamponade. Larger scale, refractory bleeding from small arterioles occasionally requires direct electrocautery using microbipolar forceps. In this manner, standard of care dictates that complete hemostasis be achieved using these techniques at the point of discovery and prior to proceeding with the remainder of the procedure. By definition, such practice facilitates visualization at the implantation site and ensures correct placement of the Scaffold.

The Investigator will place the prepared Scaffold lengthwise into the cavity in the epicenter of the lesion using the optimal surgical tool, such as bayoneted forceps or the size-matched Cupped Forceps. An appropriate size Scaffold must allow insertion into the lesion cavity without creating excessive tissue tension (for example, causing tissue blanching or bulging of the spinal cord). The Investigator must use intraoperative ultrasound to confirm placement of the Scaffold in the lesion cavity. If the Scaffold causes excessive tissue tension, it must be removed and disposed of according to instructions in the Site Instruction Manual. The Investigator must then choose another size Scaffold and ensure that the Scaffold is trimmed, if necessary, such that implantation as described above does not result in excessive tissue tension.

Next, the Investigator will close the dura and the surgical wound, and dress the wound according to standard clinical practice. If there is significant spinal cord edema or swelling such that a standard primary dural closure would compress spinal cord tissue, a duraplasty can be considered. Following surgery, resting vital signs will be monitored and neurological examinations will be conducted in a manner consistent with standard post-anesthesia care. In addition, the site will document the time on ventilator support post-Scaffold implant.

During the 72-hours post-Scaffold implant, changes in ventilator parameters due to worsening of pulmonary function will be documented, including any change from partial to full mechanical ventilation or a longer-than-expected time to be weaned from ventilation. For changes in ventilator parameters that are necessitated by a worsening of pulmonary function, including changes from partial to full mechanical ventilation or a longer-than-expected time to be weaned from ventilation, the Investigator will assess if the worsening is due to the Scaffold or the Scaffold implant procedure.

Thorough neurological exams and Vital Capacity (VC) for subjects who are not ventilator dependent will be conducted post-Scaffold implantation at 24-hours, 48-hours, 72-hours, 1-week, and at discharge.

All relevant information regarding the preparation and implantation of the Scaffold will be recorded on the surgical source document, including (in chronological order below):

- 1 Surgery start date/time — the date/time of the first incision

- 2 Scaffold implant start date/time — the date/time the dura is opened/entered if already open
- 3 Scaffold implant stop date/time — the date/time the dura is closed
- 4 Surgery stop date/time — the date/time of closing the skin after all surgical procedures and the Scaffold implant are complete

In addition, the Scaffold length, implant location and any problems encountered (e.g., Scaffold fracture, inability to place Scaffold, Scaffold migration, need to secure Scaffold) will be recorded on the surgical source documents. A photo of the intraoperative ultrasound image of the Scaffold in the spinal cord should be included in the source documents along with the photo of the pre-Scaffold spinal cord implantation site. Sites will be asked to take video of the Scaffold implantation procedures according to guidelines described in the Site Instruction Manual.

7.3 Rehabilitation

The goal of post-SCI rehabilitation is to maximize the study subject's level of function in the home and community environments. Rehabilitation should begin once a subject is stable and able to participate. Rehabilitation minimally includes physical and occupational therapy.

The inpatient rehabilitation recommended for study subjects should include at least 3 hours of therapy (usually 2 hours of physical therapy and 1 hour of occupational therapy) 6x/week for an estimated 3—4 weeks. Once the subjects are discharged, outpatient physical therapy should include a minimum of 1 hour of physical therapy 3x/week, and should continue for approximately 2-months. The rehabilitation therapy should focus on mat activities, transfer training, balancing, and possibly trial ambulation with assistive devices. Rehabilitation information will be documented on the Rehabilitation Therapy Log (Section 7.7.14).

Not Applicable.

7.4 Investigational Product Accountability

The Investigator (or designee) will receive the Investigational Product (Scaffolds and Cupped Forceps), and is responsible for the correct storage, management, and handling of the Investigational Product as described in the Instructions For Use (Appendix E) and the Site Investigational Product Management Plan found in the Site Instruction Manual.

7.5 Packaging, Labeling, and Storage

Scaffolds are available in various sizes (See Table 1 below). The Scaffold dimensional tolerances allow for a +5% and -15% range for the diameter and a $\pm 10\%$ range for the length (Table 1).

Table 1	
Scaffold Diameter	Scaffold Length
2mm (1.7–2.1mm)	10mm (9.0–11.0mm)
3mm (2.55–3.15mm)	10mm (9.0–11.0mm)

Each Scaffold will be packaged individually. In addition, each site will be provided with custom size-matched Cupped Forceps to handle the Scaffold during preparation, trimming, and implantation as appropriate. The Scaffolds are fragile and must be handled during preparation with the size-matched Cupped Forceps to ensure the Scaffold is not damaged. Note that the Cupped Forceps must be sterilized by the site prior to each use.

Scaffolds will be accompanied by package labels indicating product name, part number, unique identification number, revision number and lot number; company name and address; manufacture expiration date; a ‘Single Use Only’ label; ‘Sterile’ label; a ‘For Investigational Use Only’ identification statement; and label part number and revision number. Sites should refer to the Site Instruction Manual for additional details on Scaffold and Cupped Forceps inventory management. The ‘Instructions for Use’ (Appendix E) contains details on intended use; product description; product handling, warnings, and precautions; indications and contraindications and a Surgical Technique Guide that includes a step-by-step description of the Scaffold preparation and implantation procedure with corresponding figures.

The site should bring all available Scaffolds and sterilized Cupped Forceps into the operating room for the Scaffold implant surgery.

7.6 Demographics and Baseline Assessments

Demographics and Baseline Assessments will be collected and recorded for all subjects.

7.6.1 Demographics

For all subjects, demographic information will be collected at the screening visit and includes age, gender, ethnicity, and race.

7.6.2 Medical and Surgical History

The Investigator or designee will document all study subjects’ general medical and surgical history at the screening visit. At each subsequent study visit, the subject’s condition since the prior study visit will be evaluated. Any change in the subject’s medical condition after enrollment will be assessed to determine if

it meets the definition of a safety event (AE/ADE), serious safety event (SAE/SADE), or a stopping rule and if so, will be documented on the Safety Event eCRF.

7.6.3 Spinal Cord Injury Assessment

The spinal cord injury-related data will be collected for all study subjects at screening and will include: date, time, and cause of the injury; complete ISNCSCI exam including NLI, AIS grade, sensory scores and motor scores; size and location of the spinal cord injury as assessed by MRI; and details of all prior SCI therapies/procedures in the field and before study participation.

7.7 Safety Assessments Description

Study subjects will undergo all safety assessments according to the schedule of assessments, which is indicated in each section below.

7.7.1 Prior and Concomitant Medications

Subjects may receive medications to treat safety events and routine treatment for underlying medical conditions as deemed necessary by the Investigator. At each visit, the site will obtain a complete listing of all medications currently being taken by the subject. Any changes, additions or deletions in the administration of concomitant medications will be recorded in the eCRF. The medication information documented will include the name, indication, dosage, and the dates of start and discontinuation.

All medications and other treatments taken by a subject beginning 30 days before Scaffold implantation and continuing throughout the subject's participation in the study will be recorded up to and including the 12-month Long-term Follow-up Visit. Thereafter, Concomitant Medications information will not be collected or recorded in the eCRFs.

7.7.2 Prior and Concomitant Interventions and Procedures

Information regarding diagnostic or therapeutic interventions or procedures will be documented along with time, date, and reason for the intervention or procedure. If an intervention or procedure is implemented to treat a safety event, the safety event must be recorded on the eCRF, along with all relevant information

All diagnostic or therapeutic interventions or procedures beginning 30 days before Scaffold implantation and continuing throughout the subject's participation will be recorded up to and including the 12-month Long-term Follow-up Visit. Thereafter, Concomitant Interventions, and procedures information will not be collected or recorded in the eCRFs.

7.7.3 Vital Sign Measurements

Resting vital signs, including the resting blood pressure, resting pulse, respiratory rate, and temperature will be measured at all study visits. Weight and height (actual, self-reported or family-reported) will be collected at screening and BMI will be calculated based on reported weight and height. Subjects will have vital signs recorded at each visit.

Vital signs will be monitored before, during, and after surgery, including heart rate, systolic and diastolic blood pressure, mean arterial pressure (MAP), oxygenation and ventilation rate. Source documentation (e.g., anesthesia flow sheets) will be collected, and significant changes will be documented and noted as safety events if appropriate.

7.7.4 Physical Examination, including Weight and Height

A complete physical examination (Head, Ears, Eyes, Nose and Throat (HEENT), cardiovascular, respiratory, gastrointestinal, neurological unrelated to SCI, dermatologic, and musculoskeletal systems) will be performed at pre-specified study visits. The Investigator should include assessment of any sexual problems prior to the spinal cord injury during the screening physical examination. The Investigator may perform a physical examination at any time during the study if indicated by change in a subject's medical history or condition. Relevant changes in the subject's condition at any evaluation will be recorded.

Any clinically significant physical abnormalities (with the exception of surgical scars) noted at the hospital discharge and Follow-up/Primary Endpoint Follow-up/Long-term Follow-up Visits through the 24-month Long-term Follow-up Visit that were not present at screening should be recorded as safety events.

Physical exams will be conducted at screening, discharge, 6-months, 12-months, and 24-months post-Scaffold Implantation.

7.7.5 Clinical Laboratory Tests

All study visits require blood samples collected for routine clinical laboratory testing, including:

- Hematology: Complete Blood Count (CBC) with Differential, consisting of white blood cell (WBC) and red blood cell count, platelet count, hemoglobin, and differential counts (total neutrophils, eosinophils, basophils, lymphocytes, and monocytes).
- Comprehensive Metabolic Panel (CMP): blood urea nitrogen (BUN), glucose, creatinine, sodium, potassium, chloride, calcium, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), carbon dioxide.

Subjects will have blood samples collected for the required clinical laboratory assessments at all study visits. In addition, at the screening visit, serum pregnancy testing, blood type and coagulation tests (PT, PTT, INR), blood alcohol, and urine drug toxicology will also be performed. Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) will be assessed at screening, discharge, 1-month, 2-months, and 3-months. The results of the screening laboratory tests must be received and confirmed with the eligibility criteria before the subjects proceed to Scaffold implantation.

7.7.6 Neurological Examinations

Neurological examinations include 11 body systems in which findings are either normal or abnormal. Neurological examinations also include 5 tendon reflexes and each will be scored on a 5-point scale (0=absent, 1=reduced, 2=normal, 3=increased, and 4=clonus) for left and right side. In addition, the presence/absence of hip abduction/adduction and great toe flexion/extension on the left and right sides will be assessed for using a 2-point scale (0=absent; 1=present).

Neurological examinations will be performed at screening, on the day of open spine surgery, and at all study visits after implantation of the Scaffold. The additional assessment of the presence/absence of hip abduction/adduction and great toe flexion/extension will be conducted beginning at hospital discharge and for the remaining study visits.

7.7.7 Magnetic Resonance Imaging (MRI)

MRI assessment of acute SCI is focused on identifying the site, type, and severity of injury, and to evaluate different pathologic features such as degree of spinal cord compression, intramedullary spinal cord hemorrhage, and edema. All study MRIs should be conducted without contrast but MRIs with and/or without contrast for the retrospectively identified subjects will be acceptable.

The screening MRI is required to estimate the contusion dimensions (length and anteroposterior diameter), determine the contusion location, and identify presence or absence of a cavity, parenchymal sparing, atrophic changes of the cord, and areas of edema and hemorrhage.

The follow-up MRIs will be used to assess the presence or absence of cyst formation, where a cyst is defined as a well-defined, fluid-filled area of tissue loss within the spinal cord that is isointense with cerebrospinal fluid (CSF) on all MRI sequences. The follow-up MRIs will also be used to assess atrophic changes of the cord, parenchymal sparing, areas of edema and hemorrhage, and, if possible, to assess the Scaffold. If the subject cannot have an MRI for any medical reason at any of the Follow-up or Long-term Follow-up Visits, a CT scan without contrast may be obtained.

The minimum required MRI sequences for all study MRIs, including maximum slice / gap thickness, are as follows:

- Sagittal T1-weighted Images — 3 mm/1mm
- Sagittal T2-weighted Images — 3 mm/1mm
- Axial T2-weighted Images — 5 mm/1mm
- Axial T1-weighted Images — 5 mm/1mm

There are additional recommended MRI sequences to be considered when medically appropriate, including Short Tau Inversion Recovery (STIR) and Gradient Echo Images (GRE) sequences. Refer to the Site Instruction Manual for details.

MR images and an MRI report (or CT images and report, if MRI not medically feasible at Follow-up/Primary Endpoint Follow-up/Long-term Follow-up Visits) should be included in the source documents and provided to the study Sponsor per the instructions in the Site Instruction Manual. For more specific details on the recommended MRI sequence acquisition parameters, please see the Site Instruction Manual.

The study MRI images are also sent to a central core radiology CRO, where they are stored, managed, and analyzed by an independent central neuroradiologist.

The Investigator will use the subject's screening MRI, and any other available imaging study such as CT or intraoperative ultrasound, to confirm the inclusion criterion that an eligible spinal contusion is present prior to proceeding to Scaffold implant. Follow-up MRI studies will be performed after Scaffold implantation at 72-hours, 3-months, 6-months (Primary Endpoint), 12-months and 24-months.

7.7.8 Intraoperative Ultrasound

Intraoperative ultrasound will be used to characterize the contusion, such as the contusion size, location, and presence or absence of a cavity. Ultrasound images of the spinal cord, as well as ultra-sound recordings (if available), should be included in the source documents and provided to the Sponsor.

An ultrasound will be performed intraoperatively and prior to the Scaffold implantation to confirm the contusion size and location, and presence or absence of a cavity. A second intraoperative ultrasound will be performed after Scaffold implantation to record placement of the Scaffold.

7.7.9 Beck Depression Inventory II (BDI-II) (Appendix K)

The Beck Depression Inventory II (BDI-II), created by Aaron T. Beck, is a 21-question multiple-choice self-report inventory, one of the most widely used psychometric tests for measuring the severity of

depression. In its current version, the BDI-II is designed for individuals aged 13 and over, and comprises items relating to symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex. The questionnaire may be administered orally by study personnel who record the subject's responses. The subject should be instructed to select the statement that best describes the way (s)he has been feeling during the past two weeks including the present day.

The BDI-II is scored by adding up the score (0—3) of each of the 21 questions, and the assessment of the scores are as described below.

0—13 Minimal depression

14—19 Mild depression

20—28 Moderate depression

29—63 Severe depression

A score of 17 or higher may indicate the presence of depression and further evaluation by a mental health professional should be considered. A subject who gives a rating of 2 or 3 on item 2 (hopelessness) or item 9 (suicide ideation) should be closely scrutinized for suicide potential.

The BDI-II will be used to assess the subject's mood at hospital discharge and at months 1, 2, 3, 6, and 12.

7.7.10 Intraoperative Neuromonitoring - Somatosensory Evoked Potentials (SSEPs)

Somatosensory evoked potentials (SSEP) will be performed intra-operatively prior to proceeding to Scaffold implantation. The SSEP should be performed after the completion of the spine stabilization surgery and prior to the durotomy to determine if there is a clear and significant signal through the injury site based on the judgment of the Investigator. If there is a clear signal through the injury site, the subject does not meet the inclusion/exclusion criteria for the study, must not have the Scaffold implanted, and should be withdrawn from the study. These subjects are categorized as "enrolled but not treated" and should be followed for safety through hospital discharge as described in Section 6.5.

The site should record the SSEPs performed prior to initiating the Scaffold implant procedure and document the presence or absence of a clear and significant signal through the injury site.

Additional SSEPs Required for Subjects with T2 or T3 NLI

As an additional safety measure, median and ulnar nerve SSEP monitoring will be performed on all subjects with a T2 or T3 neurological level of injury to identify potential loss of neurologic function of the hand at

the C8 and T1 neurologic levels. The SSEP monitoring should be performed for the duration of the investigational procedure (from durotomy through Scaffold placement and dural closure). The median nerve signals may be used as a control for the C8 and T1 levels as these signals also include contribution from C7. An adequate baseline should be obtained per institutional protocol to ensure interpretable recordings from both median and ulnar SSEPs prior to beginning the investigational procedure (i.e., prior to the durotomy). Should the SSEP recordings indicate potential loss of function, appropriate steps should be taken per institutional guidelines such as adjustment of anesthesia, operating procedure, etc. The Investigator should determine whether the Scaffold can be placed safely if intraoperative neuromonitoring indicates a deterioration prior to Scaffold placement.

The Investigator may also utilize additional modes of intraoperative neuromonitoring such as MEPs, if the risk of upper extremity movement is outweighed by the potential benefit. If the surgical procedure includes anterior cord manipulation, stronger consideration should be given to use of MEPs of the abductor pollicis brevis (C8, T1).

The site should record the neuromonitoring performed during the investigational procedure if there was a deterioration in the signal, and if any actions were taken.

7.7.11 Monitoring of Pulmonary Function

Changes in pulmonary function, as indicated by changes in ventilator parameters, will be monitored during open spine surgery (durotomy, myelotomy, Scaffold implant, dural closure) and during the 72-hours post-Scaffold implant. Any change from partial to full mechanical ventilation or a longer-than-expected time to be weaned from mechanical ventilation during the 72-hours post-Scaffold implant will be documented. For changes in ventilator parameters that are necessitated by a worsening of pulmonary function, including changes from partial to full mechanical ventilation or a longer-than-expected time to be weaned from ventilation, the Investigator will assess if the worsening is due to the Scaffold or the Scaffold implant procedure. When assessing causality of worsening of pulmonary function to either the Scaffold or the procedure to implant the Scaffold, consider the following muscles of respiration and the nerves that innervate them, and whether any may have been damaged during the investigational procedure:

- Diaphragm – major respiratory muscle – phrenic nerve – (C3 to C5) innervation
- Intercostal muscles – minor respiratory muscles – thoracic segmental nerve innervation
- Accessory muscles of respiration – sternocleidomastoid and scalene muscles – accessory nerve (cranial nerve XI) and cervical nerves (C3-C6) respectively

The site will record the ventilator parameter changes associated with worsening pulmonary function, including change from partial to full mechanical ventilation, or a longer-than-expected time to be weaned from ventilation, and corresponding assessment of causality in the source document/eCRF. Any worsening of pulmonary function associated with need for change in ventilator parameters will also be reviewed by a physician member of the DSMB to assist with assessment of causality to the Scaffold or the procedure to implant the Scaffold.

7.7.12 Vital Capacity (VC)

Vital Capacity (VC) is the maximum amount of air a person can expel from their lungs after a maximum inhalation, and can be used as an indicator of overall pulmonary function in SCI patients. VC is measured with a spirometer, which is a tool for measuring the volume of air inspired and expired by the lungs.

The site will obtain VC from all subjects who are not ventilator dependent at the Screening Visit and at the 24-hour, 48-hour, 72-hour and 1-week Follow-up Visits, and at Hospital Discharge.

7.7.13 Assessment of Skeletal Maturity (Subjects ages 16 and 17 only)

Subjects who are 16–17 years of age may be less skeletally mature than subjects 18 years and older. To enable assessment of the degree to which skeletal maturity at the time of surgery may affect Long-term outcome, a baseline measure of skeletal maturity will be obtained before hospital discharge, but is not required prior to open spine surgery/Scaffold implant. An accepted measure of skeletal maturity must be employed, such as bone age as determined by hand and wrist x-ray or Risser stage as determined by iliac crest x-ray. X-rays obtained during the preoperative period may be used for this assessment.

The Risser classification is used to grade skeletal maturity based on the level of ossification and fusion of the iliac crest apophyses. Classification is as follows:

- Stage 0: no ossification center at the level of iliac crest apophysis
- Stage 1: apophysis over 25% of the iliac crest
- Stage 2: apophysis over 25–50% of the iliac crest
- Stage 3: apophysis over 50–75% of the iliac crest
- Stage 4: apophysis over >75% of the iliac crest
- Stage 5: complete ossification and fusion of the iliac crest apophysis

Method for assessing skeletal maturity and results will be documented in the eCRF.

7.7.14 Rehabilitation Therapy Log

A comprehensive rehabilitation program is recommended for all study subjects as outlined in Section 7.3.

Rehabilitation information, including therapy type, start and stop date, program setting (individual or group), and frequency will be collected in the Rehabilitation Therapy Log and recorded in the eCRFs at hospital discharge and at the 1, 2, 3, 6 and 12-month Follow-up Visits.

7.7.15 General Health Assessment

After the last in-clinic study Long-term Follow-up Visit at 24-months post-implantation of the Scaffold, the subjects will be contacted via telephone on the annual anniversary of the date of the Scaffold implantation (+/- 14 days). The site staff will conduct a general health assessment using the General Health Assessment CRF which will collect subject-reported information on their health throughout the past year, including information on any Serious Safety Events. If the subject reports a neurologic deterioration consisting of loss of bowel or bladder function or complete loss of motor function at any joint that had at least 2+ movement at the prior examination, the subject will be asked to return to the clinic for a follow-up evaluation.

7.8 Efficacy Assessments Description

7.8.1 International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) Scale (Appendix F)

Neurological status will be assessed by the Investigator or a designated trained medical professional according to the International Standards for Neurological Classification of SCI (ISNCSCI) as developed by American Spinal Injury Association (ASIA). Effort should be made to have a single assessor perform the ISNCSCI exams. The ISNCSCI examinations determine the sensory and motor levels, the Neurological Level of Injury (NLI), and the ASIA Impairment Scale (AIS) grade. Sensory function will be tested bilaterally by pinprick (sharp) and light touch sensation. The motor examination will include a bilateral assessment (manual muscle testing score of 0–5 per muscle group) of 10 myotomes. In addition, a rectal examination will be used to assess deep anal pressure sensation and voluntary anal contraction to determine the completeness of the injury. In accordance with the AIS, the injury is considered complete (AIS A) when there is no motor and sensory function in the lowest sacral segments. The 5-grade ASIA Impairment Scale (AIS) will be used to determine the completeness of a subject's injury. Any variables that may affect the ability to obtain a reliable ISNCSCI exam should be eliminated (e.g., temporarily eliminating medication that would interfere with a valid ISNCSCI exam for ventilated subjects). The results from these tests will be used to establish baseline neurological scores, to confirm reliable AIS A status within the 8 hours prior to open spine surgery, and to assess the subject's AIS classification at follow-up examinations. In addition, for consistency in dermatome mapping and documentation of NLI, the ISNCSCI assessor should mark the right and left sensory levels at the right and left nipple line (as instructed in ISNCSCI exam guidelines)

with small horizontal lines and indicate the NLI on the subject. A photograph should be taken and filed with the source documents at each ISNCSCI examination. Changes in NLI should be verified against the NLI at previous exams based on the source documents and the photograph of the NLI.

The ISNCSCI exam will be performed at screening, within the 8 hours prior to spine surgery, at hospital discharge, and at each Follow-up/Long-term Follow-up Visit after discharge up to and including 24-month Long-term Follow-up Visit. At each study visit post-Scaffold implantation, NLI and the motor scores are compared to the pre-surgery ISNCSCI results, using the NLI photographs as appropriate, to determine if a Study Stopping Rule has been triggered (> 2 level deterioration in NLI and/or > 5 point decrease in motor score).

7.8.2 Pain Assessment (Appendix G)

Pain will be assessed using the International Spinal Cord Injury Pain Form and will focus on pain interference with activities, mood and sleep, and on the worst pain problems that a subject had during the last 7 days. The site will interview the subject regarding their pain, including questions on the location of the pain and the frequency of occurrences of pain, and complete the required assessments. The pain assessment at hospital discharge visit will be used as the baseline.

Pain assessment will be performed at hospital discharge and at each Follow up/Long-term Follow-up Visit up to and including the 12-month Long-term Follow-up Visit.

7.8.3 Bowel and Bladder Function Assessments (Appendix H)

Bowel and Bladder function will be assessed using the International Spinal Cord Injury Bowel and Lower Urinary Tract Function (Bladder) Forms. The site will interview the subject on various aspects of their Bowel and Bladder function, including awareness of the need to defecate/urinate, method of bowel emptying/bladder empty, frequency of leakage or incontinence, etc. and will complete the required assessments.

Bowel and Bladder function will be assessed at hospital discharge and at each Follow up/Long-term Follow-up Visit up to and including the 12-month Long-term Follow-up Visit.

7.8.4 Sexual Function (Appendix L)

Sexual function will be assessed using the International Spinal Cord Injury Male and Female Sexual Function Basic Data Sets (version 2.0). The sexual function assessments are designed to record data on sexual function for individuals with spinal cord lesions, and to standardize the collection and reporting of information on sexual function in daily practice.

The site will interview the subject on various aspects of their sexual function, including their interest in discussing sexual issues and any sexual dysfunction related to the spinal cord injury, and will complete the required assessments.

Sexual function will be assessed prior to hospital discharge and at post-Scaffold implant study visits at 1, 2, 3, 6 and 12-months.

7.8.5 Spinal Cord Independence Measure (SCIM) III (Appendix I)

The Spinal Cord Independence Measure III (SCIM III) is, at present, the only comprehensive rating scale that measures the ability of patients with spinal cord lesions (SCL) to perform everyday tasks according to their value for the patient. SCIM III covers 19 tasks, all activities of daily living, grouped into four areas of function (subscales): Self-care (scored 0–20), Respiration and Sphincter Management (0–40), Mobility in Room and Toilet (0–10), and Mobility Indoors and Outdoors (0–30). The final score ranges from 0 to 100, with 0 requiring total assistance and 100 being completely independent.

SCIM III will be administered at hospital discharge and at each Follow up/Long-term Follow-up Visit up to and including the 12-month Long-term Follow-up Visit.

7.8.6 Ferrans and Powers Quality of Life Index – Spinal Cord Injury Version 3 (QLI-SCI III) (Appendix J)

The Quality of Life Index was developed by Carol Estwing Ferrans and Marjorie Powers in 1984 to measure quality of life in terms of satisfaction with life. The QLI measures both satisfaction and importance regarding various aspects of life. Importance ratings are used to weight satisfaction responses, so that scores reflect satisfaction with the aspects of life that are valued by the individual. The QLI produces five scores: quality of life overall and in four domains (health and functioning, psychological/spiritual domain, social and economic domain, and family).

A number of versions of the QLI have been developed for use with various disorders and the general population, and have been reported in more than 200 published studies. A common set of items forms the basis for all versions, and items pertinent to each disorder were added to create the illness-specific versions. The version being used in this study is specific to Spinal Cord Injury.

QLI-SCI III will be administered at hospital discharge and at each Follow up/Long-term Follow-up Visit up to and including the 12-month Long-term Follow-up Visit.

7.9 Study Observations and Procedures by Visits

7.9.1 Screening Visit (Visit 1)

Subjects meeting the eligibility criteria listed in Section 6 may be screened for the study after the nature and purpose of the protocol have been explained to them, and they or a legally authorized representative have voluntarily granted **written** informed consent to participate. All subjects will have a screening evaluation after informed consent has been obtained and within the 7 days prior to the Scaffold implantation such that all results are received and reviewed to confirm that the subject meets the study inclusion/exclusion criteria. If clinical assessments are conducted during post-injury care and before informed consent is obtained, they may be used for the study once informed consent is obtained. The following safety-related procedures will be performed at the screening visit for all subjects:

- Informed consent
- Demographics (Section 7.6.1)
- Medical and surgical history (Section 7.6.2)
- Spinal cord injury assessment (Section 7.6.3)
- Prior and concomitant medications, interventions, and procedures (Section 7.7.1)
- Measurement of resting vital signs (Section 7.7.3)
- Complete physical examination including interview regarding sexual function prior to injury (Section 7.7.4)
- Clinical laboratory tests including screening laboratory tests - serum pregnancy test, blood alcohol and urine drug toxicology, blood type and coagulation test (Section 7.7.5)
- Erythrocyte Sedimentation Rate (ESR) & C-Reactive Protein (CRP)
- Neurological exam (Section 7.7.6)
- ISNCSCI Exam (Section 7.8.1)
- MRI without contrast (Section 7.7.7)
- Vital Capacity for subjects not ventilator dependent (Section 7.7.12)
- For subjects ages 16, 17, assessment of skeletal maturity must be performed prior to hospital discharge, but is not required prior to open spine surgery/Scaffold implant (Section 7.7.13). X-rays obtained during the preoperative period may be used for this assessment.

7.9.2 Open Spine Surgery and Scaffold Implantation (Visit 2)

The open spine surgery during which the Scaffold will be implanted ideally should be performed within 24-hours of injury, but Scaffold implantation must begin ≤ 7 days from the time of the spinal cord injury. The required study assessments are listed below.

Before Surgery: On the day of surgery, the following safety assessments are required before surgery:

- Measurement of resting vital signs (Section 7.7.3)
- Clinical laboratory tests (Section 7.7.5)
- Neurological exam (Section 7.7.6)
- Confirmatory ISNCSCI Exam within the 8 hours prior to surgery (Section 7.8.1)
- Ventilator settings for subjects who are on temporary ventilator support

Scaffold Implant Procedure: The following assessments will be conducted intraoperatively:

- Vital signs will be monitored before, during, and after surgery, including heart rate, systolic and diastolic blood pressure, mean arterial pressure (MAP), oxygenation and ventilation rate. Source documentation (e.g., anesthesia flow sheets) will be collected, and significant changes will be documented and noted as safety events if appropriate. SSEP will be performed on all subjects prior to the durotomy to determine if there is a clear and significant signal through the injury site based on the judgment of the Investigator (Section 7.7.10). If there is a clear signal through the injury site, the subject does not meet the inclusion/exclusion criteria for the study, must **not** have the Scaffold implanted, and should be withdrawn from the study. These subjects are categorized as “enrolled but not treated” and should be followed for safety through hospital discharge as described in Section 6.5.
 - For subjects with a T2 or T3 neurological level of injury, intraoperative neuromonitoring minimally consisting of median and ulnar nerve SSEPs will be performed to identify potential loss of neurologic function of the hand at the C8 and T1 neurologic levels Refer to Section 7.7.10 for details.
- Documentation of changes in ventilator parameters due to worsening of pulmonary function (Section 7.7.11). If changes in ventilator settings are necessitated by worsening of pulmonary function, the Investigator will assess if the worsening is due to the Scaffold implant procedure.
- After eligibility is confirmed, the Scaffold implantation procedure can be performed according to the Instructions for Use (Appendix E), including the following
 - Collection of a sample of the spontaneous exudate to be submitted to pathology for routine examination/testing, for example H&E staining for histology. Note that irrigated tissue

fragments and cells may best be collected in a test tube for subsequent preparation of a cell pellet by centrifugation.

- Intraoperative ultrasound with photograph prior to Scaffold implantation to confirm the contusion size and location, and presence or absence of a cavity (Section 00)
- Intraoperative ultrasound with photograph after Scaffold implantation to document placement of Scaffold in the spinal cord (Section 7.7.8)
- Video of the Scaffold implant procedure

Post-Surgery: Immediately after surgery, the following safety assessments will be performed:

- Measurement of resting vital signs (Section 7.7.3)
- Clinical laboratory tests (Section 7.7.5)
- Neurological exam (Section 7.7.6)
- Ventilator settings for subjects who are on temporary ventilator support. During the 72-hours post-Scaffold implant, changes in ventilator parameters due to worsening of pulmonary function including any change from partial to full mechanical ventilation or a longer-than-expected time to be weaned from ventilation will be documented and the Investigator will assess if any of these changes are due to the Scaffold or the Scaffold implant procedure.
- Concomitant medications, interventions, and procedures (Section 7.7.1, 7.7.2)
- Safety event monitoring (Section 8)

7.9.3 Follow-up Post-Scaffold Implant and Prior to Hospital Discharge (Follow-up Visits 3 – 6)

Subjects will be cared for following the hospital standard of care for spinal cord surgery patients. The following study specific assessments will be performed post-Scaffold implant at 24-hours (± 6 hours), 48-hours (± 6 hours), 72-hours (± 8 hours) and 1-week (± 1 day):

- Measurement of resting vital signs (Section 7.7.3)
- Clinical laboratory tests (Section 7.7.5)
- Neurological exam (Section 7.7.6)
- Vital Capacity for subjects not ventilator dependent (Section 7.7.12)
- Concomitant medications, interventions, and procedures (Section 7.7.1, 7.7.2)
- Safety event monitoring (Section 8)
- MRI without contrast at 72-hour Follow-up Visit only (Section 7.7.7)

7.9.4 Hospital Discharge (Visit 7)

Subjects will have the following procedures performed on the day of hospital discharge. Note that the assessments must be performed on the date of discharge, and there is no visit window.

- Measurement of resting vital signs (Section 7.7.3)
- Complete physical examination (Section 7.7.4)
- Clinical laboratory tests (Section 7.7.5)
- Erythrocyte Sedimentation Rate (ESR) & C-Reactive Protein (CRP)
- Neurological examinations including hip abduction/adduction and great toe flexion/extension (Section 7.7.6)
- Vital Capacity for subjects not ventilator dependent (Section 7.7.12)
- ISNCSCI Exam (Section 7.8.1) and comparison of NLI and motor score to the pre-surgery ISNCSCI results to determine if a Study Stopping Rule has been triggered (> 2 level deterioration in NLI and/or > 5-point decrease in motor score)
- Baseline pain assessment (Section 7.8.2)
- SCIM III (Section 7.8.5)
- QLI-SCI III (Section 7.8.6)
- BDI-II (Section 7.7.9)
- Rehabilitation Therapy Log (Section 7.7.14)
- Concomitant medications, interventions, and procedures (Section 7.7.1, 7.7.2)
- Safety event monitoring (Section 8) including a check for deterioration of NLI by > 2 levels which would trigger a Study Stopping Rule
- For subjects ages 16, 17, if not already completed, assessment of skeletal maturity must be performed prior to hospital discharge (Section 7.7.13)

7.9.5 Follow-Up Visits (Visits 8 – 10)

Following hospital discharge, subjects will be scheduled for in-clinic visits at the following time points post-Scaffold implant: 1-month (± 3 days), 2-months (± 4 days), and 3-months (± 7 days). The following study assessments will be conducted during the post-Scaffold implant Follow-up Visits:

- Measurement of resting vital signs (Section 7.7.3)
- Clinical laboratory tests (Section 7.7.5)
- Erythrocyte Sedimentation Rate (ESR) & C-Reactive Protein (CRP) (Section 7.7.5)

- Neurological examinations including hip abduction/adduction and great toe flexion/extension (Section 7.7.6)
- ISNCSCI Exam (Section 7.8.1) and comparison of NLI and motor score to the pre-surgery ISNCSCI results to determine if a Study Stopping Rule has been triggered (> 2 level deterioration in NLI and/or > 5 point decrease in motor score)
- Pain assessment (Section 7.8.2)
- Bowel and Bladder function assessments (Section 7.8.3)
- Sexual Function (Section 7.8.4)
- SCIM III (Section 7.8.5)
- QLI-SCI III (Section 7.8.6)
- BDI-II (Section 7.7.9)
- MRI without contrast **at 3-months only** (Section 7.7.7)
- Rehabilitation Therapy Log (Section 7.7.14)
- Concomitant medications, interventions, and procedures (Section 7.7.1, 7.7.2)
- Safety event monitoring (Section 8) including a check for deterioration of NLI by > 2 levels which would trigger a Study Stopping Rule

7.9.6 Primary Endpoint - 6-month Follow-up (Visit 11)

The 6-month Primary Endpoint Follow-up Visit is the timepoint at which the primary endpoint analysis is conducted. The 6-month Primary Endpoint Follow-up Visit is scheduled at 6-months (± 30 days) post-Scaffold implantation.

The following study assessments will be conducted:

- Measurement of resting vital signs (Section 7.7.3)
- Complete physical examination (Section 7.7.4)
- Clinical laboratory tests (Section 7.7.5)
- Neurological examinations including hip abduction/adduction and great toe flexion/extension (Section 7.7.6)
- MRI without contrast (Section 7.7.7)
- Pain assessment (Section 7.8.2)
- ISNCSCI Exam (Section 7.8.1) and comparison of NLI and motor score to the pre-surgery ISNCSCI results to determine if a Study Stopping Rule has been triggered (> 2 level deterioration in NLI and/or > 5-point decrease in motor score)
- Bowel and Bladder function assessments (Section 7.8.3)

- Sexual Function (Section 7.8.4)
- SCIM III (Section 7.8.5)
- QLI-SCI III (Section 7.8.6)
- BDI-II (Section 7.7.9)
- Rehabilitation Therapy Log (Section 7.7.14)
- Concomitant medications, interventions, and procedures (Section 7.7.1, 7.7.2)
- Safety event monitoring (Section 8) including a check for deterioration of NLI by > 2 levels which would trigger a Study Stopping Rule

7.9.7 Long-term Follow-Up Visits (Visits 12 -21)

In-clinic (12-months and 24-months):

The final in-clinic study visits will be conducted at 12-months (± 30 days) and 24-months (± 30 days) post-Scaffold implant. The following study assessments are required at these visits:

- Measurement of resting vital signs (Section 7.7.3)
- Complete physical examination (Section 7.7.4)
- Clinical laboratory tests (Section 7.7.5)
- Neurological examinations including hip abduction/adduction and great toe flexion/extension (Section 7.7.6)
- MRI without contrast (Section 7.7.7)
- ISNCSCI Exam (Section 7.8.1) and comparison of NLI and motor score to the pre-surgery ISNCSCI results to determine if a Study Stopping Rule has been triggered (> 2 level deterioration in NLI and/or > 5-point decrease in motor score)
- Safety event monitoring (Section 8) including a check for deterioration of NLI by > 2 levels which would trigger a Study Stopping Rule

In addition, the following assessments will be conducted at the 12-month Long-term Follow-up Visit only:

- Pain assessment (Section 7.8.2)
- Bowel and Bladder function assessments (Section 7.8.3)
- Sexual Function (Section 7.8.4)
- SCIM III (Section 7.8.5)
- QLI-SCI III (Section 7.8.6)
- BDI-II (Section 7.7.9)

- Rehabilitation Therapy Log (Section 7.7.14)

Telephone (Visits 14 – 21)

For years 3 through 10, the site will contact the subjects via telephone on or about the annual anniversary of the date of their Scaffold implantation (date of Scaffold implantation \pm 60 days) to collect general health information, including any serious safety events. If the subject reports a neurologic deterioration consisting of loss of bowel or bladder function or complete loss of motor function at any joint that had at least 2+ movement at the prior examination, the subject will be asked to return to the clinic for a follow-up evaluation.

7.9.8 End-of-Study Assessment

The end-of-study assessment will capture the date of the final study visit, whether or not the subject completed the study, and the reason for early withdrawal if the subject did not complete the study.

An end-of-study assessment will be conducted over the telephone at the Long-term Follow-up Visit at year 10 \pm 60 days or earlier if the subject withdraws from the study at any time between hospital discharge and the 10-year Long-term Follow-up Visit.

7.10 Study Stopping Rules

The study may be held or terminated should safety events occur that are related to the Scaffold and/or implant procedure, and distinct from a safety event that may be associated with standard-of-care spine stabilization surgery or sequelae considered part of the normal course of a non-penetrating SCI following such surgery, as determined by the DSMB. Following urgent consultation with the DSMB and regulatory authorities as appropriate, the study may be stopped if a subject experiences:

1. A fatal or severe allergic reaction to the Scaffold as manifested by anaphylactic symptoms such as rash, wheezing, blood pressure change, histiocytosis, and lymphedema, or another fatal or severe allergic reaction to the Scaffold.
2. Clearly defined septic cord abscess.
3. Actual parenchymal abscess at the site of the implant.

Note that if a wound infection or a spinal cord abscess is suspected, an MRI without contrast will be obtained to rule out cord abscess or spreading parenchymal injury. Equivocal findings on MRI would prompt cerebrospinal fluid (CSF) sampling to rule out meningitis and/or cord abscess and to obtain culture to guide antibiotic treatment.

4. Ascending Neurological Level of Injury (NLI) by more than 2 levels compared to the Pre-Surgery Visit NLI.
5. Motor deterioration of at least a 5-point change of the motor score compared with Pre-Surgery Visit motor score.

Examples of medical events that would not halt the study include soft tissue wound infection or dehiscence, surgical injury to the cord, or progressive neurological deterioration that would be normally expected for an AIS A subject, as determined by the DSMB. Because the study is being conducted in complete SCI patients, significant clinical progression of the contusion is not expected but there may be limited changes in the neurological exam. However, there should be no degradation in sensory or motor neurological function beyond that typically seen in the AIS A subject (i.e., a typical AIS A subject could have degradation in neurological exam involving 2 or fewer sensory levels/NLI or motor deterioration of less than a 5-point change of the motor score compared with the pre-surgery exam). It will be impossible to distinguish minor neurologic worsening specifically attributable to side effects of the Scaffold from the normal course of a contusion injury. Therefore, stoppage of the study for neurological worsening would only be considered for significant unanticipated events such a change in NLI indicating a greater than 2-dermatome level worsening.

Should there be an occurrence of deterioration in a subject's sensory or motor score following implantation of the Scaffold that is serious and possibly, probably, or definitely related to the Scaffold (SADE – see Section 8.2.2 for details), the site must report the event to the Sponsor designer within 24 hours (see Section 8.5 for details). Further subject enrollment will be held to allow for review of the event by the Sponsor, FDA, and the DSMB.

7.11 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will be formed to monitor and review the study results. The DSMB will comprise an independent group of at least 3 members (ideally a neurosurgeon, a physical medicine and rehabilitation physician, and a statistician) that has no formal involvement with the subjects or the conduct of the study, and function independently from the Sponsor and the Contract Research Organization hired to conduct the study. In collaboration with the Sponsor, the DSMB will develop a charter defining its membership, responsibilities, meeting format/schedule, and reporting. The DSMB charter will be finalized prior to enrolling the first subject.

The DSMB chair will be notified of all serious safety events, UADEs, Safety Events of Interest (Section 8.3) and Study Stopping Rules (Section 7.10) via a MedWatch form, and will have the opportunity to convene a DSMB meeting to review any safety events of concern.

The DSMB will meet on a regular basis as outlined in the DSMB Charter, but not less than twice per year. The DSMB will be empowered to meet ad hoc at the discretion of the DSMB chair, Investigator, or Sponsor in the event of a Serious Safety Event, Unanticipated Adverse Device Effect (UADE – see Section 8.2.3 for details), Safety Event of Interest (Section 8.3), or safety events that meet Study Stopping Rules (Section 7.10). Study results including all safety data, established study hold rules, and established study Stopping Rules will be reviewed periodically according to the DSMB charter to determine if there are safety concerns with the Scaffold that require early study termination.

7.12 Appropriateness of Assessments

The efficacy measures utilized include the AIS grading, NLI, and the ISNCSCI motor and sensory scores. Safety measures used in this study are standard for clinical studies of investigational products in SCI subjects.

8 SAFETY EVENTS

The Investigator is responsible for the detection, documentation and follow-up of all safety events meeting the criteria and definitions outlined below.

8.1 Definition of Safety Event

A safety event is any untoward medical occurrence, unintended disease or injury or any untoward clinical sign (including a clinically significant abnormal laboratory finding) in subjects whether or not related to the investigational product (Scaffold) or to the procedures involved (including any procedure in the clinical study protocol).

8.1.1 Not Device or Procedure Related — Adverse Event (AE)

Safety events that are not related to the investigational device or the procedure to implant the investigational device are referred to as Adverse Events (AEs).

8.1.2 Device or Procedure Related — Adverse Device Effect (ADE)

An Adverse Device Effect (ADE) is a safety event related to the use of an investigational medical device. This includes any safety event resulting from insufficiencies or inadequacies in the Instructions For Use (Appendix E), the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. This includes any event that is a result of a use error or intentional misuse.

8.2 Definitions of Serious Safety Events

A safety event is serious if the event:

- Led to a death.
- Led to a serious deterioration in health that either:
 - Resulted in a life-threatening illness or injury, or
 - Resulted in an injury or permanent impairment of a body structure or a body function, or
 - Required in-subject hospitalization or prolongation of existing hospitalization, or
 - Resulted in medical or surgical intervention to prevent life-threatening illness
- Led to fetal distress, fetal death, or a congenital abnormality or birth defect

This includes Scaffold deficiencies that might have led to a serious adverse event if:

- Suitable action had not been taken, or
- Intervention had not been made, or
- If circumstances had been less fortunate. These are handled under the safety event reporting system.

A planned hospitalization for a pre-existing condition, or a procedure required by the clinical study protocol, without a serious deterioration in health, is not considered to be a serious safety event.

8.2.1 Not Device or Procedure Related — Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is a safety event that has resulted in any of the consequences characteristic of a serious safety event (Section 8.2) and that is not device or procedure related.

8.2.2 Device or Procedure Related — Serious Adverse Device Effect (SADE)

A Serious Adverse Device Effect (SADE) is a device or procedure-related safety event that has resulted in any of the consequences characteristic of a serious safety event (Section 8.2) and is an event by its nature, incidence, severity, or outcome that has been previously identified in the Risk Management section of the Report of Prior Investigations and Instructions for Use.

8.2.3 Unanticipated — Unanticipated Adverse Device Effect (UADE)

An Unanticipated Adverse Device Effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, an Investigational product, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the clinical study protocol, the risk section of Instructions for Use, the Report of Prior Investigations, or application (including a supplementary plan or application), or any other unanticipated serious problem

associated with an investigational product that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.3 Safety Events of Interest

Because this is an early feasibility study, safety events of interest have been identified for assessment of potential risk associated with the use of the Scaffold. Note that the DSMB will be notified of all safety events of interest, and will review all safety data periodically.

Safety events of interest for assessment of potential risk associated with the use of the Scaffold

1. Scaffold migration or malposition
2. Untoward physiologic reaction to PLGA-PLL materials
3. Scaffold-related loss of motor or sensory neurologic function
4. Increased inflammatory response
5. Persistent cerebrospinal fluid leak
6. Damage to adjacent structures post-Scaffold implant
7. Re-operation or removal of the Scaffold
8. Hemorrhage into or around the spinal cord causing neurologic deficit or possible need for further surgery
9. Surgical infection
10. Increased anesthesia time
11. Adhesion between the spinal cord and dura
12. Postoperative symptomatic or asymptomatic intraspinal cyst or syrinx

8.4 Safety Event Assessments

All safety events will be monitored in conjunction with the study assessment schedule and will be reported to the FDA on an annual basis in the IDE Progress Report and in the Clinical Study Report.

8.4.1 Assessment of Intensity

The Investigator will make an assessment of intensity for each safety event reported. The intensity of each safety event recorded on the eCRF should be assigned to one of the following:

- Mild: an event that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities
- Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: an event that prevents normal everyday activities

A safety event that is assessed as “severe” should not be confused with a **serious** safety event (SAE or SADE). *Severity* is a term used to describe the intensity of a specific event, and both serious and non-serious safety events can be assessed as severe. The event itself, however, may be of relatively minor medical significance (such as a severe headache). This is not the same as **serious**, which is based on the subject’s or event’s outcome or on action criteria usually associated with events that pose a threat to a subject’s life or functioning. See Section 8.2.1 for definition of SAE and Section 8.2.2 for definition of SADE.

8.4.2 Assessment of Causality

The Investigator will assess the relationship between each safety event and both the Scaffold and the procedure to implant the Scaffold using the definitions listed below. Note that a safety event may be related to the Scaffold or the procedure to implant the Scaffold or both. The Investigator should assess causality of each safety event to the Scaffold independent from the procedure and to the procedure independent from the Scaffold.

Investigational Product – Scaffold

- **Definitely Related:** The safety event has a strong temporal relationship to the Scaffold. The safety event is most likely explained by Scaffold. The safety event is consistent with a known response to the Scaffold. Another etiology is unlikely or significantly less likely.
- **Probably Related:** The safety event has a strong temporal relationship to the Scaffold. The safety event is more likely explained by the Scaffold than by another cause.
- **Possibly Related:** The safety event has a reasonable temporal relationship to the Scaffold. The safety event could have been due to another equally likely cause.
- **Not Related:** The subject did not receive the Scaffold **OR** the safety event has no temporal relationship to the Scaffold **OR** the safety event has a much more likely alternate etiology **OR** the safety event is due to underlying injury or concurrent illness or effect of another drug.

Procedure to Implant the Investigational Product (Scaffold)

- **Definitely Related:** The safety event has a strong temporal relationship to the procedure to implant the Scaffold. The safety event is most likely explained by the procedure to implant the Scaffold. The safety event is consistent with a known response to the procedure to implant Scaffold. Another etiology is unlikely or significantly less likely.
- **Probably Related:** The safety event has a strong temporal relationship to the procedure to implant the Scaffold. The safety event is more likely explained by the procedure to implant the Scaffold than by another cause.

- Possibly Related: The safety event has a reasonable temporal relationship to the procedure to implant the Scaffold. The safety event could have been due to another equally likely cause.
- Not Related: The subject did not have the procedure to implant the Scaffold **OR** the safety event has no temporal relationship to the procedure to implant the Scaffold **OR** the safety event has a much more likely alternate etiology **OR** the safety event is due to underlying injury or concurrent illness or effect of another drug.

Even in situations in which minimal information is available for the initial safety event, it is important that the Investigator always make an assessment of causality for every event before transmitting the Serious Safety Event Report form or the safety event eCRF page(s) to the Sponsor. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The Investigator may change his or her opinion of causality in light of follow-up information and amend the Serious Safety Event Report form and safety event eCRF page(s) accordingly.

8.4.3 Assessment of Outcome

All safety events must be followed until they are resolved, the condition stabilizes, the events are otherwise explained, or the subject is lost to follow-up. The Investigator will assess the outcome of the event by using the following:

- Resolved: The event resolved or the subject recovered without sequelae. An event (either serious or nonserious) occurred and had an endpoint, and the subject experienced no restrictions. Examples include stent placement for coronary artery disease (an investigational product implanted is not a sequela), an appendectomy (a scar is not a sequela), a postoperative wound infection, or an upper respiratory tract infection.
- Resolved with sequelae: The event has at least one secondary outcome that may result in permanent disability, functional limitation, or both. Such sequelae are usually limited to serious safety events. Examples include hip replacement resulting in foot drop (foot drop is not the intended outcome but is a risk of surgery), stroke resulting in paralysis, or emboli formation after a bacterial infection resulting in a renal infarct and loss of renal function.
- Not resolved: At the end of the study, a non-serious event either has not changed in intensity or may not have recovered to baseline values, and the outcome is unknown. Examples include headache, low-grade fever, or nausea.
- Unknown: The subject has withdrawn from the study prematurely or is lost to follow-up, and the status of the event is unknown.
- Death

8.5 Serious Safety Events, Safety Events of Interest, and Safety Events that Meet Study Stopping Rules Reporting Requirements

Once the Investigator determines that a safety event meets the definition of *serious* (SAE or SADE), or is a safety event of interest (Section 8.3), or meets the study Stopping Rules (Section 7.10), the Investigator or their designee must notify the Sponsor or designee within 24-hours of becoming aware of the event.

Any SAE/SADE or any outcome of death due to any cause, which occurs during the course of this study, regardless of relationship to the investigational product (Scaffold), must be reported to the Sponsor designee immediately (within 24-hours) on the Serious Safety Event Report (SAE, SADE, UADE) Form.

DP Clinical, Inc.

During business hours:	+1-301-294-6226
After business hours:	+1-301-412-0105
Toll free number (US only):	877-294-7400
Fax number:	+1-301-294-4561
Email:	jbarta@dpclinical.com

Note: Medical judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.

In the initial communication (email and/or fax), the Investigator must provide the completed Serious Safety Event Report (SAE, SADE, UADE, Safety Event of Interest, Safety Events that Meet Study Stopping Rules) Form and the following eCRF pages, completed to the greatest extent possible:

- Safety events
- Medical and surgical history
- Concomitant medications

Also, the following documents are to be forwarded: any laboratory results, diagnostic test results, or medical reports relevant to the SAE/SADE/UADE/Safety Event of Interest/Safety Events that Meet Study Stopping Rules.

Email transmission is the preferred method to transmit SAE/SADE/UADE/Safety Event of Interest/Safety Events that Meet Study Stopping Rules information. In rare circumstances and in the absence of e-mail capacity, notification by fax or telephone is acceptable, with a copy of the Serious Safety Event Report (SAE, SADE, UADE, Safety Event of Interest, Safety Events that Meet Study Stopping Rules) Form and

eCRF pages sent by overnight mail. Initial notification via telephone does not replace the need for the Investigator to complete the Serious Safety Event Report (SAE, SADE, UADE, Safety Event of Interest, Safety Events that Meet Study Stopping Rules) Form and eCRF pages within the time frames outlined.

If the complete information regarding an SAE/SADE/UADE/Safety Event of Interest/Safety Events that Meet Study Stopping Rules is not available, the Investigator must not wait to receive additional information before notifying the Sponsor of the event. The Serious Safety Event Report Form must be updated when additional information is received. Follow-up information received on all SAEs/SADEs/UADEs/Safety Event of Interest/Safety Events that Meet Study Stopping Rules must be forwarded to the Sponsor using the same procedure and timelines as for an initial report.

Should there be a safety event due to deterioration in a subject's sensory or motor score following implantation of the investigational product that is serious and possibly, probably, or definitely related to either the investigational product or the procedure to implant the investigational product (SADE), further subject enrollment will be held to allow for review of the event by the Sponsor, DSMB, FDA, and other relevant Regulatory Authorities in accordance with applicable national and local regulations.

8.6 Unanticipated Safety Event Reporting Requirements

If the Investigator determines that a safety event meets the definition of unanticipated (UADE), the Investigator or their designee must notify the Sponsor or Sponsor's designee within 24-hours.

All UADEs will be reported to the Sponsor or Sponsor's designee within 24-hours of Investigator awareness on the Serious Safety Event Report (SAE, SADE, UADE) Form.

DP Clinical, Inc.

During business hours:

+1-301-294-6226

After business hours:

+1-301-412-0105

Toll free number (US only):

877-294-7400

Fax number:

+1-301-294-4561

Email:

jbarta@dpclinical.com

An evaluation of a UADE will be immediately conducted and results of the evaluations will be reported to FDA, relevant Regulatory/Competent Authorities, all reviewing IRBs/RECs/REBs, the DSMB and participating Investigators in accordance with the applicable national and local regulations. An example of a UADE might be an unanticipated clinically significant decrease in neuromotor function affecting two or more dermatomes superior to the site of injury that is possibly, probably, or definitely related to the investigational product.

8.7 Follow-up of Safety Events

After the occurrence of a safety event, the Investigator is required to follow each subject proactively and provide further information on the subject's condition. All safety events documented at a previous subject visit are designated as ongoing and will be reviewed at subsequent visits.

SAE/SADE/UADE/Safety Event of Interest/Safety Events that Meet Study Stopping Rules will be followed until the event resolves, the condition stabilizes, the event is otherwise explained, the subject is lost to follow-up or death occurs. The Investigator will ensure that follow-up information provided to the Sponsor includes results of any additional laboratory tests or investigations, histopathologic examinations including autopsy, or consultations with other healthcare professionals that serve to clarify the nature of the event, the cause of the event, or both.

New or updated information will be recorded on the originally-completed Serious Safety Event Report Form and eCRF pages, with all changes signed and dated by the Investigator. The updated Serious Safety Event Report Form and eCRF pages should be resubmitted to the Sponsor within the time frames outlined in Section 8.5 and Section 8.6.

8.8 Regulatory Reporting Requirements for Unanticipated Adverse Device Effects

The Investigator must promptly report all UADEs to the Sponsor in accordance with the procedures detailed in Section 8.5 and Section 8.6. The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of UADEs by the Investigator to the appropriate contact is essential so that UADEs that are observed with increasing occurrence be reported, and legal obligations and ethical responsibilities regarding the safety of other subjects are met.

An Investigator letter will be prepared for all UADEs (safety events attributable to study investigational product and unanticipated) according to Sponsor policy and forwarded to all Investigators and study sites as required. The purpose of the Investigator letter is to fulfill specific regulatory and Good Clinical Practice (GCP) requirements regarding the investigational product being assessed.

The Investigator or responsible person must also comply with requirements related to the reporting of UADEs to their IRB/Research Ethics Committees (REC)/Research Ethics Board (REB).

8.9 Precautions

Female subjects should be instructed to notify the Investigator immediately if they become pregnant within the 12-month period after Scaffold implantation. The subject will continue to be followed in the study for safety purposes until delivery or through the last follow-up visit (whichever occurs first), allowing for modification to the study-required assessments based on the safety of the assessments for pregnancies. In addition, pregnancy outcomes must be collected for the female partners of any males who received the Scaffold for the 12-month period following Scaffold implantation. The Sponsor must be notified of all pregnancies reported to the Investigator on the Pregnancy Report Form (see Section 8.5 for contact information) within 24-hours of Investigator awareness. The Pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and or newborn complications.

8.10 Investigational Product Events

Site staff will document all Scaffold events observed during the study and enter required data into the Investigational Product Event eCRF. An investigational product event includes any observation of the investigational product not behaving as intended. Examples of investigational product events for the Scaffold are:

- Scaffold does not appear as intended per the Instructions for Use (See Appendix E) at the time of removal of the sterile barrier
- Scaffold breaks while trimming
- Scaffold is damaged in any way during implantation procedures

An investigational product event could occur any time between when the Scaffold packaging is opened through the preparation and implantation of the Scaffold.

Each investigational product event will be assessed by the Investigator to determine if it is associated with a safety event, and any safety events identified will be managed according to details in Section 8.

All investigational product events will be reported to the Sponsor or designated representative within 24-hours of becoming aware.

9 STATISTICAL METHODOLOGY

9.1 Determination of Sample Size

The sample size was determined for the purpose of the study without a formal statistical hypothesis. A sample size of up to 36 subjects was selected to make it highly probable that there will be 20 subjects in the Primary Endpoint Analysis Set. At the 6-month Primary Endpoint Follow-up Visit, if a proportion of 25.0% of subjects is observed to have an improvement in AIS of at least 1 grade, then the 95% confidence interval will extend from 8.66% to 49.10% when the exact binomial method is employed.

9.2 Study Endpoints

9.2.1 Safety Endpoints

Safety endpoints will include:

1. General safety assessments
 - Incidence of all safety events (AEs/ADEs) of any kind/seriousness
 - Incidence of all serious safety events (SAEs/SADEs)
 - Incidence of unanticipated ADEs (UADEs)
2. Incidence of the following safety events of interest for assessment of the potential risk that may be associated with the use of Scaffold:
 - Scaffold migration or malposition
 - Untoward physiologic reaction to PLGA-PLL materials
 - Scaffold-related loss of motor or sensory neurologic function
 - Increased inflammatory response
 - Persistent cerebrospinal fluid leak
 - Damage to adjacent structures post Scaffold implant
 - Re-operation or removal of the Scaffold
 - Hemorrhage into or around the spinal cord causing neurologic deficit or possible need for further surgery
 - Surgical infection
 - Increased anesthesia time
 - Adhesion between the spinal cord and dura
 - Postoperative symptomatic or asymptomatic intraspinal cyst or syrinx

- Post-Scaffold implant on-ventilator time for subjects with sensory deterioration of 2 or more dermatomes determined by either ISNCSCI pinprick or light touch exam as compared to subjects without sensory deterioration of 2 or more dermatomes.
3. Incidence of the following safety events for assessment of the potential risk associated with neurosurgical procedures
 - Soft tissue wound infection or dehiscence
 - Surgical injury to the cord
 - Progressive neurological deterioration beyond that normally expected
 - Bacterial meningitis
 - Cord abscess
 - Failure to alter the natural course of healing from a spinal cord injury
 4. Incidence of the following safety events for assessment of the most common general risks of surgery and spinal surgery:
 - Adverse reactions to the anesthetic
 - Postoperative pneumonia
 - Blood clots in the legs or elsewhere (deep vein thrombosis) that may travel to the lungs (pulmonary embolus)
 - Infection at the site of surgery
 - Blood loss during surgery requiring a transfusion
 - Injury to the nerves or spinal cord resulting in pain or further paralysis
 - Instrumentation breaking, dislodging, or irritating the surrounding tissues
 - Pain from the surgery itself
 5. Findings of clinical laboratory tests, including routine blood chemistry and hematology tests
 6. Findings from vital signs measurements
 7. New onset or worsening of depression by BDI-II

9.2.2 Efficacy Endpoints

Primary Efficacy Endpoint: Improvement in AIS grade of one or more levels

Secondary Efficacy Endpoints:

1. Changes in NLI, sensory scores, motor scores
2. Changes in spinal cord anatomy

Exploratory Endpoints:

3. Changes in bowel function, bladder function, and sexual function
4. Changes in pain
5. Changes in SCIM III
6. Changes in QLI-SCI III

9.2.3 Pharmacokinetic Endpoints

None

9.3 General Considerations for Statistical Analysis

This is an HDE Probable Benefit study with a small sample size, thus the results will be presented primarily via data tabulation and listed by subject ID and time course. Group descriptive statistics and cumulative statistics will be utilized if appropriate. The following description provides a general principle and details will be documented in the Statistical Analysis Plan (SAP), which will be completed prior to the 6-month Follow-up primary endpoint database lock.

9.3.1 Analysis Datasets

Safety Set: The Safety Set includes all enrolled subjects (i.e., subjects who have signed an Informed Consent Form) that passed the screening assessments. The Safety Set will serve as the analysis set for demographic and safety endpoints.

All Treated Analysis Set: The All Treated Analysis Set includes all subjects who have a successful Scaffold implant. The All Treated Analysis Set will serve as the analysis set for all efficacy endpoints.

Primary Endpoint Analysis Set: The Primary Endpoint Analysis Set includes all subjects in the All Treated Analysis Set who have no major protocol deviations (Section 9.4.3) and have completed the 6-month Primary Endpoint Follow-up Visit. The Primary Endpoint Analysis Set will serve as the analysis set for the primary efficacy endpoint.

Separate efficacy tabulations will be performed for the subjects enrolled prior to conversion of the study from a pilot study to a pivotal probable benefit study and on the subset of pediatric subjects (under age 22 at time of enrollment).

9.3.2 Test Hypothesis and p Value Justification

No formal statistical hypothesis will be examined due to the sample size.

9.3.3 Procedures for Handling Missing Data and Outliers

Unless indicated otherwise, no imputation will be done for missing data.

There will be no imputation of missing 6-month Primary Endpoint Follow-up Visit AIS assessment. For the purpose of a secondary analysis, any subject who does not have a 6-month Primary Endpoint Follow-up Visit for any reason including premature study withdrawal, will be deemed not to have an increase of at least 1 grade on AIS assessment at the 6-month Primary Endpoint Follow-up Visit unless they were assessed as AIS C or better in at least the final two examinations.

Missing safety event start dates or partial start dates that do not allow for assessment of the event as having begun before or after the Scaffold implantation will result in the event being considered as having started after the Scaffold implantation spine surgery.

9.3.4 Definitions for Assessment Windows

This is an HDE Probable Benefit study of the Scaffold. Various reference time points will be selected for assessment of changes in safety and efficacy endpoints in the study. Time will be measured as Study Day defined according to CDISC standard. That is, the date of open spine surgery/Scaffold implant is Study Day 1. The date before the surgery is Study Day -1. All measurements taken will be displayed in chronological order of the study day to visualize the profile of changes over time. Windows for Follow-up/Long-term Follow-up (post-Scaffold implantation) Visits for purposes of analysis will be the same as those described in Section 7.9 of the protocol.

9.4 Study Population Summaries

Population summaries, including subject demographics, will be provided for the Safety Set.

9.4.1 Disposition

The summary tables will provide frequency counts for subject disposition:

- All subjects enrolled (signed a consent form)
- Subjects with a successful Scaffold implant
- Subjects without a successful Scaffold implant
 - With procedure (durotomy performed)
 - Without procedure (no durotomy performed)
- Subjects who completed the Primary Endpoint Visit
- Subjects who completed the 12 and 24-month Long-term Follow-up Visits
- Subjects who discontinued from the study and reason for discontinuation

Identification numbers for discontinued subjects will also be included in the analyses and all study termination information will be provided in data listings.

9.4.2 Demographics and Baseline Injury and Disease Characteristics

The demographic summary will include descriptive statistics for age, sex, race, ethnicity, weight, height, BMI, and cause of injury at screening, and will be presented by study arm.

Baseline disease characteristics will include AIS grade, NLI, and motor/sensory scores as determined by pre-surgery ISNCSCI Exam, Risser Staging for subjects age 16 and 17, and general medical and surgical history findings.

9.4.3 Protocol Deviations

A protocol deviation is defined as any change, divergence, or departure from the study design or procedures defined in the protocol. Except for emergency situations, this study must be conducted as described in this protocol. If a deviation is necessary to protect the life and physical well-being of the subject, the deviation should be reported to the IRB/REC/REB and Sponsor as soon as possible but no later than 72-hours after the deviation. All protocol deviations will be documented in the analyses.

A subset of the protocol deviations can be identified as major protocol deviations. A major protocol deviation is defined as a protocol deviation that may significantly affect the completeness, accuracy, and/or reliability of the study data (major data protocol deviation) or that may significantly affect a subject's rights, safety, or well-being (major GCP protocol deviation). Prior to database lock, all documented protocol deviations in the study will be reviewed to identify all major protocol deviations by a data review team including representatives from clinical operations, medical, data management, and statistics, and the major protocol deviations will be categorized as either major data protocol deviations or major GCP protocol deviations. Subjects with major data protocol deviations may be excluded from specific data analyses. Final decisions will be documented and databased.

A summary of protocol deviations will be provided in a listing.

9.4.4 Treatment Compliance

No formal summary of treatment compliance will be produced for this Scaffold implantation study.

9.4.5 Prior and Concomitant Medications, Interventions, and Procedures

All prior and concomitant medications, interventions, and procedures will be tabulated. Prior and concomitant medications will be coded to the therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug classifications version March 2014 or higher.

Medications and interventions will be summarized separately.

9.5 Safety Evaluations

9.5.1 Extent of Exposure

The Scaffold is a bioresorbable material, and based upon pre-clinical testing, is expected to be cleared from the site of implant within four to eight weeks. Analysis of study participation will be provided, but as with Treatment Compliance no analysis of Extent of Exposure is applicable for this study.

9.5.2 Safety Events

The Medical Dictionary for Regulatory Activities (Version 17 or higher) will be used to classify all safety events with respect to system organ class and preferred term. Summary of safety events will include:

1. General safety assessments
 - Incidence of all safety events (AEs/ADEs) of any kind/seriousness
 - Incidence of all serious safety events (SAEs/SADEs)
 - Incidence of unanticipated ADEs (UADEs)
2. Incidence of the following safety events of interest for assessment of potential risk associated with the use of the Scaffold
 - Scaffold migration or malposition
 - Untoward physiologic reaction to PLGA-PLL materials
 - Scaffold-related loss of motor or sensory neurologic function
 - Increased inflammatory response
 - Persistent cerebrospinal fluid leak
 - Damage to adjacent structures post Scaffold implant
 - Re-operation or removal of the Scaffold
 - Hemorrhage into or around the spinal cord causing neurologic deficit or possible need for further surgery
 - Surgical infection
 - Increased anesthesia time
 - Adhesion between the spinal cord and dura
 - Postoperative symptomatic or asymptomatic intraspinal cyst or syrinx

- Post-Scaffold implant on-ventilator time for subjects with sensory deterioration of 2 or more dermatomes determined by either ISNCSCI pinprick or light touch exam as compared to subjects without sensory deterioration of 2 or more dermatomes.
3. Incidence of the following safety events for assessment of risk associated with neurosurgical procedures:
- Soft tissue wound infection or dehiscence
 - Surgical injury to the cord
 - Cerebrospinal fluid (CSF) leakage
 - Progressive neurological deterioration beyond that normally expected
 - Bacterial meningitis
 - Cord abscess
 - Failure to alter the natural course of healing from a spinal cord injury
4. Incidence of the following safety events for assessment of most common general risks of surgery and spinal surgery:
- Adverse reactions to the anesthetic
 - Postoperative pneumonia
 - Blood clots in the legs and elsewhere (deep vein thrombosis) that may travel to the lungs (pulmonary embolus)
 - Infection at the site of surgery
 - Blood loss during surgery requiring a transfusion
 - Injury to the nerves or spinal cord resulting in pain or further paralysis
 - Instrumentation breaking, dislodging or irritating the surrounding tissues
 - Pain from the surgery itself

All summary tables will provide the total number of safety events and number of subjects with each safety event. The safety event dataset will be reviewed to identify all events and to group the identified events into different categories for the analysis. The calculation of safety event incidence will be based on the number of subjects per safety event system organ class and preferred term. For each subject who has multiple safety events classified to the same preferred term and system organ class, that safety event will be tabulated under the worst category for that safety event. Summary tables will be presented by seriousness, intensity, and causality. Safety events leading to study discontinuation or death will be tabulated separately. All safety event information will be provided in data listings.

9.5.3 Clinical Laboratory Tests

Laboratory values will be collected at all clinical study visits. Observed laboratory values at each study visit, and changes as compared to the Pre-surgery Visit, will be summarized.

9.5.4 Vital Sign Measurements

Resting vital signs will be collected at all clinical study visits. Observed resting vital sign values at each study visit and changes as compared to the Pre-surgery Visit will be summarized.

9.5.5 Beck Depression Inventory II (BDI-II)

BDI-II results at Hospital Discharge, if available, will be used as the reference time point (baseline) to assess changes in subjects' severity of depression at all follow-up visits (months 1, 2, 3, 6, and 12). Observed values for total score and changes from baseline will be presented. Question 9 on the BDI-II that deals with suicidal thoughts will be tabulated separately.

9.5.6 Subgroup Analyses for Safety Endpoints

Separate Safety Event tabulations will be performed for the subjects enrolled prior to conversion of the study from a pilot study to a pivotal probable benefit study.

9.6 Efficacy Analysis

9.6.1 Primary Endpoint Analysis — Change in AIS Grade

The primary endpoint analysis is the proportion of subjects from the Primary Endpoint Analysis Set who have an improvement of at least 1 grade on AIS assessment at the 6-month Primary Endpoint Follow-up Visit. The number and percent of subjects with an improvement of at least 1 grade on AIS assessment will be presented. If the proportion of subjects who demonstrate an improvement of at least 1 grade on AIS is at or above 25% the study will be deemed a success using this preset Objective Performance Criterion (OPC) of $\geq 25\%$ as a measure of success.

The primary endpoint analysis will also be conducted utilizing the All Treated Analysis Set. This analysis will be performed in the same manner as described above as a confirmatory analysis. In addition, a sensitivity analysis will be performed that will impute a value for any missing AIS grade at the 6-month Primary Endpoint Follow-up Visit. Any subject who does not have a 6-month Primary Endpoint Follow-up Visit for any reason including premature study withdrawal, will have the primary endpoint imputed to not having an improvement of at least 1 grade on AIS assessment at the 6-month Primary Endpoint Follow-up Visit unless they were assessed as AIS C or better at the last two study visits.

9.6.2 Secondary Efficacy Analyses

9.6.2.1 Changes in AIS Grade, Neurological Level of Injury, Motor, and Sensory Scores

AIS Grade, NLI, motor levels and sensory levels at the pre-surgery visit, 1-month, 2-months, 3-months, 6-months, 12-months and 24-months will be summarized. Observed values and change from the baseline will be presented. The confirmatory ISNCSCI exam performed within 8 hours prior to surgery (pre-surgery ISNCSCI) will be used as baseline visit.

ISNCSCI motor and sensory levels over time for each subject will be graphically displayed.

These analyses will be conducted separately on the Primary Endpoint Analysis Set and the All Treated Analysis Set.

9.6.2.2 Changes in Spinal Cord Anatomy

MR Images (axial and sagittal T1 and T2-weighted images at minimum) are obtained at Screening and 72-hours, 3-months, 6-months, 12-months, and 24-months post-implant. Characteristics of spinal cord anatomy will be assessed by a Board-certified neuroradiologist central reader and will include the following analyses: spinal cord dimensions (above, at, and below level of injury), lesion size and location, cyst presence or absence including size and location, if present. Observed values and change from baseline will be presented by treatment arm. The Screening MRI will be used as the baseline. These analyses will be performed on the All Treated Analysis Set.

9.6.3 Exploratory Endpoints

9.6.3.1 Changes in Bowel, Bladder, and Sexual Function

Bowel, Bladder, and Sexual Function at 1-month, 2-months, 3-months, 6-months, and 12-months post-Scaffold implantation will be summarized. Observed values and change from baseline will be presented. The 1-month Follow-up Visit will be used as the baseline visit. These analyses will be performed on the All Treated Analysis Set.

9.6.3.2 Changes in Pain

Pain interference with activities, mood and sleep, and the worst pain problems that a subject had during the last 7 days at hospital discharge, 1-month, 2-months, 3-months, 6-months, and 12-months will be summarized. Observed values and change from baseline will be presented. Pain data at hospital discharge will be used as the baseline visit for the assessment of changes in pain. These analyses will be performed on the All Treated Analysis Set.

9.6.3.3 Changes in SCIM III

SCIM III at hospital discharge and at months 1, 2, 3, 6, and 12 will be summarized. Observed values and change from baseline will be presented. SCIM III results at hospital discharge will be used as the baseline visit. Subjects with improvement will be identified. Analysis will include total score as well as scores for each sub-domain. These analyses will be performed on the All Treated Analysis Set.

9.6.3.4 Changes in QLI-SCI III

QLI-SCI III at hospital discharge and at months 1, 2, 3, 6, and 12 will be summarized. Observed values and change from baseline will be presented. QLI-SCI III results at hospital discharge will be used as the baseline visit. Subjects with improvement will be identified. Analysis will include total score as well as scores for each sub-domain. These analyses will be performed on the All Treated Analysis Set.

9.6.4 Covariate Analyses for Efficacy

No covariance analysis is planned.

9.6.5 Subgroup Analyses for Efficacy

Separate efficacy tabulations will be performed for the subjects enrolled prior to conversion of the study from a pilot study to a pivotal probable benefit study. Additionally, separate efficacy analyses will also be performed on the subset of pediatric subjects (under age 22 at time of enrollment).

9.7 Interim Evaluation

One interim evaluation was performed at the time the first 5 subjects received the Scaffold implant and completed the 6-month post-Scaffold implantation Follow-up Visit. The purpose of the interim evaluation was to support conversion of the pilot study into an HDE probable benefit study enrolling up to 36 subjects to achieve 20 subjects in the Primary Endpoint Analysis Set.

Subjects who received the Scaffold are to be followed for 24-months in clinic, and then the subjects will be followed annually by telephone contact for an additional 8 years. The clinical database will be locked after all subjects complete their 6-month Primary Endpoint Follow-up Visits for the Primary Endpoint Analysis and writing of the Clinical Study Report is completed. Data collected during the Long-term Follow-up will be reported via the format of IDE annual update.

A DSMB will be formed to evaluate safety and efficacy on an on-going basis. See Section 7.11 for additional information.

10 STUDY ADMINISTRATION

10.1 Regulatory and Ethical Considerations

10.1.1 Regulatory Authority Approval

The Sponsor will obtain approval to conduct the study from the appropriate regulatory agencies in accordance with any applicable country-specific regulatory requirements before any site may initiate the study in that country.

10.1.2 Ethical Conduct of the Study and Ethics Approval

This study will be conducted according to GCP; US 21Code of Federal Regulations (CFR) Part50 (Protection of Human Subjects); US 21CFR Part56 (IRBs); US 21CFR Part54 (Financial Disclosure); International Conference on Harmonization (ICH) Guidance for Industry, E6GCP: Consolidated Guidance; the Nuremberg Code; NH&MRC National Statement on Ethical Conduct in Human Research (2007); the principles of the Declaration of Helsinki (Recommendations guiding Medical Doctors in Biomedical Research Involving Human Subjects) where applicable, and with all applicable regulatory requirements in accordance with national and local regulations.

10.1.2.1 Institutional Review Board (IRB)/Research Ethics Committees (REC)/Research Ethics Board (REB)

The Investigator (or Sponsor, where applicable) is responsible for ensuring that this protocol, the site's informed consent form, and any other information that will be presented to potential subjects (e.g., advertisements or information that supports or supplements the informed consent form) are reviewed and approved by the appropriate IRB/REC/REB. The Investigator agrees to allow the IRB/REC/REB direct access to all relevant documents. The IRB/REC/REB must be constituted in accordance with all applicable regulatory requirements. The Sponsor will provide the Investigator with relevant documents or data needed for IRB/REC/REB review and approval of the study. Before any investigational product is shipped to the site, the Sponsor must receive copies of a list of IRB/REC/REB members, the approved informed consent form, and any other information that the IRB/REC/REB has approved for presentation to potential subjects.

If the protocol, the informed consent form, or any other information that the IRB/REC/REB has approved for presentation to potential subjects is amended, the Investigator is responsible for ensuring that the IRB/REC/REB reviews and approves, where applicable, these amended documents. The Investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form,

including obtaining IRB/REC/REB approval of the amended form, before new subjects consent to take part in the study using the new version of the form. The Investigator must promptly forward to the Sponsor copies of the IRB/REC/REB approval of the amended informed consent form or other information and the approved amended informed consent form or other information. IRB/REC/REB approval of the consent forms must be obtained in addition to the approval given for the clinical study. Regulatory review and approval may be required in some countries before IRB/REC/REB approval can be sought. Subjects who already may have been consented with the older consent form and for whom an amended consent form is relevant must be re-consented using the approved, amended forms.

10.1.2.2 General Considerations

The ethical standards defined within GCP are intended to ensure that:

- Human subjects are provided with an adequate understanding of the possible risks of their participation, and that they have a free choice to participate or not.
- The study is conducted with diligence and in conformance with the protocol in such a way as to ensure the integrity of the findings.
- The potential benefits of the research justify the risks.

InVivo Therapeutics Corporation is the Sponsor of study InVivo-100-101. The Sponsor is responsible for all of the following:

- Selecting qualified Investigators
- Providing Investigators with the information they need to conduct the investigation properly
- Training the Investigators in the proper storage, handling, and use of the Scaffold
- Ensuring proper monitoring of the investigation
- Ensuring that appropriate regulatory agencies and all participating Investigators are properly informed of significant new information regarding the risks associated with the use of the Scaffold

10.1.3 Informed Consent

The Sponsor will provide Investigators with a sample informed consent form. Investigators are encouraged to use the sample form; however, they may adapt the information to suit the needs of their institution, if necessary (although it must reflect the required elements of informed consent specified in 21 CFR Part 50.25 and other country regulations where a study site is located). The final informed consent form must be accepted by the Sponsor and approved by the IRB/REC/REB. Investigators must provide the Sponsor with an unsigned copy of the final informed consent form before and after it is approved by the IRB/REC/REB. If any new information becomes available that might affect subjects' willingness to

participate in the study, or if any amendments to the protocol require changes to the informed consent form, the Sponsor will provide Investigators with a revised informed consent form. The IRB/REC/REB must provide written approval of any revisions to the informed consent form in advance of its use.

Investigators must provide subjects with all the information necessary to make an informed decision about their participation, including the nature and intended purpose of the study, possible benefits, and possible risks.

All information in the informed consent form should be provided in a language (whether written or spoken) that is as nontechnical as practical and that is understandable to the subjects.

Before written informed consent is obtained, the subject should be given ample time and opportunity to inquire about the details of the study. All questions must be answered to the satisfaction of the subject (or a legally authorized representative).

Before a subject undergoes procedures specific to the protocol, the informed consent form must be signed and dated by the subject (or legally authorized representative) and any other signatories as required by the IRB/REC/REB. If clinical assessments are conducted during post-injury care and before informed consent is obtained, they may be used for the study once informed consent is obtained.

After all required signatures have been obtained, a copy of the informed consent form should be provided to the subject, and the original must be kept on file at the site and made available for review by the Sponsor. Documentation of the informed consent discussion must be noted in the subject's case history.

10.1.4 Investigator Reporting Requirements

The Investigator is responsible for completing and maintaining adequate and accurate eCRFs and source documentation. Source documentation constitutes original records (first point of entry, either hard copy or electronic), which may include progress notes, medication administration records, operation reports, laboratory reports, discharge summaries, and so on.

10.2 Study Monitoring

The Sponsor is responsible for ensuring the proper conduct of the study with regard to subject protection, ethics, protocol adherence, site procedures, and integrity of the data. At regular intervals during the study, the Sponsor's study monitors will engage the study site via visits to the site, telephone calls, emails, and letters in order to review study progress and eCRF completion, and to address any concerns or questions regarding study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: subjects' informed consent documents, subject recruitment procedures, subjects' and sites' compliance with the study procedures, source-data verification, Scaffold accountability, use of concomitant

therapy by subjects, safety event documentation and reporting, and quality of data. The study monitor will be DP Clinical, 9201 Corporate Boulevard, Suite #350, Rockville, MD 20850.

At the monitoring visits, the progress of the study will be discussed with the Investigator, or representative. The Investigator and site staff are expected to cooperate with the study monitor and be available during at least a portion of the monitoring visit for monitoring activities, which may include answering questions and providing any missing information.

10.3 Quality Assurance

The Sponsor, a regulatory authority, or an IRB/REC/REB representative may visit the study site at any time during or after completion of the study to perform audits or inspections. The purpose of a Sponsor audit or regulatory inspection is to examine systematically and independently all study-related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements in accordance with national and local regulations. Investigators should contact the Sponsor immediately if contacted by a regulatory agency about an inspection at their site.

10.4 Study and Site Closure

If the Sponsor, Investigator, or officials from regulatory agencies discover conditions that indicate that the study should be halted or that a study site should be closed, this action may be taken after appropriate consultation between the Sponsor and Investigator. Conditions that may warrant termination include, but are not limited to:

- Discovery of an unanticipated, serious, or unacceptable risk to the subjects enrolled in the study
- Submission of knowingly false information from the research facility to the Sponsor, study monitor, or regulatory agencies
- Failure of the Investigator to comply with GCP (e.g., ICH guidelines, regulatory agency guidelines)
- Insufficient adherence to protocol requirements or an unacceptably high rate of missing, erroneous, or improperly collected data
- Evidence of sufficient technical problems with the study that one could believe with a high degree of certainty that subjects are being exposed to the Scaffold without a realistic expectation of evaluable data
- A decision on the part of the Sponsor to suspend or discontinue testing evaluation or development of the Scaffold

- Failure of the Investigator to enroll subjects into the study at an acceptable rate

10.5 Records Retention

10.5.1 Health Insurance Portability and Accountability Act of 1996

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subjects' health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45CFR Parts 160 and 164 (the Health Insurance Portability and Accountability Act of 1996 privacy regulation). The Investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with the privacy regulations of the Health Insurance Portability and Accountability Act and in a form satisfactory to the Sponsor.

10.5.2 Financial Disclosure

Participating Investigators will provide the Sponsor with a signed Financial Disclosure Form (Appendix D).

10.5.3 Access to Original Records

Regulatory authorities expect that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation to ensure data integrity. "Original" in this context is defined as the first documentation of an observation and does not differentiate between hard-copy and electronic records.

10.5.4 Archiving of Study-related Documents

Study records must be retained either for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the Scaffold. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. The Sponsor will notify the Investigator as to when these documents no longer need to be retained.

10.6 Provision of Study Results and Information to Investigators

When a clinical study report is completed, the Sponsor will provide the major findings to the Investigators.

The Sponsor may list and summarize the results from coded samples by subject number in the clinical study report. In this event, the Investigator and study staff would have access to the research results and would

be able to link the results to a particular subject. The Investigator and study staff would be directed to hold this information confidentially.

10.7 Information Disclosure and Inventions

10.7.1 Ownership

All information provided by the Sponsor, and all data and information generated by the site as part of the study including imaging, photography and videography (other than a subject's medical records), are the sole property of InVivo Therapeutics Corporation.

All rights, title, and interests in any inventions, know-how, or other intellectual or industrial property rights that are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of InVivo Therapeutics Corporation and are hereby assigned to InVivo Therapeutics Corporation.

If a written contract is executed between InVivo Therapeutics Corporation and the study site for the conduct of the study, and that contract includes ownership provisions inconsistent with this statement, that contract's ownership provisions shall apply rather than this statement.

10.7.2 Confidentiality

All information provided by InVivo Therapeutics Corporation, and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the Investigator and other site staff. This information and data will not be used by the Investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to the following: 1) information that becomes publicly available through no fault of the Investigator or site staff, 2) information that must be disclosed in confidence to an IRB/REC/REB or DSMB solely for the evaluation of the study results, 3) information that must be disclosed in order to provide appropriate medical care to a study subject, or 4) study results that may be published as described in Section 10.7.3. If a written contract for the conduct of the study is executed and that contract includes confidentiality provisions inconsistent with this statement, then the contract's confidentiality provisions shall apply rather than this statement.

10.7.3 Publication

The first scientific publication or disclosure of study results in a scientific forum shall be a complete, joint, multicenter publication or disclosure coordinated by InVivo Therapeutics Corporation. Thereafter, any secondary scientific publications will reference the original publication(s). If no multicenter scientific

publication is submitted for publication within 9 months of study database hard lock, then the site shall be free to disclose its own results, subject to Sponsor rights under Section 10.7.1.

Before submitting material for publication, presentation, or use for instructional purposes, or before otherwise disclosing the study results generated by the site (collectively, a “publication”), the Investigator shall provide InVivo Therapeutics Corporation with a copy of the proposed publication and allow InVivo Therapeutics Corporation a period of at least 90 days to review the proposed publication. Proposed publications shall not include either InVivo Therapeutics Corporation confidential information (other than the study results) or the personal data (such as name or initials) of any subject.

At InVivo Therapeutics Corporation’s request, the submission or other disclosure of a proposed publication will be delayed a further 90 days to allow InVivo Therapeutics Corporation to seek patent or similar protection of any inventions, know-how, or other intellectual or industrial property rights disclosed in the proposed publication.

If a written contract is executed for the conduct of the study and that contract includes publication provisions inconsistent with this statement, that contract’s publication provisions shall apply rather than this statement.

10.7.4 Data Management

The Investigator (or designee) will collect subject data by using the eCRF defined by and provided by the Sponsor or designee; subject data necessary for analysis and reporting will be entered into a validated database or data system. Clinical data management will be performed in accordance with applicable standards and data-cleaning procedures. Database lock will occur when data management quality-control procedures are completed. The Sponsor will retain an electronic copy of the eCRFs and a copy of the clinical database, and the Investigator will retain an electronic copy of the eCRFs.

Subject data may also be collected electronically. In addition, validated laboratory data may be transmitted electronically from the clinical laboratory to Sponsor or its designee.

The Investigator or designee must record all required data using the previously specified data collection method defined in this protocol. An explanation must be documented for any critical data points. The Investigators must sign and date a declaration on the eCRF attesting that they are responsible for the quality of all data recorded and that the data represent a complete and accurate record of each subject’s participation.

10.7.5 Data Security

Access to the data will be strictly controlled.

10.8 Subject Tracking

Study investigational product accountability logs, a subject identification log (to be retained by the Investigator only), a subject screen failure log, and a subject enrollment log will be used to track subject participation.

11 REFERENCES

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3. Saunders, L.L., et al., *Epidemiology of Pediatric Traumatic Spinal Cord Injury in a Population-Based Cohort, 1998-2012*. Top Spinal Cord Inj Rehabil, 2015. **21**(4): p. 325-32.
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6. Wyndaele, M. and J.J. Wyndaele, *Incidence, prevalence and epidemiology of spinal cord injury: what learns a worldwide literature survey?* Spinal Cord, 2006. **44**(9): p. 523-9.
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8. Crowe, M.J., et al., *Apoptosis and delayed degeneration after spinal cord injury in rats and monkeys*. Nat Med, 1997. **3**(1): p. 73-6.
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10. Blight, A.R., *Cellular morphology of chronic spinal cord injury in the cat: analysis of myelinated axons by line-sampling*. Neuroscience, 1983. **10**(2): p. 521-43.
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14. Zariffa, J., et al., *Characterization of neurological recovery following traumatic sensorimotor complete thoracic spinal cord injury*. Spinal Cord, 2011. **49**(3): p. 463-71.
15. Fawcett, J.W., et al., *Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: spontaneous recovery after spinal cord injury and statistical power needed for therapeutic clinical trials*. Spinal Cord, 2007. **45**(3): p. 190-205.
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APPENDIX A: Summary of Study Procedures

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14-21	Unscheduled Visit
Visit Name	Screening	Surgery	24-hours Post-implant	48-hours Post-implant	72-hours Post-implant	1-week Post-implant	Hospital Discharge	1-month Follow-up	2-months Follow-up	3-months Follow-up	Primary Endpoint 6-months	12-months Long-term Follow-up	24-months Long-term Follow-up	Annual Telephone Visits ⁶	
Visit Windows		≤ 96 hours	±6 hrs	±6 hrs	±8 hrs	±1 day	-	±3 days	±4 days	±7 days	±30 days	±30 days	±30 days	±60 days	
Informed Consent	X														
Demographics and Medical/Surgical History	X														
Skeletal Maturity/Bone Age (ages 16–17)							X ⁷								
Complete Physical Examination	X						X				X	X	X		X
Screening Labs ¹	X														
Comprehensive Metabolic Panel ² , Hematology ³	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Erythrocyte Sedimentation Rate, C-Reactive Protein	X						X	X	X	X					X
Vital Signs (for intraop vitals, see Section 7.7.3)	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Vital Capacity for subjects not ventilator dependent	X	X	X	X	X	X	X								
Neuro Exam (include hip abd/add, great toe flex/ext)	X	X ⁴	X ⁴	X ⁴	X ⁴	X	X	X	X	X	X	X	X		X
Pain Assessment							X	X	X	X	X	X			X
ISNCSCI exam	X	X ⁵					X	X	X	X	X	X	X		X
MRI (without contrast)	X				X					X	X	X	X		
SSEP (Section 7.7.10)		X													
Pulmonary function monitoring (Section 7.7.11)		X	X	X	X										
Intraoperative Ultrasounds with photograph		X													
Scaffold Implantation with videography		X													
Bowel, Bladder and Sexual Function Assessments								X	X	X	X	X			X
SCIM III, QLI-SCI III, BDI-II							X	X	X	X	X	X			
Prior & Concomitant Meds/Interventions/Procedures	X	X	X	X	X	X	X	X	X	X	X	X			X
Rehabilitation Therapy Log							X	X	X	X	X	X			
Annual General Health Assessment														X	
End of Study (Year 10 or last study visit only)														X	
Safety Event Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	X

1 Screening Labs include a serum Pregnancy Test, Blood Alcohol/Urine Drug Toxicology, Blood Type, and Coagulation Test (PT, PTT, INR).

2 **CMP**: BUN, glucose, creatinine, sodium, potassium, chloride, calcium, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, carbon dioxide.

3 **Hematology**: CBC w/Diff, WBC, RBC, platelet count, hemoglobin differential counts.

4 Following surgery, site will perform neurological exam per standard of care.

5 Confirmatory ISNCSCI must be within 8 hrs before surgery.

6 Annual visits for years 3 - 10 are telephone contacts and not clinic visits.

7 May be performed anytime between screening and Hospital Discharge.

APPENDIX B: Investigator Obligations

As an Investigator, you are responsible for ensuring that the study is conducted according to the protocol, the signed Statement of Investigator, and all applicable regulations.

Debarment

Individuals ineligible to conduct or be involved with clinical studies, including those ineligible as a result of debarment under the Generic Drug Enforcement Act of 1992, will not be allowed to conduct or work on studies sponsored by InVivo Therapeutics Corporation. You are required to disclose immediately to the Sponsor, in writing, if any person involved in the conduct of the study is debarred pursuant to a hearing by FDA under this antifraud law or if any proceeding for debarment is pending or is (to the best of your knowledge) threatened.

Institutional Review Board / Research Ethics Committee/Research Ethics Board

You are required to obtain initial and continuing review and approval by an IRB/REC/REB that complies with the requirements specified in 21CFR Part 56 and other applicable regulatory requirements in accordance with national and local regulations. Before initiating the trial, you must have written approval from the IRB/REC/REB for the protocol, informed consent form, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to the subjects. You must submit a Report of Prior Investigations and any updates to the IRB/REC/REB for review. The IRB/REC/REB must also provide written approval of any amendments to the protocol that affect the conduct of the study and any changes to the informed consent form in advance of use. If the duration of the study is longer than 1 year, re-approval by the IRB/REC/REB must be obtained on a yearly basis (or at more frequent intervals if required by the IRB/REC/REB). All IRB/REC/REB approvals must be forwarded to the Sponsor.

You must provide reports of all SAEs/SADEs/Safety Events of Interest/Safety Events that meet Study Stopping Rules from your site to the IRB/REC/REB. You are also responsible for providing the IRB/REC/REB with Safety Reports of any SAEs/SADEs/Safety Events of Interest/Safety Events that meet Study Stopping Rules from any other study conducted with the Scaffold. The latter will be provided to you by the Sponsor.

Confidentiality and Safety of Subjects

You are responsible for protecting the rights, safety, and welfare of subjects under your care and for the control of the investigational product (Scaffold and Cupped Forceps) under investigation.

You are responsible for keeping a record of all screened subjects, including full names and last known addresses. All subjects will be identified on the eCRFs by initials and subject numbers. Demographic information including date of birth, sex, and race will also be recorded on the eCRFs. Confidentiality of subject data will be maintained in accordance with local laws.

Study-related Records

You are required to maintain complete and accurate study documentation in compliance with current GCP standards and all applicable federal, state, and local laws, rules, and regulations related to the conduct of a clinical study.

You are required to make all study documentation promptly available for inspection, review, or audit at your study site upon request by the Sponsor, its representatives, or any appropriate regulatory agencies.

Accountability of the Investigational Product (Scaffold)

You or your designee (e.g., a pharmacist) is responsible for accountability of the Scaffolds and Cupped Forceps at the site. You or your designee must maintain records of the product's delivery to the site, inventory at the site, proper storage and handling, disposal, or return of unused or damaged units, use by each subject, and the return to the Sponsor or alternative disposition of any unused product. These records must include dates; quantities; batch, serial, or lot numbers; and expiration dates (if applicable).

You should ensure that the Scaffolds and Cupped Forceps are used only in accordance with the protocol.

APPENDIX C: Investigator Agreement

By signing below I confirm that I have read this Protocol and the sections of the IDE regulations concerning the responsibilities of Investigators 21 CFR Part 812 (Subpart E) and records and reports (Subpart G). In addition, I have read 21 CFR 812.43(c). In accordance with these regulations, I hereby certify the following:

- I will conduct the Clinical Evaluation (investigation) of the Scaffold Study sponsored by InVivo Therapeutics in accordance with the regulations listed above and in accordance with the agreement, the Investigational Plan and any future amendments, the IDE and other applicable FDA regulations.
- I also certify that I will conduct the investigation of the Scaffold in accordance with the conditions of approval imposed by the reviewing Institutional Review Board or Independent Ethics Committee and FDA.
- I have provided a copy of my current (updated within the last 12-months) curriculum vitae, including the extent and type of my relevant experience with pertinent dates and locations.
- I certify that I have not been involved in an investigation that was terminated for noncompliance at the insistence of Sponsor, Institutional Review Board or Independent Ethics Committee, or FDA or will provide an explanation of the circumstances that led to termination of a study that I was involved in or that was terminated.
- I certify that I will supervise all testing of the Scaffold involving human subject at my investigational site and that I will ensure that the requirements for obtaining informed consent are met.
- I agree to provide sufficient accurate financial disclosure information for myself and my immediate family members (spouse and children), if any, to allow Sponsor to submit complete and accurate certification or disclosure statement as required under 21 CFR part 54. I commit to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study.
- I will assume responsibility for the proper conduct of the study at this site.
- I currently hold an active medical license to practice in the state in which this study will be conducted and confirm that I have no pending state medical board actions against myself in this state or in any other state in which I have practiced.
- I will not implement any deviation from, or changes to, the Investigational Plan without agreement of the Sponsor and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to eliminate an immediate hazard to subject(s).
- I am aware of and will comply with all applicable Federal, State, and local regulations and guidelines for the conduct of a clinical investigation.

Principal Investigator Signature **Date** ____ / ____ / ____
DD MMM YYYY

Principal Investigator Name (print)..... **Title**.....

Institution at which study will be conducted.....

Address.....

City, State..... **Zip Code**.....

Email..... **Telephone**.....

APPENDIX D: Financial Disclosure Form

Please complete information below, return original signed version to DP Clinical, and retain a copy for your files.

Name: Institution:

Check as appropriate: ☐ Principal Investigator ☐ Sub-Investigator

List the names of all corporations, partnerships, limited liability companies or other business entities (if any) with whom you are affiliated or doing business (other than your Institution) that may have received payments from InVivo Therapeutics, Corp.

.....
.....

Are you aware of any arrangement with InVivo Therapeutics, Corp. whereby the compensation paid to you, your spouse or any dependent children, for services in connection with conducting the Trial, was (i) in the form of an equity interest in InVivo Therapeutics, Corp. or (ii) was in any way based on the sales of the tested product which was the subject of the Trial or (iii) the value of such compensation was affected by the outcome of the study?

☐ YES ☐ NO

If YES, please describe

Do you, your spouse or any dependent children (individually or together) own stock and/or stock options of InVivo Therapeutics, Corp. in excess of \$50,000 value? ☐ YES ☐ NO

If YES, please describe

Do you, your spouse or dependent children have any proprietary interest (e.g., property or other financial interest including but not limited to patents, trademarks, copyrights or licensing arrangements) in the tested product which is the subject of the Trial? ☐ YES ☐ NO

If YES, please describe

Are you aware of any arrangements whereby InVivo Therapeutics, Corp. has made at any time during the trial or during the one year period following Completion of the Trial any payment(s) in an aggregate amount of more than \$25,000 (excluding the costs of conducting the Trial) to you, your spouse or any of your dependent children, or to your Institution to support your activities (e.g., grants to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria)? ☐ YES ☐ NO

If YES, please describe

The undersigned certifies that the responses to the above questions are, to the best of his/her knowledge, complete and accurate and agrees to notify InVivo Therapeutics, Corp. in the event that any of the responses change during the course of the investigation and in the period of one year following completion of the study.

Investigator Signature

Date ____/____/____
DD MMM YYYY

Investigator Name (print).....

Title.....

APPENDIX E: Instructions for Use (Rev 13 dated 29 June 2017)

InVivo Therapeutics Corporation
One Kendall Square, Building 1400 East
Cambridge, MA 02139 USA
617-863-5500

A. INVESTIGATIONAL PRODUCT DESCRIPTION

The *Neuro-Spinal Scaffold*™ (“Scaffold”) is a porous bioresorbable polymer comprising poly(lactic-co-glycolic acid)-b-poly-L-lysine (PLGA-PLL), a synthetic biomaterial that is designed to degrade naturally within the body over a time course that provides cell growth, appositional healing, and tissue remodeling during the process of recovery following spinal cord injury. The Scaffold is cylindrical in shape, comes in two sizes (2mm diameter x 10mm length; 3mm diameter x 10mm length), and is fragile due to the highly porous design. The Scaffold is intended to be selected and trimmed to the appropriate length to fit the intraspinal contusion cavity. Because the Scaffold is fragile, it must be handled with the size-matched Cupped Forceps during preparation.

The Scaffold is intended to be used in traumatic spinal cord injury (SCI), the most common injury type. The Scaffold is implanted at the time of open spine surgery, ideally within 24-hours from the time of injury but no longer than 7 days from the time of injury. A durotomy is performed to expose the injury site. The injury site may present as an intact spinal cord, with the area of injured spinal cord tissue not visible as it is in the center of the cord (contusion or “closed” injury), or a macerated spinal cord, with the area of injured spinal cord tissue exposed (compound or “open” injury). The injured cord is then irrigated with isotonic saline to wash away any superficial hemorrhagic material or devitalized tissue. If the injury site is a contusion or closed injury, an arachnoid/pial incision will be made over the injury site allowing direct access to the injured parenchyma. A myelotomy is then performed to access the epicenter of the lesion. The Investigator will capture a sample of the spontaneous exudate if present and submit to pathology for routine examination/testing, for example Hematoxylin and Eosin (H&E) staining for histology. The exposed lesion epicenter is further irrigated for the purposes of debridement as necessary with isotonic saline to remove additional areas of hemorrhage and necrotic tissue within the cavity. A Scaffold is wetted and trimmed if necessary on one end only to obtain the desired length needed to fit the cavity such that there is space within the cavity to avoid undue tension on the spinal cord surrounding the lesion site. The Scaffold is then gently implanted into the epicenter of the lesion cavity using the optimal forceps to minimize force on the Scaffold during implantation, such as the bayonet forceps or the Cupped Forceps, depending on the exposure of the cavity.

B. INVESTIGATIONAL PRODUCT HANDLING

Scaffolds are provided sterile and should be stored in their original packaging. Scaffolds not required for immediate use must be kept in adequate room temperature storage conditions (15°–25° C) until use. Sites will document the temperature of the Scaffold storage area as directed in the Site Instruction Manual.

C. INTENDED USE / INDICATIONS

The Scaffold is intended for use in patients age 16–70 years, diagnosed with a T2-T12 NLI functionally complete (AIS A) spinal cord injury, for whom open spine surgery (e.g., laminectomy, spine stabilization), which allows access to the dura of the injured spinal cord, is recommended as an option. The Scaffold is intended to be implanted in a cavity at the epicenter of the spinal cord contusion during open spine surgery. The Scaffold is intended to act as a physical substrate for cell growth, appositional healing, and tissue remodeling, and preserve the structural integrity of the cord. The Scaffold is intended for use in recent (≤ 7 days) spinal cord injuries that do not involve penetrating injury to the cord or complete severing of the cord.

D. INCLUSION CRITERIA for Scaffold Implant

1. AIS A classification of traumatic spinal cord injury at neurological level of injury T2 to T12 confirmed by a qualified medical professional at the time of open spine surgery
2. Recent injury (must receive Scaffold within 7 days from injury)
3. Non-penetrating SCI (contusion injury) that is no less than approximately 4 mm in diameter by MRI

Note: The Scaffold is MR Safe. It contains no ferromagnetic or electrically conductive materials. The use of MRI to image PLGA-based implants has been evaluated in preclinical research, including spinal cord injury. No safety concerns were identified in these studies. Similarly, MRI has been studied in the clinic to visualize PLGA-based devices with no adverse effects. These studies support the use of MRI to safely image the InVivo Investigational PLGA-based Scaffold. Do not take non-implanted accessories used to aid in introduction of the Scaffold device such as the Cupped Forceps and other instruments into the MR environment. They have not been evaluated for safety in the MR environment.

4. Requires open spine surgery (subjects requiring either posterior surgical approach or posterior plus anterior approach will be eligible)
5. Informed consent obtained
6. 16–70 years of age, inclusive
7. Hemodynamically stable and deemed a suitable candidate for surgery

E. CONTRAINDICATIONS for Scaffold Implant

1. Spinal cord injury outside of T2–T12 neurological level of injury
2. Spinal cord injury classified as AIS B, C, D or E, or inability to determine AIS classification
3. No discrete cavity (existing or created by irrigation/myelotomy) in the contused spinal cord in which a Scaffold can be placed
4. Evidence of clear and significant Somatosensory Evoked Potentials (SSEP) transmission through the injury site before Scaffold implantation (based on the judgment of the Investigator)
5. Known hypersensitivity to PLGA or PLL (e.g., hypersensitivity to absorbable sutures containing PLGA)
6. Hemodynamic instability
7. Patient **does not meet** all inclusion/exclusion criteria per protocol

F. WARNINGS

The correct sizing and placement of the Scaffold is extremely important.

The Scaffold must be handled with the size-matched Cupped Forceps during preparation to ensure it is not damaged.

The Scaffold must not be tampered with (handled or manipulated outside of guidelines in IFU), as tampering may adversely affect the performance or increase the likelihood of Scaffold breakage.

G. PRECAUTIONS

CAUTION: Investigational device. Limited by Federal (United States) law to investigational use. To be used by Qualified Investigators only, exclusively for clinical investigations.

CAUTION: Familiarity with, and attention to, the surgical technique recommended for this investigational device (Scaffold) is required for best results.

CAUTION: Do not use if the Scaffold is damaged or the sterile packaging is damaged or the sterility is compromised in any way.

CAUTION: The highly porous Scaffolds are fragile and should be handled with care. Avoid bending

- or applying excessive force during implantation/placement.
- CAUTION: The size-matched Cupped Forceps must be used for Scaffold handling during Scaffold preparation and may be used to implant the Scaffold at the Investigator's discretion.
- CAUTION: When using the Cupped Forceps, grasp the Scaffold by completely encircling the Scaffold. Do not use the tips of the Cupped Forceps to pinch the Scaffold as this may increase the likelihood of Scaffold breakage

H. PREOPERATIVE PLANNING/POSTOPERATIVE CARE

Accepted surgical practices should be followed for preoperative and postoperative care.

I. ADVERSE EFFECTS

The common general risks of surgery may include any of the following:

1. Allergic reactions (including reaction to IV antibiotic, local anesthetic, sedative, dressing materials, wound care products, etc.)
2. Anaphylactic shock
3. Anesthesia risks
4. Angina
5. Bleeding (requiring or not requiring transfusion)
6. Blood clots
7. Cellulitis
8. Dermatitis
9. Convulsions
10. Death
11. Erythema
12. Edema
13. Failure to heal (bone fusion or wound)
14. Fever
15. Hypotension
16. Hypertension
17. Hypoglycemia
18. Infection, Incision
19. Infection, Sepsis
20. Laboratory values, abnormal
21. Mental Status, altered/confused
22. Myocardial Infarction
23. Non-improvement
24. Stress Ulcer
25. Pneumonia
26. Hematuria
27. Pulmonary Embolus
28. Deep Venous Thrombosis
29. Rash, Generalized Skin
30. Renal Failure/Insufficiency
31. Stroke
32. Thrombocytopenia/thrombosis induced by heparin
33. Incision site complications
34. Instrumentation breaking, dislodging or irritating the surrounding tissues
35. Pain from the surgery itself

The risks associated with neurosurgical and spinal procedures include the following:

1. Infection, Myelitis
2. Loss of bladder, bowel, or sexual function
3. Muscle weakness
4. Nerve Injury
5. Osteomyelitis/Diskitis
6. Pain (back or legs)
7. Spinal cord edema
8. Syrinx formation/Syringomyelia
9. Transient Ischemic Attack (TIA)
10. Paralysis
11. Surgical injury to the cord
12. Cerebrospinal fluid (CSF) leakage, which could result in positional headaches, an increase in the risk of infection, and wound complications
13. Progressive neurological deterioration beyond that normally expected
14. Bacterial meningitis
15. Cord abscess
16. Failure to alter the natural course of healing from a spinal cord injury
17. Intradural surgery risks, including intradural hemorrhage within the neuraxis (with or without excess CSF egress); neurologic deficit as a consequence of spinal cord manipulation and myelotomy with consequent deterioration; dorsal column dysfunction, which manifests with loss of proprioception (loss of joint sensation), sensory loss, bowel and bladder dysfunction, and paralysis; and intradural infection.
18. Autonomic dysreflexia and spasticity
19. Dural graft replacement
20. Increased risk with administration of steroids








The risks associated with the specific use of the Scaffold include the following:

1. Scaffold migration or malposition
2. Untoward physiologic reaction to PLGA-PLL materials
3. Scaffold-related loss of motor or sensory neurologic function
4. Increased inflammatory response
5. Persistent cerebrospinal fluid leak
6. Damage to adjacent structures post-Scaffold implant
7. Re-operation or removal of the Scaffold
8. Hemorrhage into or around the spinal cord causing neurologic deficit or possible need for further surgery
9. Surgical infection
10. Increased anesthesia time
11. Adhesion between the spinal cord and dura
12. Postoperative symptomatic or asymptomatic intraspinal cyst or syrinx
13. In the acute period after injury, there may be some transient loss of residual function below the level of spinal cord injury that could be damaged by the Scaffold

J. STERILIZATION

Scaffolds are provided sterile and must be stored in their original packaging until use. Scaffolds are single-use devices, thus do not clean or re-sterilize a Scaffold that has been in contact with or contaminated by blood or other non-sterile substances. The manufacturer and distributor assume no responsibility for the cleaning and re-sterilization of Scaffolds or reusable instruments performed by the individual or hospital.

K. LABEL SYMBOL DEFINITIONS

SYMBOL	DESCRIPTION
	Manufactured by
	Catalogue Number
	Lot Number
	Date of Manufacture
	Use by
	Storage Temperature Range
	Single use only

L. ITEMS NEEDED FOR PROCEDURE TO IMPLANT INVESTIGATIONAL PRODUCT

InVivo will provide the site with Scaffolds and sized-matched Cupped Forceps as outlined in the Site Instruction Manual. Sites should bring all available Scaffolds and sterilized Cupped Forceps to the Scaffold implant procedure.

The site will need to ensure the following items are available for the procedure to implant Scaffold:

- Standard surgical forceps
- Bayonet surgical forceps
- Tissue retractors
- Isotonic solution (saline)
- 16 to 21-gauge needle
- Syringe
- Scalpel

M. SELECTION AND PREPARATION OF INVESTIGATIONAL PRODUCT

SELECTION AND PREPARATION OF THE SCAFFOLD (STEPS 1 – 11 BELOW) SHOULD BE PERFORMED AFTER CONTUSION SIZE HAS BEEN CONFIRMED VIA DIRECT VISUALIZATION AND/OR INTRAOPERATIVE ULTRASOUND

Note: Perform preoperative MRI (without contrast) to characterize the size of the contusion.

Note: The Scaffold must be wetted prior to trimming and implantation.

Note: The Scaffold size should be selected and the Scaffold should be trimmed if necessary to allow for space between the Scaffold and the surrounding contused spinal cord tissue to avoid excessive tension on the surrounding spinal cord tissue (e.g., causing blanching of the tissue or bulging of the spinal cord).

Note: Ensure the correct size-matched Cupped Forceps are used when handling the Scaffold and that the Cupped Forceps completely encircle the Scaffold when grasping to ensure the Scaffold is not damaged in any way.

Steps 1 to 3 below to be performed OUTSIDE of the sterile field

1. Remove foil pouch from cardboard box. *Note: Foil pouch is **NOT** sterile.*
2. Remove double blister tray system from foil pouch. *Note: The exterior of the double blister tray system is **NOT** sterile.*

Top View of Blister Tray



3. Using tabs on corner of Tyvek® lid, carefully peel sterile barrier away from outer blister tray. *Note: Scaffold wetting should begin as soon as possible after removal of sterile barrier. If there is any concern about sterility of the Scaffold being compromised, discard and select another Scaffold.*

Blister Tray System with Tabs Identified



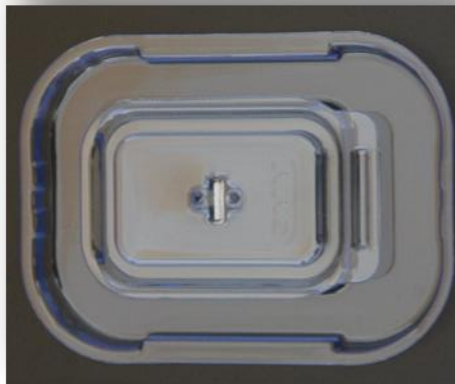
4. Present entire blister tray assembly to sterile O.R. staff. The sterile O.R. staff, using aseptic technique, can then lift the sterile inner tray away from the outer tray either by grasping the middle of the inner tray or grasping one of the edges of the inner tray with either their hands or sterile forceps using care not to touch the edges of the outer tray, as the outer adhesive edges of the outer tray may not be sterile.

Sterile Inner Tray Containing Scaffold Separated from Outer Blister Tray



5. Place inner tray and tray lid containing the Scaffold onto sterile staging area. Do not remove tray lid.

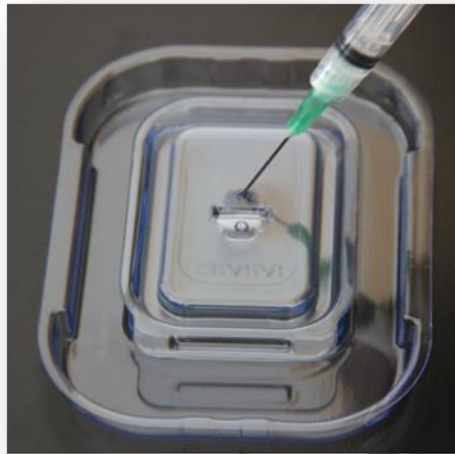
Inner Tray Containing Scaffold Covered by Tray Lid



6. Fill inner tray with isotonic saline using a needle (16 to 21 gauge) and syringe. Insert needle in either hydration port in the tray lid and fill inner tray with isotonic solution until fluid flows from opposing hydration port. Make sure that fluid surrounds the Scaffold and that no bubbles are present. Recommended wetting time is at least 15 seconds and not more than 30 minutes.

Note: Depending on the standard practices for neurosurgical procedures at the site, the saline used to wet the Scaffold can be room temperature or warmed up to a maximum of 110°F.

Filling Inner Tray with Isotonic Saline



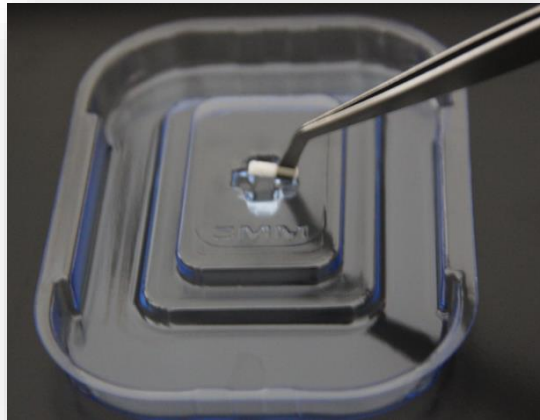
7. After wetting time (at least 15 seconds and not more than 30 minutes) has elapsed, carefully remove tray lid using pull tab. The Scaffold may stick to the lid during lid removal, and can still be used provided it is intact and has not had sterility compromised. Use the size-matched Cupped Forceps to gently remove the Scaffold from the lid.

Lid Removed from Blister Tray to Expose Wetted Scaffold



8. Use size-matched InVivo Therapeutics Cupped Forceps to remove Scaffold from inner tray via relief cavity (or gently from the tray lid, if the Scaffold stuck to the lid during lid removal) and transfer onto sterile, hard surface (e.g., petri dish, stainless steel pan or tray).

**Removal of Wetted Scaffold from Sterile
Blister Tray with Size-matched Cupped Forceps**

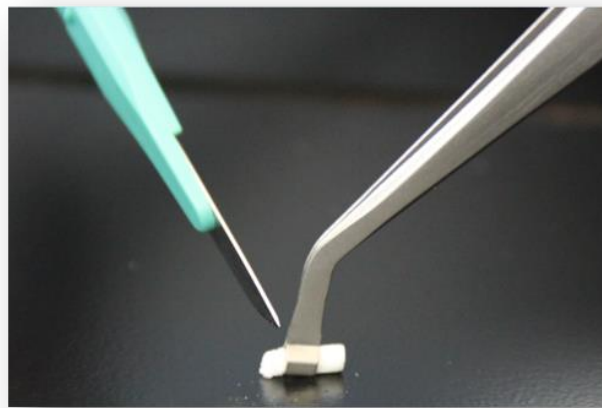


Note: *Hold Cupped Forceps so that the cupped closure is facing downwards and the Scaffold is fully encircled when grasping. Do not use the tips of the Cupped Forceps to pinch the Scaffold as this may increase the likelihood of Scaffold breakage. Failure to use forceps correctly may damage the Scaffold.*

Note: *The Scaffold should be implanted within 25 minutes of being removed from the inner tray. If more than 25 minutes have passed, do not use this Scaffold. See Site Instruction Manual for instruction on handling of prepared but unused Scaffolds. Choose a new Scaffold and begin Scaffold preparation procedure again.*

9. Place a sterile ruler on level surface next to the Scaffold for trimming, using a microscope if necessary.
10. Using a gentle sawing motion, trim Scaffold on one end only using sterile #10 or #11 scalpel. Use edge of the size-matched InVivo Therapeutics Cupped Forceps as trimming guide. Remove excess Scaffold piece and dispose according to standard practice for medical waste. Scaffold length and diameter should now allow for space between the Scaffold and surrounding contused spinal cord tissue to avoid tissue tension in the spinal cord.

Trim the Wetted Scaffold



11. Transport tray/pan/petri dish containing only trimmed Scaffold to operative field for implantation.

Note: If at any time during the Scaffold preparation, wetting, handling, or trimming, the Scaffold breaks, put the broken Scaffold aside and begin the Scaffold preparation process with another Scaffold. After the Scaffold implant, document the broken Scaffold as an Investigational Product Event, including a photograph of the broken Scaffold as appropriate. See Site Instruction Manual for instruction on disposing of opened but unused Scaffolds.

N. INVESTIGATIONAL PRODUCT IMPLANTATION

Note: Intraoperative vital signs will be monitored before, during, and after surgery, including blood pressure, heart rate, systolic and diastolic blood pressure, mean arterial pressure (MAP), oxygenation and ventilation. Source documentation (e.g., anesthesia flow sheets) will be collected, and significant changes will be documented and noted as safety events if appropriate.

Note: Scaffold is to be implanted after the spine stabilization and/or decompression procedure.

Note: An SSEP assessment (tibial or sciatic) must be conducted on all subjects prior to opening the dura to determine if there is clear and significant evidence of signal transmission through the injury site based on the judgment of the Investigator. If a clear signal is present indicating transmission through the injury site, the subject does not qualify for the Scaffold implant. The subject should be withdrawn from the study and is categorized as “enrolled but not treated.” See protocol Section 6.5 Discontinuation of Subjects for details.

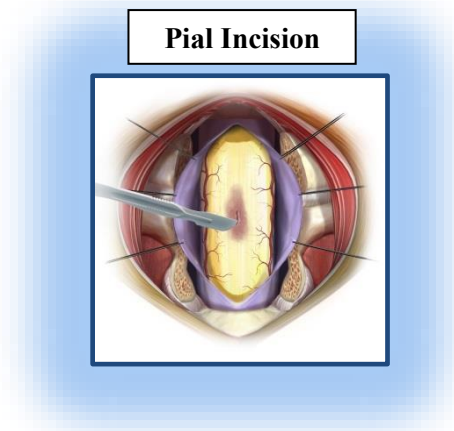
For subjects with a T2 or T3 neurological level of injury, bilateral intraoperative median and ulnar nerve SSEP monitoring is performed as an added safety precaution for the investigational procedure from durotomy through Scaffold placement and dural closure. An adequate baseline should be obtained per institutional protocol to ensure interpretable recordings from both median and ulnar SSEPs prior to the durotomy. Should the SSEP recordings indicate potential loss of function, appropriate steps should be taken per institutional guidelines such as adjustment of anesthesia, operating procedure, etc. The Investigator should determine whether the Scaffold can be placed safely if this deterioration occurs prior to Scaffold placement. The Investigator may also utilize additional modes of intraoperative neuromonitoring such as MEPs, if the risk of upper extremity movement is outweighed by the potential benefit. If the surgical procedure includes anterior cord manipulation, stronger consideration should be given to use of MEPs of the abductor pollicis brevis (C8, T1).

1. Flood the surgical field with saline and perform intraoperative ultrasonic imaging to assess the contusion size, presence or absence of a cavity within the contusion, contusion configuration, and location.
2. Perform a durotomy over the area of maximal contusion or extend an existing dural tear to expose the contusion site. Tack dural edges laterally in standard fashion. The contusion site may present as an intact spinal cord, with the area of injured spinal cord tissue not visible as it is in the center of the cord (contusion or “closed” injury), or a macerated spinal cord, with the area of injured spinal cord tissue exposed (compound or “open” injury). Capture a sample of the spontaneous exudate if present and submit to pathology for routine examination/testing, for example H&E

staining for histology. Note that irrigated tissue fragments and cells may best be collected in a test tube for subsequent preparation of a cell pellet by centrifugation. Irrigate the injured cord with isotonic saline to wash away any superficial hemorrhagic material or devitalized tissue.

Note: *Local hemostasis is secured using standard of care neurosurgical methods that are routinely used for human spinal cord surgery, and which were also utilized and validated for Scaffold implantation in the preclinical non-human animal studies. Because the spinal cord blood supply only involves capillary and small arteriolar vessels, clip or suture ligation is not indicated for procedures on the spinal cord. Rather, current surgical standard of care involves control of capillary bleeding using temporary topical application of bovine thrombin using hemostatic collagen sponges (e.g., GelfoamTM) and gentle cotton pledget tamponade. Larger scale, refractory bleeding from small arterioles occasionally requires direct electrocautery using microbipolar forceps. In this manner, standard of care dictates that complete hemostasis be achieved using these techniques at the point of discovery and prior to proceeding with the remainder of the operation. By definition, such practice facilitates visualization at the implantation site and ensures correct placement of the Scaffold.*

3. Inspect dorsal cord for areas of maximal surface contusion or spinal cord maceration to select an optimal area for Scaffold placement.
4. If injury is closed, perform an arachnoid/pial incision over the lesion, followed by a myelotomy, allowing direct access to the injured parenchyma.



5. After the epicenter of the lesion has been exposed, it is further irrigated for the purposes of debridement as necessary with isotonic saline to remove additional areas of hemorrhage and necrotic tissue within the cavity, and to create or further define a cavity for Scaffold implantation.
6. Using direct visualization and intraoperative ultrasound, confirm the size of the cavity and confirm that the Scaffold was trimmed to the appropriate size to allow for adequate space between the Scaffold and surrounding injured spinal cord tissue and avoid tissue tension when Scaffold is implanted lengthwise into spinal cord.

Note: *If the Scaffold size will not fit the contusion cavity properly, do not use. See Site Instruction Manual for instruction on handling of prepared but unused Scaffolds. Choose a new Scaffold and repeat the preparation of the Scaffold to ensure there will be adequate space between the Scaffold*

and surrounding contused spinal cord tissue to avoid tissue tension when implanted lengthwise into spinal cord.

7. Expose the cavity using standard surgical forceps to retract the cord edges, if necessary.
8. Based on the exposure of the cavity, choose the optimal surgical tool (e.g., bayonet forceps, size-matched Cupped Forceps) to implant the Scaffold, avoiding bending or excessive force on the Scaffold. Remove the Scaffold from the tray/pan/petri dish and gently place lengthwise into the mid-portion (epicenter) of the lesion where the cavity is exposed.
9. Confirm proper placement of Scaffold using direct visualization and ultrasound, and ensure that there is no excessive trans-mural tension (e.g., causing tissue blanching or bulging of the spinal cord). If Scaffold implantation results in tissue tension, remove the Scaffold and refer to the Site Instruction Manual for instruction on disposal of used Scaffolds. Choose another Scaffold and trim such that implantation does not result in excessive tissue tension.
10. Close the dura in standard watertight fashion, and externally fortify durotomy. If there is significant spinal cord edema or swelling such that a standard primary dural closure would compress spinal cord tissue, a duraplasty can be considered.

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Muscle Function Grading

- 0 = total paralysis
 1 = palpable or visible contraction
 2 = active movement, full range of motion (ROM) with gravity eliminated
 3 = active movement, full ROM against gravity
 4 = active movement, full ROM against gravity and moderate resistance in a muscle specific position
 5 = (normal) active movement, full ROM against gravity and full resistance in a functional muscle position expected from an otherwise unimpaired person
 5+ = (normal) active movement, full ROM against gravity and sufficient resistance to be considered normal if identified inhibiting factors (i.e. pain, disease) were not present
 NT = not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of > 50% of the normal ROM)

Sensory Grading

- 0 = Absent
 1 = Altered, either decreased/impaired sensation or hypersensitivity
 2 = Normal
 NT = Not testable

When to Test Non-Key Muscles:

In a patient with an apparent AIS B classification, non-key muscle functions more than 3 levels below the motor level on each side should be tested to most accurately classify the injury (differentiate between AIS B and C).

Root level

Shoulder: Flexion, extension, abduction, adduction, internal and external rotation	C5
Elbow: Supination	
Elbow: Pronation	C6
Wrist: Flexion	
Finger: Flexion at proximal joint, extension.	C7
Thumb: Flexion, extension and abduction in plane of thumb	
Finger: Flexion at MCP joint	C8
Thumb: Opposition, adduction and abduction perpendicular to palm	
Finger: Abduction of the index finger	T1
Hip: Adduction	L2
Hip: External rotation	L3
Hip: Extension, abduction, internal rotation	L4
Knee: Flexion	
Ankle: Inversion and eversion	
Toe: MP and IP extension	
Hallux and Toe: DIP and PIP flexion and abduction	L5
Hallux: Adduction	S1

ASIA Impairment Scale (AIS)

A = Complete. No sensory or motor function is preserved in the sacral segments S4-S5.

B = Sensory incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5 (light touch or pin prick at S4-S5 or deep and pressure) AND no motor function is preserved more than three levels below the motor level on either side of the body.

C = Motor incomplete. Motor function is preserved at the most caudal sacral segments for voluntary and contraction (VMC) OR the patient meets the criteria for sensory incomplete status (sensory function preserved at the most caudal sacral segments [S4-S5] by LL, PP or DAP), and has some sparing of motor function more than three levels below the posterior motor level on either side of the body.

(This includes key or non-key muscle functions to determine motor incomplete status.) For AIS C – less than half of key muscle functions below the single NLI have a muscle grade ≥ 3 .

D = Motor incomplete. Motor incomplete status as defined above, with at least half (half or more) of key muscle functions below the single NLI having a muscle grade ≥ 3 .

E = Normal. If sensation and motor function as tested with the SACSQ are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

Using ND: To document the sensory, motor and NLI levels, the ASIA Impairment Scale grade, and/or the zone of partial preservation (ZPP) when they are unable to be determined based on the examination results.



INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY



Steps in Classification

The following order is recommended for determining the classification of individuals with SCI.

- Determine sensory levels for right and left sides.**
 The sensory level is the most caudal intact dermatome for both pin prick and light touch sensation.
- Determine motor levels for right and left sides.**
 Defined by the lowest key muscle function that has a grade of at least 3 (on supine testing), providing the key muscle functions represented by segments above that level are judged to be intact (graded as a 5).
 Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal.

- Determine the neurological level of injury (NLI)**
 This refers to the most caudal segment of the cord with intact sensation and angravity (3 or more) muscle function strength, provided that there is normal (intact) sensory and motor function rostrally respectively.
 The NLI is the most cephalad of the sensory and motor levels determined in steps 1 and 2.

- Determine whether the injury is Complete or Incomplete.**
 (i.e. absence or presence of sacral sparing)
 If voluntary and contraction – No AND all S4-S5 sensory scores = 0 AND deep anal pressure = No, then injury is Complete.
 Otherwise, injury is Incomplete.

- Determine ASIA Impairment Scale (AIS) Grade:**
 Is injury Complete? IF YES, AIS=A and can record ZPP (lowest dermatome or myotome on each side with some preservation)
 NO
 Is injury Motor Complete? IF YES, AIS=B
 NO
 (No-voluntary and contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)

Are at least half (half or more) of the key muscles below the neurological level of injury graded 3 or better?



If sensation and motor function is normal in all segments, AIS=E
 Note: AIS E is used in follow-up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact; the ASIA Impairment Scale does not apply.

APPENDIX G: PAIN ASSESSMENT

Source: <http://www.iscos.org.uk/international-sci-pain-data-sets>

INTERNATIONAL SCI PAIN BASIC DATA SET Version 2.0 incl. training cases-2013-06-11

INTERNATIONAL SPINAL CORD INJURY PAIN BASIC DATA SET

DATA COLLECTION FORM – Version 2.0

Date of data collection: YYYY/MM/DD

Have you had any pain during the last seven days including today:

☐ No ☐ Yes

If yes:

Please note that the time period during the last week applies to all pain interference questions.

In general, how much has pain interfered with your day-to-day activities in the last week?

No interference ☐ 0 - ☐ 1 - ☐ 2 - ☐ 3 - ☐ 4 - ☐ 5 - ☐ 6 - ☐ 7 - ☐ 8 - ☐ 9 - ☐ 10 Extreme interference

In general, how much has pain interfered with your overall mood in the last week?

No interference ☐ 0 - ☐ 1 - ☐ 2 - ☐ 3 - ☐ 4 - ☐ 5 - ☐ 6 - ☐ 7 - ☐ 8 - ☐ 9 - ☐ 10 Extreme interference

In general, how much has pain interfered with your ability to get a good night's sleep?

No interference ☐ 0 - ☐ 1 - ☐ 2 - ☐ 3 - ☐ 4 - ☐ 5 - ☐ 6 - ☐ 7 - ☐ 8 - ☐ 9 - ☐ 10 Extreme interference

How many different pain problems do you have?

☐ 1; ☐ 2; ☐ 3; ☐ 4; ☐ ≥ 5

Please describe your three worst pain problems:

INTERNATIONAL SCI PAIN BASIC DATA SET Version 2.0 incl. training cases-2013-06-11

Worst pain problem:

Pain locations /sites (can be more than one, so check all that apply): right (R), midline (M), or left (L)	R	M	L	Type of pain Intensity and duration of pain Treatment of pain
Head				Type of pain (check one):
Neck/shoulders				Nociceptive <input type="checkbox"/> Musculoskeletal <input type="checkbox"/> Visceral <input type="checkbox"/> Other
throat				
neck				
shoulder				
Arms/hands				Neuropathic <input type="checkbox"/> At-level SCI <input type="checkbox"/> Below-level SCI <input type="checkbox"/> Other
upper arm				
elbow				
forearm				
wrist				
hand/fingers				
Frontal torso/genitals				<input type="checkbox"/> Other
chest				<input type="checkbox"/> Unknown
abdomen				
pelvis/genitalia				
Back				Intensity and duration of pain: Average pain intensity in the last week: 0 = no pain; 10 = pain as bad as you can imagine <input type="checkbox"/> 0; <input type="checkbox"/> 1; <input type="checkbox"/> 2; <input type="checkbox"/> 3; <input type="checkbox"/> 4; <input type="checkbox"/> 5; <input type="checkbox"/> 6; <input type="checkbox"/> 7; <input type="checkbox"/> 8; <input type="checkbox"/> 9; <input type="checkbox"/> 10
upper back				
lower back				
Buttocks/hips				Date of onset: YYYY/MM/DD
buttocks				
hip				
anus				
Upper leg/thigh				Are you using or receiving any <u>treatment</u> for your pain problem: <input type="checkbox"/> No <input type="checkbox"/> Yes
Lower legs/feet				
knee				
shin				
calf				
ankle				
foot/toes				

INTERNATIONAL SCI PAIN BASIC DATA SET Version 2.0 incl. training cases-2013-06-11

Second worst pain problem:

Pain locations /sites (can be more than one, so check all that apply): right (R), midline (M), or left (L)	R	M	L	Type of pain Intensity and duration of pain Treatment of pain
Head				Type of pain (check one):
Neck/shoulders				Nociceptive
throat				<input type="checkbox"/> Musculoskeletal
neck				<input type="checkbox"/> Visceral
shoulder				<input type="checkbox"/> Other
Arms/hands				Neuropathic
upper arm				<input type="checkbox"/> At-level SCI
elbow				<input type="checkbox"/> Below-level SCI
forearm				<input type="checkbox"/> Other
wrist				
hand/fingers				
Frontal torso/genitals				<input type="checkbox"/> Other
chest				
abdomen				<input type="checkbox"/> Unknown
pelvis/genitalia				
Back				Intensity and duration of pain:
upper back				Average pain intensity in the last week:
lower back				0 = no pain; 10 = pain as bad as you can imagine
Buttocks/hips				<input type="checkbox"/> 0; <input type="checkbox"/> 1; <input type="checkbox"/> 2; <input type="checkbox"/> 3; <input type="checkbox"/> 4; <input type="checkbox"/> 5;
buttocks				<input type="checkbox"/> 6; <input type="checkbox"/> 7; <input type="checkbox"/> 8; <input type="checkbox"/> 9; <input type="checkbox"/> 10
hip				
anus				
Upper leg/thigh				Date of onset: YYYY/MM/DD
Lower legs/feet				Are you using or receiving any <u>treatment</u> for your
knee				pain problem:
shin				<input type="checkbox"/> No <input type="checkbox"/> Yes
calf				
ankle				
foot/toes				

INTERNATIONAL SCI PAIN BASIC DATA SET Version 2.0 incl. training cases-2013-06-11

Third worst pain problem:

Pain locations /sites (can be more than one, so check all that apply): right (R), midline (M), or left (L)	R	M	L	Type of pain Intensity and duration of pain Treatment of pain
Head				Type of pain (check one): Nociceptive <input type="checkbox"/> Musculoskeletal <input type="checkbox"/> Visceral <input type="checkbox"/> Other Neuropathic <input type="checkbox"/> At-level SCI <input type="checkbox"/> Below-level SCI <input type="checkbox"/> Other <input type="checkbox"/> Other <input type="checkbox"/> Unknown Intensity and duration of pain: Average pain intensity in the last week: 0 = no pain; 10 = pain as bad as you can imagine <input type="checkbox"/> 0; <input type="checkbox"/> 1; <input type="checkbox"/> 2; <input type="checkbox"/> 3; <input type="checkbox"/> 4; <input type="checkbox"/> 5; <input type="checkbox"/> 6; <input type="checkbox"/> 7; <input type="checkbox"/> 8; <input type="checkbox"/> 9; <input type="checkbox"/> 10 Date of onset: YYYY/MM/DD Are you using or receiving any <u>treatment</u> for your pain problem: <input type="checkbox"/> No <input type="checkbox"/> Yes
Neck/shoulders				
throat				
neck				
shoulder				
Arms/hands				
upper arm				
elbow				
forearm				
wrist				
hand/fingers				
Frontal torso/genitals				
chest				
abdomen				
pelvis/genitalia				
Back				
upper back				
lower back				
Buttocks/hips				
buttocks				
hip				
anus				
Upper leg/thigh				
Lower legs/feet				
knee				
shin				
calf				
ankle				
foot/toes				

APPENDIX H: BOWEL AND BLADDER FUNCTION ASSESSMENTS

Source: http://www.commondataelements.ninds.nih.gov/SCI.aspx#tab=Data_Standards

INTERNATIONAL SPINAL CORD INJURY DATA SETS BOWEL FUNCTION BASIC DATA SET—DATA FORM

Date performed: YYYYMMDD ☐ Unknown

Gastrointestinal or anal sphincter dysfunction unrelated to the spinal cord lesion:

☐ No ☐ Yes, specify _____ ☐ Unknown

Surgical procedures on the gastrointestinal tract:

- ☐ No ☐ Appendectomy, date performed YYYYMMDD
☐ Cholecystectomy, date performed YYYYMMDD
☐ Colostomy, date last performed YYYYMMDD
☐ Ileostomy, date last performed YYYYMMDD
☐ Other, specify: _____, date last performed YYYYMMDD
☐ Unknown

Awareness of the need to defecate (within the last four weeks):

- ☐ Normal (direct)
☐ Indirect (For example: Abdominal cramping or discomfort—Abdominal muscle spasms—Spasms of lower extremities—Perspiration—Piloerection—Headache—Chills)
☐ None
☐ Unknown

Defecation method and bowel care procedures (within the last four weeks):

	Main	Supplementary
Normal defecation	<input type="checkbox"/>	<input type="checkbox"/>
Straining/bearing down to empty	<input type="checkbox"/>	<input type="checkbox"/>
Digital ano-rectal stimulation	<input type="checkbox"/>	<input type="checkbox"/>
Suppositories	<input type="checkbox"/>	<input type="checkbox"/>
Digital evacuation	<input type="checkbox"/>	<input type="checkbox"/>
Mini enema (Clysm \leq 150 ml)	<input type="checkbox"/>	<input type="checkbox"/>
Enema (> 150 ml)	<input type="checkbox"/>	<input type="checkbox"/>
Colostomy	<input type="checkbox"/>	<input type="checkbox"/>
Sacral anterior root stimulation	<input type="checkbox"/>	<input type="checkbox"/>
Other method, specify _____	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Unknown		

Average time required for defecation (within the last four weeks):

- ☐ 0–5 min ☐ 6–10 min ☐ 11–20 min ☐ 21–30 min
☐ 31–60 min ☐ More than 60 min ☐ Unknown

Frequency of defecation (within the last four weeks):

- ☐ Three times or more per day ☐ Twice daily ☐ Once daily
☐ Not daily but more than twice every week
☐ Twice every week ☐ Once every week
☐ Less than once every week, but at least once within the last four weeks
☐ No defecation within the last four weeks
☐ Not applicable ☐ Unknown

Frequency of fecal incontinence (within the last three months):

- ☐ Two or more episodes per day ☐ One episode per day
☐ Not every day but at least once per week
☐ Not every week but more than once per month
☐ Once per month
☐ Less than once per month ☐ Never
☐ Unknown

Need to wear pad or plug (within the last three months):

- ☐ Daily use ☐ Not every day but at least once per week
☐ Not every week but at least once per month
☐ Less than once per month ☐ Never
☐ Unknown

Medication affecting bowel function/constipating agents (within the last four weeks):

- ☐ No ☐ Yes, anticholinergics
 ☐ Yes, narcotics
 ☐ Yes, other, specify: _____

Oral laxatives (within the last four weeks):

- ☐ No ☐ Yes, osmotic laxatives (drops)
 ☐ Yes, osmotic or bulking laxatives (tablets or granulates)
 ☐ Yes, irritant laxatives (drops)
 ☐ Yes, irritant laxatives (tablets)
 ☐ Yes, prokinetics
 ☐ Yes, other, specify: _____
☐ Unknown

Perianal problems (within the last year):

- ☐ None ☐ Haemorrhoids ☐ Perianal sores ☐ Fissures ☐ Rectal prolapse
☐ Other, specify _____ ☐ Unknown

Date of data collection: YYYYMMDD

Urinary tract impairment unrelated to spinal cord lesion:

☐ No ☐ Yes, specify _____ ☐ Unknown

Awareness of the need to empty the bladder:

☐ No ☐ Yes ☐ Not applicable ☐ Not known

Bladder emptying:

	Main	Supplementary
Normal voiding	<input type="checkbox"/>	<input type="checkbox"/>
Bladder reflex triggering		
Voluntary (tapping, scratching, anal stretch, etc.)	<input type="checkbox"/>	<input type="checkbox"/>
Involuntary	<input type="checkbox"/>	<input type="checkbox"/>
Bladder expression		
Straining (abdominal straining, Valsalva's manoeuvre)	<input type="checkbox"/>	<input type="checkbox"/>
External compression (Credé manoeuvre)	<input type="checkbox"/>	<input type="checkbox"/>
Intermittent catheterisation		
Self-catheterisation	<input type="checkbox"/>	<input type="checkbox"/>
Catheterisation by attendant	<input type="checkbox"/>	<input type="checkbox"/>
Indwelling catheter		
Transurethral	<input type="checkbox"/>	<input type="checkbox"/>
Suprapubic	<input type="checkbox"/>	<input type="checkbox"/>
Sacral anterior root stimulation	<input type="checkbox"/>	<input type="checkbox"/>
Non-continent urinary diversion/ostomy	<input type="checkbox"/>	
Other method, specify _____	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Unknown		

Average number of voluntary bladder emptyings per day during the last week ____

Any involuntary urine leakage (incontinence) within the last three months:

☐ No ☐ Yes, average daily ☐ Yes, average weekly ☐ Yes, average monthly
☐ Not applicable ☐ Unknown

Collecting appliances for urinary incontinence:

☐ No ☐ Yes, condom catheter/sheath
☐ Yes, diaper/pad
☐ Yes, ostomy bag
☐ Yes, other, specify _____
☐ Unknown

Any drugs for the urinary tract within the last year:

- ☐ No
- ☐ Yes, bladder relaxant drugs (anticholinergics, tricyclic antidepressants, etc.)
 - ☐ Yes, sphincter/bladder neck relaxant drugs (alpha adrenergic blockers, etc.)
 - ☐ Yes, antibiotics/antiseptics: ☐ For treatment of urinary tract infection
☐ For prophylactic reasons
 - ☐ Yes, other, specify _____
- ☐ Unknown

Surgical procedures on the urinary tract:

- ☐ No
- ☐ Yes, supra-pubic catheter insertion, date last performed YYYYMMDD
 - ☐ Yes, bladder stone removal, date last performed YYYYMMDD
 - ☐ Yes, upper urinary tract stone removal, date last performed YYYYMMDD
 - ☐ Yes, bladder augmentation, date last performed YYYYMMDD
 - ☐ Yes, sphincterotomy/urethral stent, date last performed YYYYMMDD
 - ☐ Yes, botulinum toxin injection, date last performed YYYYMMDD
 - ☐ Yes, artificial sphincter, date last performed YYYYMMDD
 - ☐ Yes, ileovesicostomy, date last performed YYYYMMDD
 - ☐ Yes, ileoureterostomy, date last performed YYYYMMDD
 - ☐ Yes, continent catheterizable valves, date last performed YYYYMMDD
 - ☐ Yes, sacral anterior root stimulator, date performed YYYYMMDD
 - ☐ Yes, other, specify _____, date performed YYYYMMDD
- ☐ Unknown

Any change in urinary symptoms within the last year:

- ☐
- No
- ☐
- Yes
- ☐
- Not applicable
- ☐
- Unknown

APPENDIX I: SPINAL CORD INDEPENDENCE MEASURE (SCIM III)

Source: <http://www.rehab.research.va.gov/jour/07/44/1/pdf/catzappend.pdf>

SCIM-SPINAL CORD INDEPENDENCE MEASURE		EXAM 1	2	3	4	5	6
Self-Care		DATE <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>					
1. Feeding (cutting, opening containers, pouring, bringing food to mouth, holding cup with fluid)		<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>					
0. Needs parenteral, gastrostomy, or fully assisted oral feeding							
1. Needs partial assistance for eating and/or drinking, or for wearing adaptive devices							
2. Eats independently; needs adaptive devices or assistance only for cutting food and/or pouring and/or opening containers							
3. Eats and drinks independently; does not require assistance or adaptive devices							
2. Bathing (soaping, washing, drying body and head, manipulating water tap). A-upper body; B-lower body							
A. 0. Requires total assistance		<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>					
1. Requires partial assistance							
2. Washes independently with adaptive devices or in a specific setting (e.g., bars, chair)							
3. Washes independently; does not require adaptive devices or specific setting (not customary for healthy people) (adss)							
B. 0. Requires total assistance		<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>					
1. Requires partial assistance							
2. Washes independently with adaptive devices or in a specific setting (adss)							
3. Washes independently; does not require adaptive devices (adss) or specific setting							
3. Dressing (clothes, shoes, permanent orthoses: dressing, wearing, undressing). A-upper body; B-lower body							
A. 0. Requires total assistance		<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>					
1. Requires partial assistance with clothes without buttons, zippers or laces (cwobzl)							
2. Independent with cwobzl; requires adaptive devices and/or specific settings (adss)							
3. Independent with cwobzl; does not require adss; needs assistance or adss only for hzl							
4. Dresses (any cloth) independently; does not require adaptive devices or specific setting							
B. 0. Requires total assistance		<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>					
1. Requires partial assistance with clothes without buttons, zips or laces (cwobzl)							
2. Independent with cwobzl; requires adaptive devices and/or specific settings (adss)							
3. Independent with cwobzl without adss; needs assistance or adss only for hzl							
4. Dresses (any cloth) independently; does not require adaptive devices or specific setting							
4. Grooming (washing hands and face, brushing teeth, combing hair, shaving, applying makeup)		<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>					
0. Requires total assistance							
1. Requires partial assistance							
2. Grooms independently with adaptive devices							
3. Grooms independently without adaptive devices							
SUBTOTAL (0-20)		<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>					
Respiration and Sphincter Management							
5. Respiration		<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>					
0. Requires tracheal tube (TT) and permanent or intermittent assisted ventilation (IAV)							
2. Breathes independently with TT; requires oxygen, much assistance in coughing or TT management							
4. Breathes independently with TT; requires little assistance in coughing or TT management							
6. Breathes independently without TT; requires oxygen, much assistance in coughing, a mask (e.g., peep) or IAV (bipap)							
8. Breathes independently without TT; requires little assistance or stimulation for coughing							
10. Breathes independently without assistance or device							
6. Sphincter Management - Bladder		<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>					
0. Indwelling catheter							
3. Residual urine volume (RUV) > 100cc; no regular catheterization or assisted intermittent catheterization							
6. RUV < 100cc or intermittent self-catheterization; needs assistance for applying drainage instrument							
9. Intermittent self-catheterization; uses external drainage instrument; does not need assistance for applying							
11. Intermittent self-catheterization; continent between catheterizations; does not use external drainage instrument							
13. RUV < 100cc; needs only external urine drainage; no assistance is required for drainage							
15. RUV < 100cc; continent; does not use external drainage instrument							
7. Sphincter Management - Bowel		<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>					
0. Irregular timing or very low frequency (less than once in 3 days) of bowel movements							
5. Regular timing, but requires assistance (e.g., for applying suppository); rare accidents (less than twice a month)							
8. Regular bowel movements, without assistance; rare accidents (less than twice a month)							
10. Regular bowel movements, without assistance; no accidents							
8. Use of Toilet (perineal hygiene, adjustment of clothes before/after, use of napkins or diapers).		<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>					
0. Requires total assistance							
1. Requires partial assistance; does not clean self							
2. Requires partial assistance; cleans self independently							
4. Uses toilet independently in all tasks but needs adaptive devices or special setting (e.g., bars)							
5. Uses toilet independently; does not require adaptive devices or special setting							
SUBTOTAL (0-40)		<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>					

Mobility (room and toilet)

DATE

1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	----

9. Mobility in Bed and Action to Prevent Pressure Sores

0. Needs assistance in all activities: turning upper body in bed, turning lower body in bed, sitting up in bed, doing push-ups in wheelchair, with or without adaptive devices, but not with electric aids
2. Performs one of the activities without assistance
4. Performs two or three of the activities without assistance
6. Performs all the bed mobility and pressure release activities independently

10. Transfers: bed-wheelchair (locking wheelchair, lifting footrests, removing and adjusting arm rests, transferring, lifting feet)

0. Requires total assistance
1. Needs partial assistance and/or supervision, and/or adaptive devices (e.g., sliding board)
2. Independent (or does not require wheelchair)

11. Transfers: wheelchair-toilet-tub (if uses toilet wheelchair: transfers to and from; if uses regular wheelchair: locking wheelchair, lifting footrests, removing and adjusting armrests, transferring, lifting feet)

0. Requires total assistance
1. Needs partial assistance and/or supervision, and/or adaptive devices (e.g., grab-bars)
2. Independent (or does not require wheelchair)

Mobility (indoors and outdoors, on even surface)

12. Mobility Indoors

0. Requires total assistance
1. Needs electric wheelchair or partial assistance to operate manual wheelchair
2. Moves independently in manual wheelchair
3. Requires supervision while walking (with or without devices)
4. Walks with a walking frame or crutches (swing)
5. Walks with crutches or two canes (reciprocal walking)
6. Walks with one cane
7. Needs leg orthosis only
8. Walks without walking aids

13. Mobility for Moderate Distances (10-100 meters)

0. Requires total assistance
1. Needs electric wheelchair or partial assistance to operate manual wheelchair
2. Moves independently in manual wheelchair
3. Requires supervision while walking (with or without devices)
4. Walks with a walking frame or crutches (swing)
5. Walks with crutches or two canes (reciprocal walking)
6. Walks with one cane
7. Needs leg orthosis only
8. Walks without walking aids

14. Mobility Outdoors (more than 100 meters)

0. Requires total assistance
1. Needs electric wheelchair or partial assistance to operate manual wheelchair
2. Moves independently in manual wheelchair
3. Requires supervision while walking (with or without devices)
4. Walks with a walking frame or crutches (swing)
5. Walks with crutches or two canes (reciprocal walking)
6. Walks with one cane
7. Needs leg orthosis only
8. Walks without walking aids

15. Stair Management

0. Unable to ascend or descend stairs
1. Ascends and descends at least 3 steps with support or supervision of another person
2. Ascends and descends at least 3 steps with support of handrail and/or crutch or cane
3. Ascends and descends at least 3 steps without any support or supervision

16. Transfers: wheelchair-car (approaching car, locking wheelchair, removing arm- and footrests, transferring to and from car, bringing wheelchair into and out of car)

0. Requires total assistance
1. Needs partial assistance and/or supervision and/or adaptive devices
2. Transfers independent; does not require adaptive devices (or does not require wheelchair)

17. Transfers: ground-wheelchair

0. Requires assistance
1. Transfers independent with or without adaptive devices (or does not require wheelchair)

SUBTOTAL (0-40)

TOTAL SCIM SCORE (0-100)

APPENDIX J: FERRANS AND POWERS QUALITY OF LIFE INDEX - SPINAL CORD INJURY (QLI-SCI III)

Ferrans and Powers QUALITY OF LIFE INDEX® SPINAL CORD INJURY VERSION - III

PART I. For each of the following, please choose the answer that best describes how satisfied you are with that area of your life. Please mark your answer by circling the number. There are no right or wrong answers.

HOW <i>SATISFIED</i> ARE YOU WITH:	Very Dissatisfied	Moderately Dissatisfied	Slightly Dissatisfied	Slightly Satisfied	Moderately Satisfied	Very Satisfied
1. Your health?	1	2	3	4	5	6
2. Your health care?	1	2	3	4	5	6
3. The amount of pain that you have?	1	2	3	4	5	6
4. The amount of energy you have for everyday activities?	1	2	3	4	5	6
5. Your ability to take care of yourself without help?	1	2	3	4	5	6
6. Your ability to go places outside your home?	1	2	3	4	5	6
7. Your ability to clear your lungs?	1	2	3	4	5	6
8. The amount of control you have over your life?	1	2	3	4	5	6
9. Your chances of living as long as you would like?	1	2	3	4	5	6
10. Your family's health?	1	2	3	4	5	6
11. Your children?	1	2	3	4	5	6
12. Your ability to have children?	1	2	3	4	5	6
13. Your family's happiness?	1	2	3	4	5	6
14. Your sex life?	1	2	3	4	5	6
15. Your spouse, lover, or partner (if you have one)?	1	2	3	4	5	6
16. Not having a spouse, lover or partner (if you do not have one)?	1	2	3	4	5	6
17. Your friends?	1	2	3	4	5	6

(Please Go To Next Page)

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HOW <i>SATISFIED</i> ARE YOU WITH:	Very Dissatisfied	Moderately Dissatisfied	Slightly Dissatisfied	Slightly Satisfied	Moderately Satisfied	Very Satisfied
18. The emotional support you get from your family?	1	2	3	4	5	6
19. The emotional support you get from people other than your family?	1	2	3	4	5	6
20. Your ability to take care of family responsibilities?	1	2	3	4	5	6
21. How useful you are to others?	1	2	3	4	5	6
22. The amount of worries in your life?	1	2	3	4	5	6
23. Your neighborhood?	1	2	3	4	5	6
24. Your home, apartment, or place where you live?	1	2	3	4	5	6
25. Your job (if employed)?	1	2	3	4	5	6
26. Not having a job (if unemployed, retired, or disabled)?	1	2	3	4	5	6
27. Your education?	1	2	3	4	5	6
28. How well you can take care of your financial needs?	1	2	3	4	5	6
29. The things you do for fun?	1	2	3	4	5	6
30. Your chances for a happy future?	1	2	3	4	5	6
31. Your peace of mind?	1	2	3	4	5	6
32. Your faith in God?	1	2	3	4	5	6
33. Your achievement of personal goals?	1	2	3	4	5	6
34. Your happiness in general?	1	2	3	4	5	6
35. Your life in general?	1	2	3	4	5	6
36. Your personal appearance?	1	2	3	4	5	6
37. Yourself in general?	1	2	3	4	5	6

(Please Go To Next Page)

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PART 2. For each of the following, please choose the answer that best describes how *important* that area of your life is to you. Please mark your answer by circling the number. There are no right or wrong answers.

HOW <i>IMPORTANT</i> TO YOU IS:	Very Unimportant	Moderately Unimportant	Slightly Unimportant	Slightly Important	Moderately Important	Very Important
1. Your health?	1	2	3	4	5	6
2. Your health care?	1	2	3	4	5	6
3. Having no pain?	1	2	3	4	5	6
4. Having enough energy for everyday activities?	1	2	3	4	5	6
5. Taking care of yourself without help?	1	2	3	4	5	6
6. Being able to go places outside your home?	1	2	3	4	5	6
7. Your ability to clear your lungs?	1	2	3	4	5	6
8. Having control over your life?	1	2	3	4	5	6
9. Living as long as you would like?	1	2	3	4	5	6
10. Your family's health?	1	2	3	4	5	6
11. Your children?	1	2	3	4	5	6
12. Being able to have children?	1	2	3	4	5	6
13. Your family's happiness?	1	2	3	4	5	6
14. Your sex life?	1	2	3	4	5	6
15. Your spouse, lover, or partner (if you have one)?	1	2	3	4	5	6
16. Having a spouse, lover or partner (if you do not have one)?	1	2	3	4	5	6
17. Your friends?	1	2	3	4	5	6

(Please Go To Next Page)

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HOW IMPORTANT TO YOU IS:	Very Unimportant	Moderately Unimportant	Slightly Unimportant	Slightly Important	Moderately Important	Very Important
18. The emotional support you get from your family?	1	2	3	4	5	6
19. The emotional support you get from people other than your family?	1	2	3	4	5	6
20. Taking care of family responsibilities?	1	2	3	4	5	6
21. Being useful to others?	1	2	3	4	5	6
22. Having no worries?	1	2	3	4	5	6
23. Your neighborhood?	1	2	3	4	5	6
24. Your home, apartment, or place where you live?	1	2	3	4	5	6
25. Your job (if employed)?	1	2	3	4	5	6
26. Having a job (if unemployed, retired, or disabled)?	1	2	3	4	5	6
27. Your education?	1	2	3	4	5	6
28. Being able to take care of your financial needs?	1	2	3	4	5	6
29. Doing things for fun?	1	2	3	4	5	6
30. Having a happy future?	1	2	3	4	5	6
31. Peace of mind?	1	2	3	4	5	6
32. Your faith in God?	1	2	3	4	5	6
33. Achieving your personal goals?	1	2	3	4	5	6
34. Your happiness in general?	1	2	3	4	5	6
35. Being satisfied with life?	1	2	3	4	5	6
36. Your personal appearance?	1	2	3	4	5	6
37. Are you to yourself?	1	2	3	4	5	6

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APPENDIX K: BECK DEPRESSION INVENTORY II (BDI-II)

BDI-II

Date: _____

Name: _____ Marital Status: _____ Age: _____ Sex: _____

Occupation: _____ Education: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today**. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

<p>1. Sadness</p> <p>0 I do not feel sad.</p> <p>1 I feel sad much of the time.</p> <p>2 I am sad all the time.</p> <p>3 I am so sad or unhappy that I can't stand it.</p> <p>2. Pessimism</p> <p>0 I am not discouraged about my future.</p> <p>1 I feel more discouraged about my future than I used to be.</p> <p>2 I do not expect things to work out for me.</p> <p>3 I feel my future is hopeless and will only get worse.</p> <p>3. Past Failure</p> <p>0 I do not feel like a failure.</p> <p>1 I have failed more than I should have.</p> <p>2 As I look back, I see a lot of failures.</p> <p>3 I feel I am a total failure as a person.</p> <p>4. Loss of Pleasure</p> <p>0 I get as much pleasure as I ever did from the things I enjoy.</p> <p>1 I don't enjoy things as much as I used to.</p> <p>2 I get very little pleasure from the things I used to enjoy.</p> <p>3 I can't get any pleasure from the things I used to enjoy.</p> <p>5. Guilty Feelings</p> <p>0 I don't feel particularly guilty.</p> <p>1 I feel guilty over many things I have done or should have done.</p> <p>2 I feel quite guilty most of the time.</p> <p>3 I feel guilty all of the time.</p>	<p>6. Punishment Feelings</p> <p>0 I don't feel I am being punished.</p> <p>1 I feel I may be punished.</p> <p>2 I expect to be punished.</p> <p>3 I feel I am being punished.</p> <p>7. Self-Dislike</p> <p>0 I feel the same about myself as ever.</p> <p>1 I have lost confidence in myself.</p> <p>2 I am disappointed in myself.</p> <p>3 I dislike myself.</p> <p>8. Self-Criticalness</p> <p>0 I don't criticize or blame myself more than usual.</p> <p>1 I am more critical of myself than I used to be.</p> <p>2 I criticize myself for all of my faults.</p> <p>3 I blame myself for everything bad that happens.</p> <p>9. Suicidal Thoughts or Wishes</p> <p>0 I don't have any thoughts of killing myself.</p> <p>1 I have thoughts of killing myself, but I would not carry them out.</p> <p>2 I would like to kill myself.</p> <p>3 I would kill myself if I had the chance.</p> <p>10. Crying</p> <p>0 I don't cry any more than I used to.</p> <p>1 I cry more than I used to.</p> <p>2 I cry over every little thing.</p> <p>3 I feel like crying, but I can't.</p>
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Subtotal Page 1

Continued on Back

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11. Agitation

- 0 I am no more restless or wound up than usual.
- 1 I feel more restless or wound up than usual.
- 2 I am so restless or agitated that it's hard to stay still.
- 3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

- 0 I have not lost interest in other people or activities.
- 1 I am less interested in other people or things than before.
- 2 I have lost most of my interest in other people or things.
- 3 It's hard to get interested in anything.

13. Indecisiveness

- 0 I make decisions about as well as ever.
- 1 I find it more difficult to make decisions than usual.
- 2 I have much greater difficulty in making decisions than I used to.
- 3 I have trouble making any decisions.

14. Worthlessness

- 0 I do not feel I am worthless.
- 1 I don't consider myself as worthwhile and useful as I used to.
- 2 I feel more worthless as compared to other people.
- 3 I feel utterly worthless.

15. Loss of Energy

- 0 I have as much energy as ever.
- 1 I have less energy than I used to have.
- 2 I don't have enough energy to do very much.
- 3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

- 0 I have not experienced any change in my sleeping pattern.
- 1a I sleep somewhat more than usual.
- 1b I sleep somewhat less than usual.
- 2a I sleep a lot more than usual.
- 2b I sleep a lot less than usual.
- 3a I sleep most of the day.
- 3b I wake up 1-2 hours early and can't get back to sleep.

17. Irritability

- 0 I am no more irritable than usual.
- 1 I am more irritable than usual.
- 2 I am much more irritable than usual.
- 3 I am irritable all the time.

18. Changes in Appetite

- 0 I have not experienced any change in my appetite.
- 1a My appetite is somewhat less than usual.
- 1b My appetite is somewhat greater than usual.
- 2a My appetite is much less than before.
- 2b My appetite is much greater than usual.
- 3a I have no appetite at all.
- 3b I crave food all the time.

19. Concentration Difficulty

- 0 I can concentrate as well as ever.
- 1 I can't concentrate as well as usual.
- 2 It's hard to keep my mind on anything for very long.
- 3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

- 0 I am no more tired or fatigued than usual.
- 1 I get more tired or fatigued more easily than usual.
- 2 I am too tired or fatigued to do a lot of the things I used to do.
- 3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

- 0 I have not noticed any recent change in my interest in sex.
- 1 I am less interested in sex than I used to be.
- 2 I am much less interested in sex now.
- 3 I have lost interest in sex completely.

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Subtotal Page 2

Subtotal Page 1

Total Score

APPENDIX L: SEXUAL FUNCTION

SEXUAL FUNCTION - FEMALE

International Spinal Cord Injury Female Sexual and Reproductive Function Basic Data Set – Data Collection Form

Date of data collection: YYYYMMDD

Interest in discussing sexual issues

- ☐ Yes
- ☐ Yes, but only willing to provide information for the medical record
- ☐ No, prefers the discussion is stopped

Sexual orientation

- | | |
|---|--------------------------------------|
| <input type="checkbox"/> Heterosexual | <input type="checkbox"/> Bisexual |
| <input type="checkbox"/> Homosexual (lesbian) | <input type="checkbox"/> Asexual |
| <input type="checkbox"/> Prefer not to say | <input type="checkbox"/> Do not know |

Sexual problems prior or unrelated to the spinal cord lesion:

- ☐ No ☐ Yes, specify _____ ☐ Unknown/Not applicable

Sexual dysfunction related to the spinal cord lesion:

- ☐ Yes ☐ No ☐ Unknown/Not applicable

Psychogenic genital arousal: ☐ Normal ☐ Reduced/altered ☐ Absent ☐ Unknown/Not applicable

Reflex genital arousal: ☐ Normal ☐ Reduced/altered ☐ Absent ☐ Unknown/Not applicable

Orgasmic function: ☐ Normal ☐ Reduced/altered ☐ Absent ☐ Unknown/Not applicable

Menstruation: ☐ Normal ☐ Reduced/altered ☐ Absent ☐ Not applicable ☐ Unknown

SEXUAL FUNCTION - MALE
International Spinal Cord Injury Male Sexual Function Basic Data Set
– Data Collection Form

Date of data collection: YYYYMMDD

Interest in discussing sexual issues

- ☐ Yes
- ☐ Yes, but only willing to provide information for the medical record
- ☐ No, prefers the discussion is stopped

Sexual orientation

- | | |
|--|--------------------------------------|
| <input type="checkbox"/> Heterosexual | <input type="checkbox"/> Bisexual |
| <input type="checkbox"/> Homosexual (gay) | <input type="checkbox"/> Asexual |
| <input type="checkbox"/> Prefer not to say | <input type="checkbox"/> Do not know |

Sexual problems prior or unrelated to the spinal cord lesion:

- ☐ No ☐ Yes, specify _____ ☐ Unknown/Not applicable

Sexual dysfunction related to the spinal cord lesion:

- ☐ Yes ☐ No ☐ Unknown/Not applicable

Psychogenic Erection: ☐ Normal ☐ Reduced/altered ☐ Absent ☐ Unknown/Not applicable

Reflex Erection: ☐ Normal ☐ Reduced/altered ☐ Absent ☐ Unknown/Not applicable

Ejaculation: ☐ Normal ☐ Reduced/altered ☐ Absent ☐ Unknown/Not applicable

Orgasmic Function: ☐ Normal ☐ Reduced/altered ☐ Absent ☐ Unknown/Not applicable